Cephalosporins: A Review

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Author Disclosure
Drs Harrison and Bratcher have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives

After completing this article, readers should be able to:

1. Describe the mechanism of action of cephalosporins.
2. Delineate the two most common mechanisms of resistance to penicillins.
3. Discuss the most common adverse effects of common cephalosporins.
4. List which cephalosporins have activity against *Pseudomonas*.

Introduction

Cephalosporins are beta-lactam antimicrobials that share mechanisms of action and a similar structure with penicillins (Figure). Penicillins and cephalosporins have the same four-member "core" beta-lactam ring, but cephalosporins have an additional atom in the side ring. Modified side chains on either ring alter antimicrobial activity, resistance to beta-lactamases, or pharmacokinetics. Penicillin-susceptible pathogens usually are cephalosporin-susceptible. Exceptions are *Listeria* and *Pasteurella* sp. Cephalosporins have activity against common gram-negative organisms such as *Escherichia coli*, nontypeable *Haemophilus influenzae* (ntHi), and methicillin-susceptible *Staphylococcus aureus* (MSSA), but all methicillin-resistant *S aureus* (MRSA) and enterococci are cephalosporin-resistant. Because of minimal use or current unavailability, we will not discuss cephalothin, moxalactam, cefamandole, cefonicid, ceforanide, ceftizoxime, cefoperazone, cefpirome, cefmetazole, or cefotetan.

Mechanism of Action

To help understand the mechanism of action of cephalosporins, rigid bacterial cell walls can be considered as a series of repeating interlocking units reminiscent of floor tiles. During replication, a bacterium removes "tiles" circumferentially to allow cell division via a pinching-like action, while quickly placing new "tiles" at the ends of what have become two bacteria. This process requires enzymes to interlock replacement tiles. Such enzymes are the targets of beta-lactam antibiotics and are called penicillin-binding proteins (PBPs). Antibiotic action requires binding to PBPs, preventing them from closing the vulnerable ends on dividing bacteria and causing the natural intrabacterial hyperosmotic pressure to rupture the bacteria. Thus, beta-lactam antibiotics are bactericidal.

Bacterial Resistance Mechanisms

Beta-lactam antibiotics are highly attracted to most PBPs of susceptible pathogens. Each bacterial strain contains multiple different PBPs. Gram-negative bacteria can have different mixes of PBP than gram-positive bacteria. Different cephalosporins are attracted with different intensity to different PBPs (mostly to PBPs 2B, 1A, and 2X, but less to PBP3). PBP mutations may reduce the affinity of beta-lactam antibiotics for certain pathogens, which necessitates increased drug concentration to stop bacterial growth because the antibiotic must be in closer proximity to bind to mutated PBPs. Higher drug doses may overcome this obstacle, as in the use of high-dose amoxicillin for penicillin-nonsusceptible *Streptococcus pneumoniae* (PNSP) in acute otitis media.

Abbreviations

CSF: cerebrospinal fluid
ESBL: extended-spectrum beta-lactamase
MRSA: methicillin-resistant *Staphylococcus aureus*
MSSA: methicillin-suspectible *Staphylococcus aureus*
ntHi: nontypeable *Haemophilus influenzae*
PBP: penicillin-binding protein
PNSP: penicillin-nonsusceptible *Streptococcus pneumoniae*

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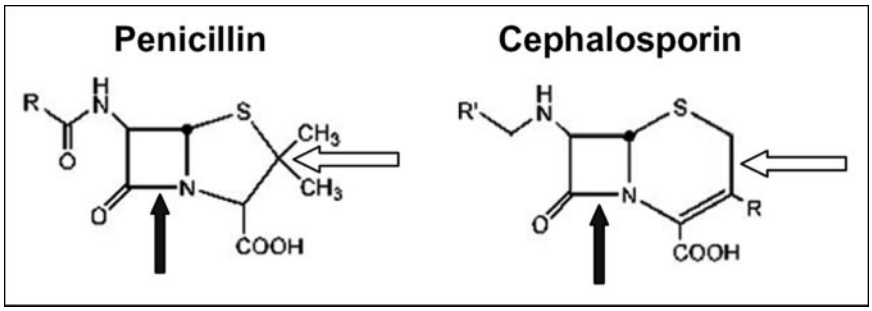

Figure. Cephalosporin versus penicillin ring structures. The solid arrows indicate the core four-member beta-lactam ring within both penicillins and cephalosporins. Open arrows indicate the five- and six-member side rings for penicillins and cephalosporins, respectively. R indicates additional side chain sites where substitutions of various chemical groups produce different antimicrobial spectra, pharmacokinetics, or stability to beta-lactamases.

Another common resistance mechanism is the production of beta-lactamase, a bacterial enzyme that breaks open the core beta-lactam ring, leaving the antibiotic unable to bind PBP. An example from ntHi is a TEM-1 beta-lactamase, which inactivates cefaclor and cefprozil. Structural changes engineered into cephalosporin rings or side chains protect vulnerable ring sites from beta-lactamase. Thus, cefuroxime or ceftriaxone are stable to many beta-lactamases, including the ntHi TEM-1. Extended spectrum beta-lactamases (ESBLs) and Amp-C beta-lactamases, seen mostly in nosocomial gram-negative pathogens, inactivate all currently available cephalosporins.

Overview of Cephalosporins

Cephalosporins are classified by "generation" (Table 1). In general, lower-generation cephalosporins have more gram-positive activity and higher-generation cephalosporins more gram-negative activity. The fourth-generation drug cefepime is the exception, with gram-positive activity equivalent to first-generation and gram-negative activity equivalent to third-generation cephalosporins. However, individual cephalosporins in the higher generations have differentiating properties that may mark them for specific indications (Tables 2 and 3). Dose and dosing intervals vary with each drug (Table 4). The penetration of cephalosporins into cerebrospinal fluid (CSF) can be affected by central nervous system inflammation (Table 5).

The adverse event profile of cephalosporins is not dissimilar to that of penicillins. Nonpruritic rashes occur in 1% to 2.8% of patients and are not a contraindication to future use. True anaphylactic reactions related to cephalosporins are rare, with an estimated risk of 0.0001% to 0.1%. Cephalosporin-induced anaphylaxis is no greater among penicillin-allergic patients according to newer evidence that established that previous rates of cross-reactivity between penicillins and cephalosporins were overestimated. Cephalosporins that share chemical side chains similar to those of penicillin or amoxicillin are more likely to cross-react, but even this risk is low (0.5%). These agents include mostly first-generation drugs (cephalexin, cefadroxil, and cefazolin). No increased risk exists for other second-, third-, or fourth-generation cephalosporins. On this basis, the American Academy of Pediatrics has endorsed oral cephalosporin use in patients who have reported penicillin allergies in their evidence-based guidelines for treatment of otitis media and sinusitis.

First-generation Cephalosporins

Spectra and Pharmacokinetics

First-generation cephalosporins are most active against gram-positive cocci, including MSSA and streptococci. They have no activity against enterococci, MRSA, or *Listeria*. All have nearly identical spectra. Oral first-generation cephalosporins, including cephalexin, cefadroxil, and cephradine, are well absorbed. Therapeutic concentrations occur in most tissues, including pleura, synovial fluids, and bone, but not middle ear fluid. Cefadroxil has a half-life of more than 1 hour and is administered every 12 hours versus every 6 to 8 hours for cephalexin. First-generation cephalosporins should not be used if bacterial meningitis is possible, due to poor CSF penetration, with or without inflammation.

Indications

First-generation cephalosporins often are used for MSSA and streptococci but are not first drugs of choice for any pediatric infection (Table 6).

Adverse Effects

Mild gastrointestinal symptoms, such as nausea, vomiting, or diarrhea, occasionally may occur with orally administered first-generation cephalosporins, and pseudomembranous colitis can develop. Mild nephrotoxicity and hepatic enzyme elevation have been reported. Other reactions include thrombocytopenia, leukopenia, eosinophilia, and drug fever.

Table 1. **Classification of Cephalosporins**

Generic Name	Trade Name	Trade Manufacturer*	Route
First-generation			
Cefadroxil	Duricef®	Bristol Myers Squibb, Princeton, NJ	PO
Cephalexin	Keflex®	Advancis Middle Brook, Germantown, MD	PO
Cephradine	Velosef®	Bristol Myers Squibb, Princeton, NJ	PO, IM, IV
Cefazolin	Ancef®	GlaxoSmith Kline, Research Triangle Park, NC	IM, IV
Second-generation			
Cefaclor	Ceclor®	Eli Lilly and Company, Indianapolis, IN	PO
Cefprozil	Cefzil®	Bristol Myers Squibb, Princeton, NJ	PO
Cefuroxime axetil	Ceftin®	GlaxoSmith Kline, Research Triangle Park, NC	PO
Cefuroxime	Zinacef®	GlaxoSmith Kline, Research Triangle Park, NC	IM, IV
Cephamycins			
Cefoxitin	Mefoxin®	Merck and Company, Whitehouse Station, NJ	IM, IV
Third-generation			
†Cefdinir	Omnicef®	Abbott, Abbott Park, IL	PO
Cefixime	Suprax®	Lupin, Baltimore, MD	PO
Cefpodoxime proxetil	Vantin®	Pfizer, New York, NY	PO
Ceftibuten	Cedax®	Shinogi, Florham Park, NJ	PO
Cefotaxime	Claforan®	Hospira, Lake Forest, IL	IM, IV
Ceftazidime	Fortaz®	GlaxoSmith Kline, Research Triangle Park, NC	IM, IV
†Ceftriaxone	Rocephin®	Roche, Nutley, NJ	IM, IV
Fourth-generation			
†Cefepime	Maxipime®	Elan, Gainesville, GA; ER Squibb and Sons, Inc, New Brunswick, NJ	IV

IM=intramuscular, IV=intravenous, PO=oral
*See *Lexi-Comp Online* for generic manufacturers, Lexi-Corp, Inc, Hudson, Ohio.
†Not manufactured as a generic medication at this time.

Second-generation Cephalosporins

Similar to their first-generation counterparts, second-generation cephalosporins rarely are drugs of first choice. Yet, they are used as second-line options for skin, soft-tissue, and respiratory infections, including acute otitis media, pneumonia, and acute bacterial sinusitis.

Spectrum

Because of greater stability against beta-lactamases of gram-negative bacteria, enhanced activity occurs among second-generation cephalosporins against many Enterobacteriaceae, *H influenzae*, and *Moraxella catarrhalis*, but they have less gram-negative activity than do third-generation cephalosporins. Second-generation cephalosporins retain good activity against gram-positive organisms, including some strains of PNSP, but have less *S aureus* activity compared with their first-generation counterparts. Cefoxitin, a cephamycin, is classified with second-generation cephalosporins but demonstrates more anaerobic activity, especially for *Bacteroides fragilis*. Cefoxitin also offers activity against rapidly growing nontuberculous mycobacteria and often is included in multiple-drug combination regimens to treat serious nontuberculous mycobacterial infections. Second-generation cephalosporins have no activity against enterococci, *Listeria*, *Pseudomonas*, MRSA, or *S epidermidis*.

Pharmacokinetics

Compared with cefaclor and cefprozil, which are well absorbed orally, the bioavailabililty of cefuroxime axetil is less than 50% but is enhanced when taken with food. Cefuroxime axetil suspension is less bioavailable than the tablet form, and dosage adjustments are necessary between these two forms. Cefuroxime axetil is hydrolyzed rapidly in the GI tract and in serum to its active parent compound, cefuroxime.

Therapeutic concentrations of second-generation cephalosporins are achieved in most tissues, including pleural and synovial fluids and bone. Of parenteral second-generation cephalosporins, cefuroxime penetrates CSF but is not recommended for treating meningitis due to its potential for delayed CSF sterilization, therapeutic failures, and more frequent hearing loss compared with ceftriaxone. Cefoxitin's anaerobic activity makes it a reasonable choice for prophylaxis of intra-abdominal or intrapelvic surgery.

Table 2. **Antimicrobial Spectra of Selected Cephalosporins Against Gram-positive Cocci Outside Cerebrospinal Fluid***

Drug	MSSA	MRSA	*Staphylococcus epidermidis*	*Streptococcus pneumoniae* (penicillin MIC <0.1 mg/L)	*Streptococcus pneumoniae* (penicillin MIC 0.1 to 1 mg/L)	*Streptococcus pneumoniae* (penicillin MIC >1.0 mg/L)	*Streptococcus agalactiae*
Cefaclor	4	0	0	4	1	0	2
Cefadroxil	4	0	1	4	1	0	2
Cephalexin	4	0	1	4	1	0	2
Cephradine	4	0	1	4	1	0	2
Cefprozil	4	0	1	4	2	0	2
Cefuroxime axetil	4	0	1	4	2	0	2
Cefpodoxime proxetil	4	0	0	4	2	0	2
Cefdinir	4	0	0	4	2	0	2
Cefixime	0	0	0	4	0	0	1
Ceftibuten	0	0	0	3	0	0	1
Cefazolin	4	0	1	4	1	0	2
Cefoxitin	4	0	0	4	1	0	2
Cefuroxime IV	4	0	1	4	3	1	3
Ceftriaxone	3 to 4	0	0	4	4	4	4
Cefotaxime	4	0	1	4	4	4	4
Ceftazidime	2	0	0	4	0	0	2
Cefepime	4	0	2	4	4	4	4

Interpretation: 4=>90% susceptible; 3=75% to 90% susceptible; 2=50% to 74% susceptible, 1=<50% susceptible; 0=poor to no activity
*All *S pyogenes* are susceptible to all cephalosporins.
IV=intravenous, MIC=minimum inhibitory concentration, MRSA=methicillin-resistant *Staphylococcus aureus*, MSSA=methicillin-susceptible *Staphylococcus aureus*

Indications

Acute otitis media and acute bacterial sinusitis are the most common pediatric indications for cephalosporin use. These agents are suggested by American Academy of Pediatrics guidelines (Table 7) for treating penicillin-allergic patients and for those who fail first-line therapy. Among the second-generation cephalosporins, cefuroxime and cefprozil have moderate activity against PNSP (active up to a penicillin minimum inhibitory concentration of 0.45 mg/L). Cefaclor has no PNSP activity. Recently increasing cefoxitin resistance of *Bacteroides* sp may limit use to alternative treatment for intra-abdominal or intrapelvic infections.

Adverse Effects

Serum sickness-like reactions, with rash, fever, and arthritis, are associated most commonly with cefaclor and cefprozil. Pseudomembranous colitis from *Clostridium difficile* appears more commonly with cefoxitin.

Intravenous Third-generation Cephalosporins

Cefotaxime and ceftriaxone have subtle differences in their antibiotic spectra, but notable differences in pharmacokinetics (long half-life plus mixed renal/biliary excretion for ceftriaxone versus shorter half-life plus nearly pure renal excretion for cefotaxime). Ceftazidime, the first "antipseudomonal" cephalosporin, has pharmacokinetics similar to those of cefotaxime. See Table 8 for parenteral drug indications.

No third-generation cephalosporin is a first-line agent for MSSA, and none is adequate as monotherapy for PNSP CSF infection. In 2003, pneumococcus breakpoints for ceftriaxone and cefotaxime were modified, differentiating resistant pneumococcus in sites other than CSF from those in CSF. For CSF infection sites, the susceptible breakpoint is 0.5 mcg/mL, the intermediate breakpoint is 1.0 mcg/mL, and the resistant breakpoint is 2.0 mcg/mL. Outside the CSF, the respective breakpoints are 1.0, 2.0, and 4.0 mcg/mL.

Ceftriaxone

SPECTRUM. Ceftriaxone is bactericidal for gram-negative pathogens, specifically all *H influenzae* (including beta-lactamase-producing strains); *M catarrhalis;* most *E coli*, *Klebsiella pneumoniae*, *Morganella*, *Neisseria, Proteus*, and *Enterobacter* sp; *Serratia marcescens;*

Table 3. **Antimicrobial Spectra of Selected Cephalosporins Against *Haemophilus, Bacteroides, Pseudomonas aeruginosa*, and Enteric Gram-negative Bacilli**

Drug	*Escherichia coli*	Beta-lactamase (-) *Haemophilus influenzae*	Beta-lactamase (+) *Haemophilus influenzae*	*Proteus vulgaris*	*Serratia* sp	*Enterobacter cloacae*	*Pseudomonas aeruginosa*	*Bacteroides fragilis*
Cefaclor	2	3	0	0	0	0	0	0
Cephalexin	3	2	1	0	0	0	0	0
Cefadroxil	2	2	1	0	0	0	0	0
Cephradine	2	2	1	0	0	0	0	0
Cefprozil	2	3	0	0	0	0	0	0
Cefuroxime axetil	2	4	3	0	0	2	0	0
Cefpodoxime proxetil	2	4	3	0	1	2	0	0
Cefdinir	3	3	3	1	1	2	0	0
Cefixime	4	4	4	3	2	3	0	0
Ceftibuten	4	4	4	3	3	3	0	0
Cefazolin	3	2	2	0	0	0	0	0
Cefoxitin	3	3	2	2	0	0	0	3
Cefuroxime IV	3	4	4	0	0	2	0	0
Cefotaxime	4	4	4	3	4	3	0	1
Ceftriaxone	4	4	4	3	4	3	0	1
Ceftazidime	4	4	4	4	4	3	4	0
Cefepime	4	4	4	4	4	4	4	1

Interpretation: 4=>90% susceptible; 3=75 to 90% susceptible; 2=50 to 74% susceptible, 1=<50% susceptible; 0=poor to no activity
IV=intravenous

and *Acinetobacter* sp (not multidrug-resistant strains from Iraq). It also is active against all group A and group B streptococci and nearly all *S pneumoniae*, including PNSP outside the CSF. The apparent in vitro activity against MSSA is not clinically reliable, except in low-inoculum infection. *S epidermidis*, other coagulase-negative staphylococci, MRSA, and all enterococci are considered resistant. Ceftriaxone has minimal anaerobic activity.

PHARMACOKINETICS. Unlike other cephalosporins, ceftriaxone is highly protein-bound. This effect prolongs its half-life (5.5 to 8.7 hours beyond the neonatal period and 9.0 to 15.5 hours in the neonate), allowing once- or twice-daily dosing. Because ceftriaxone actively displaces bilirubin from albumin, most clinicians avoid its use in neonates. It penetrates bone, joint, muscle, skin, and middle ear, with approximately 10% reaching the CSF through inflamed meninges. Up to 70% is excreted unchanged in urine, with the rest excreted unchanged into bile (stool has very high concentrations).

DOSING. Pediatric doses for treating meningitis are 100 mg/kg per day once daily or divided into two doses every 12 hours, with a 4-g maximum daily dose. Outside the meninges, the dose is 50 to 75 mg/kg once daily. For intramuscular use, dilution in 1% lidocaine (250 to 450 mg/mL) reduces injection pain.

ADVERSE EFFECTS. Adverse effects occurring in fewer than 5% of patients include thrombocytosis, transient liver function test elevations, allergic reactions, and leukopenia. There is an increasing risk of neutropenia or thrombocytopenia beginning in the second week of use, which can be as high as 15% after 2 weeks of use. *Candida* superinfection (mostly diaper rash) and diarrhea occur in 10% to 15% of patients, with eosinophilia in 6%. Ceftriaxone may cause *C difficile* colitis. Biliary sludging and pseudolithiasis appear more commonly in young patients, are dose-dependent, and occur primarily with fluid restriction or biliary stasis. An important but rare adverse effect is immune-mediated, potentially fatal hemolysis, which can occur despite prior safe treatment with ceftriaxone. Its sudden onset (less than 45 minutes after the dose) can progress to cardiac arrest in less than 2 hours. Anti-ceftriaxone immunoglobulin M immune complexes bind red blood cells, activate complement,

Table 4. **Recommended Pediatric Dosages of Cephalosporins**

Drug	Total Daily Dose (mg/kg)	Dosing Interval (h)
Oral		
Cefaclor	20 to 40	8 to 12
Cefadroxil	30	12
Cephalexin	25 to 100	6 to 8
Cefprozil	15 to 30	12
Cephradine	25 to 100	6 to 12
Cefuroxime, PO	20 to 30	12
Cefdinir	14	12 to 24*
Cefpodoxime	10	12
Cefixime	8	12 to 24
Ceftibuten	9	24
Parenteral		
Cefazolin	50 to 100	8
Cefoxitin	80 to 160	4 to 6
Cefuroxime, IV	100 to 240†	6 to 8
Ceftriaxone	50 to 100	12 to 24
Cefotaxime	100 to 300†	6 to 8
Ceftazidime	100 to 150	8
Cefepime	150	8 to 12§

IV=intravenous, PO=oral
*Recently, doses of 30 mg/kg per day were defined as being most effective pharmacodynamically(see Bowlware et al in Suggested Reading), but this dosage is not approved by the United States Food and Drug Administration.
†Rarely is a dose of <150 mg/kg per day useful.
§Recent publication questions outcome of cefepime versus comparator drugs.

and cause hemolysis. Nearly all occurrences have been reported in immunocompromised patients.

Cefotaxime

Cefotaxime and ceftriaxone are used in similar clinical scenarios because of similar spectra. Advantages of cefotaxime over ceftriaxone include no bilirubin displacement from albumin (preferred neonatal drug), better in vivo activity against MSSA, and no sludging in the gallbladder.

PHARMACOKINETICS. The half-life (3.4 to 6.4 hours in neonates versus 1.1 to 1.8 hours in older patients) requires dosing every 6 to 8 hours beyond the neonatal period. Excretion is predominantly renal (up to 36% excreted unchanged, 15% to 25% as an active metabolite, and 20% to 25% as inactive metabolites).

ADVERSE EFFECTS. Adverse effects are infrequent (<5%) and include allergy, diarrhea, and rash. *Candida* superinfection may be seen in approximately 7% of patients.

Ceftazidime

Ceftazidime has activity against most community-acquired gram-negative pathogens and *P aeruginosa*. It has been effective in treating *P aeruginosa* meningitis. However, ceftazidime has poor pneumococcal and MSSA activity and no activity against MRSA, methicillin-resistant *S epidermidis*, or enterococci. Further, the drug can induce the production of high-level cephalosporinases among mostly nosocomial gram-negative pathogens, including *Serratia*, *Pseudomonas*, *Acinetobacter*, *Citrobacter*, and *Enterobacter* (SPACE) species, thus creating resistance. Its use has been declining due to its greater potential to induce resistance than cefepime.

PHARMACOKINETICS. The 1.4- to 2.1-hour half-life allows dosing every 8 hours. Almost all of the drug is excreted renally.

ADVERSE EFFECTS. Adverse effects are nearly identical to those of cefotaxime.

Oral Third-generation Cephalosporins

Cefdinir and cefpodoxime have balanced gram-positive and gram-negative spectra. Cefdinir is very palatable; cefpodoxime is bitter. Both are active against MSSA and some PNSP, but the limit of the PNSP activity is a penicillin minimum inhibitory concentration greater than 0.45 mg/L.

Table 5. **Cephalosporin Penetration of the Cerebrospinal Fluid**

	Mean With Inflammation	Mean Without Inflammation (Intact Blood-brain Barrier)
First generation	None	None
Second generation	8% of peak serum concentrations, but widely variable	<3%
Third generation	9% to 12% of peak serum concentrations, minimal variation	<3%
Fourth generation	9% of peak serum concentrations, modest variability	<3%

Table 6. Pediatric Uses/Indications for First-generation Cephalosporins

Skin/soft-tissue Infections: Cellulitis, Abscess, Wound Infections

- Pathogens: *Staphylococcus aureus, Streptococcus pyogenes*
- Cefazolin commonly used if patient hospitalized; cephalexin if ambulatory or for transition to oral therapy
- Cephalosporins have no activity against MRSA

Pharyngitis

- Pathogens: *S pyogenes* highly susceptible to all cephalosporins, but first-generation preferred as alternative therapy due to narrow spectrum
- Once-daily cefadroxil indication may benefit compliance, but use is limited by expense
- Penicillin or amoxicillin remains drug of choice

Acute Osteomyelitis

- Pathogens: *S aureus, S pyogenes, S pneumoniae* (if penicillin-susceptible)
- Cefazolin initially followed by oral cephalexin is alternative to penicillinase-resistant penicillins
- Some experts recommend cefazolin + clindamycin combination where MRSA prevalence is high

Surgical Prophylaxis

- Pathogens: *S aureus*
- Cefazolin used for clean and clean-contaminated procedures
- Cefuroxime, a second-generation cephalosporin, also is used commonly

Uncomplicated Urinary Tract Infection

- Pathogens: *Escherichia coli, Klebsiella*, and *Proteus* (indole-negative) sp
- Cephalexin useful in ambulatory patients if susceptibility known

MRSA=methicillin-resistant *Staphylococcus aureus*.

Cefixime and ceftibuten are similar in spectra, dose, and dosing schedules, but cefixime has slightly more gram-positive activity. Ceftibuten is less active against *M catarrhalis*. Both have excellent activity against coliform bacteria and are more stable to beta-lactamases than other oral cephalosporins.

Indications

Cefpodoxime and cefdinir are used primarily for treating acute otitis media, acute bacterial sinusitis, and as once- or twice-daily regimens for penicillin-allergic patients who have group A streptococcal pharyngitis. Cefdinir appears more effective when used in twice-daily regimens and is projected to need doses more than twice those approved by the United States Food and Drug Administration to treat some ntHi and intermediate PNSP effectively.

Ceftibuten and cefixime are excellent for treating urinary tract infections or respiratory infections due to beta-lactamase-producing ntHi. Each can be used once daily to treat group A streptococcal pharyngitis. Cefixime is as effective in treating nonbacteremic pyelonephritis as parenteral ceftriaxone and is recommended for gonorrhea by the Centers for Disease Control and Prevention.

Adverse Effects

Cefdinir can produce a "bloodlike" appearance in stools when infants consume iron-containing foods. Both cefdinir and cefpodoxime are associated with about an 8% diarrhea rate, with cefpodoxime associated with higher emesis rates. Adverse effects of cefixime and ceftibuten include diarrhea in up to 10% and diaper rash in 7% of patients.

Cefepime: The Fourth-generation Cephalosporin

Cefepime is approved by the United States Food and Drug Administration for patients older than 2 months of age.

Spectrum

Its in vitro activity resembles that of cefazolin combined with ceftazidime, with effectiveness against MSSA, *S pyogenes, S pneumoniae* (PNSP outside CSF), *E coli*, *H influenzae*, *M catarrhalis*, *N gonorrhoeae*, *P aeruginosa*, *Morganella morganii*, *Proteus mirabilis, Citrobacter*, *Enterobacter*, *Klebsiella*, *Providencia*, and *Serratia* sp. It has no activity against MRSA, enterococci, ESBL- or Amp-C

Table 7. Pediatric Uses/Indications for Second-generation Cephalosporins

Acute Otitis Media and Acute Bacterial Sinusitis, Uncomplicated

- Pathogens: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*
- Cefuroxime axetil recommended as alternative but less active than amoxicillin against PNSP
- Amoxicillin remains drug of choice

Pneumonia

- Pathogens: *S pneumoniae* (penicillin-susceptible and -nonsusceptible), *H influenzae*, *M catarrhalis*
- Cefprozil and cefuroxime axetil have moderate activity against PNSP

Bone/Joint Infections Not Due to Methicillin-resistant *S aureus*: Oral Stepdown Therapy From Prior Intravenous Therapy

- Pathogens: *S aureus*, *S pyogenes*, *S pneumoniae*
- Cefprozil and cefuroxime axetil are alternatives to penicillinase-resistant penicillins and first-generation cephalosporins

Surgical Prophylaxis of Gastrointestinal and Gynecologic Procedures

- Pathogens: *Escherichia coli*, *Bacteroides fragilis*, and other anaerobes
- Cefoxitin is used commonly as a prophylactic agent

Pelvic Inflammatory Disease

- Pathogens: *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *B fragilis*, and other anaerobes
- Cefoxitin, combined with oral doxycycline, is recommended by the Centers for Disease Control and Prevention in hospitalized patients

PNSP=penicillin-nonsusceptible *Streptococcus pneumoniae*

beta-lactamase-producing gram-negative organisms, or Iraqi-derived multidrug-resistant *Acinetobacter* sp.

Indications

The clinical efficacy and safety of cefepime appear similar to those of ceftazidime (Table 8), although a recent meta-analysis raised concerns about safety in elderly people.

Pharmacokinetics

Cefepime is 85% excreted unchanged in urine. Its half-life in children and adolescents is 1.7 to 2.3 hours.

Adverse Effects

Clinical adverse effects are similar to those of cefepime and ceftazidime (9% versus 7%). Adverse effects occurring in fewer than 5% of treated patients are local reaction, phlebitis, rash, diarrhea, nausea, vomiting, pruritus, positive Coombs test, and low serum phosphorus concentrations. In addition, elevated liver function, blood urea nitrogen, or partial thromboplastin and prothrombin times are seen. Similar to any parenteral beta-lactam drug, transient neutropenia or thrombocytopenia may occur starting in the second week of use.

Summary

Cephalosporins are a diverse, extremely useful group of beta-lactam antibiotics employing a mechanism of action that requires bacterial replication for efficacy. The primary mechanisms by which bacteria develop resistance to cephalosporins include mutations of the antibiotic target (PBPs) or inactivation of the drug by beta-lactamases. The antibiotic spectra of cephalosporins, which are divided into first through fourth generations, can be grouped roughly by generation, with increasing gram-negative activity in each higher generation. In contrast, gram-positive activity decreases with increasing generation except for the first- and fourth-generation drugs, which have similar gram-positive activity.

Rather than learn all cephalosporins, it is reasonable for the clinician to be familiar with selected cephalosporins among the parenteral and oral formulations. Useful specifics facts are: ceftriaxone has pharmacokinetics that allow the least frequent dosing, cefepime and ceftazidime have anti-*Pseudomonas* activity, and cefoxitin has the most anaerobic activity. Enterococci and MRSA are resistant to all currently approved cephalosporins. No oral cephalosporin is effective against pneumococci that are highly resistant to penicillin.

Table 8. Pediatric Uses/Indications for Parenteral Third- or Fourth-generation Cephalosporins

Fever Without a Focus in Young Children

- Pathogens: *Streptococcus pneumoniae*; less commonly, *Salmonella* or meningococcus
- Ceftriaxone (50 mg/kg IM or IV) commonly used in selected febrile children without a clinical focus after cultures obtained

Complicated Pneumonia or Sinusitis (eg, pleural empyema or orbital cellulitis)

- Either cefotaxime or ceftriaxone plus either clindamycin or vancomycin
- Vancomycin with severe clinical presentation
- Pathogens usually respiratory flora
- Pneumococci, MSSA, community acquired-MRSA, and/or nontypeable *Haemophilus influenzae*
- Even penicillin-highly nonsusceptible pneumococci can be treated effectively with high doses of ceftriaxone or cefotaxime outside CNS

Meningitis*

- Newborn: Cefotaxime plus ampicillin
  - –Potential pathogens: Coliform or group B *Streptococcus*, *Listeria*, or enterococci
  - –*Listeria* and enterococci are inherently cephalosporin-resistant, so combine with ampicillin until pathogen identified
- Non-newborn: Vancomycin plus either cefotaxime or ceftriaxone
  - –Pathogens: Meningococcus or penicillin-susceptible pneumococci
  - –Penicillin-nonsusceptible pneumococcus requires empiric combination with vancomycin until pathogen identified

Recalcitrant Acute Otitis Media

- Ceftriaxone 50 mg/kg per dose in one to three IM doses over 1 to 5 days

***Neisseria gonorrhea* Infections**

- Ceftriaxone 125 mg IM once as a single dose OR
- Cefixime 400 mg PO in a single dose

Lyme Disease Central Nervous System or Joint Disease

Infections With Potential *Pseudomonas* Pathogen

- Cefepime or ceftazidime preferred due to less renal and ototoxicity plus absence of need to monitor drug concentrations
- Osteochondritis of foot (puncture): Monotherapy adequate
- Fever with neutropenia: Additional gram-positive coverage needed with ceftazidime (eg, vancomycin or oxacillin)
- Cystic fibrosis exacerbation: Various drugs added
- *Pseudomonas meningitis*, usually with aminoglycoside

CNS=central nervous system, IM=intramuscular, IV=intravenous, MRSA=methicillin-resistant *Staphylococcus aureus*, MSSA=methicillin-susceptible *Staphylococcus aureus*, PO=oral
*Meningitis doses higher than standard doses; see dosing table.

Adverse effects generally are those seen with penicillin-class drugs (diarrhea, rashes, allergic reactions), with the exception of biliary sludging, bilirubin displacement from albumin, and rarely, fatal hemolysis resulting from ceftriaxone therapy.

Suggested Reading

Bowlware KL, McCracken GH Jr, Lozano-Hernandez J, Ghaffar F. Cefdinir pharmacokinetics and tolerability in children receiving 25 mg/kg once daily. *Pediatr Infect Dis J*. 2006; 25:208–210

Gaillard JL, Abadie G, Cheron F, et al. Concentrations of ceftriaxone in cerebrospinal fluid of children with meningitis receiving dexamethasone therapy. *Antimicrob Agent Chemother*. 1994; 38:1209–1210

Pichichero M. A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. *Pediatrics*. 2005; 115:1048–1057

Prober CG. Cephalosporins: an update. *Pediatr Rev*. 1998;19: 118–127

Yahav D, Paul M, Fraser A, Sarid N, Leibovici L. Efficacy and safety of cefepime: a systematic review and meta-analysis. *Lancet Infect Dis*. 2007;7:338–348

PIR Quiz

Quiz also available online at www.pedsinreview.org.

6. You diagnose acute otitis media in a 2-year-old boy who has penicillin and sulfa allergy and attends child care in your community where carriage of penicillin-nonsusceptible *Streptococcus pneumoniae* is common. You are aware that the risk of cephalosporin-induced anaphylaxis is negligible. Among the following, the *best* choice of oral cephalosporin for treatment in this case is:

   A. Cefaclor.
   B. Cefadroxil.
   C. Cefprozil.
   D. Cefuroxime axetil.
   E. Cephalexin.

7. You identify a 3-cm nonfluctuant abscess on the shoulder of a previously well, nontoxic 3-year-old boy who has an allergy to both penicillin and sulfa. Because the incidence of MRSA is less than 5% in your community, the proper cephalosporin combined with warm compresses is likely to provide effective treatment. Under these circumstances, the *best* choice is:

   A. Cefaclor.
   B. Cefadroxil.
   C. Cefixime.
   D. Ceftriaxone.
   E. Cefuroxime axetil.

8. You diagnose bacterial meningitis in a previously well but unimmunized 5-month-old infant. Gram-positive cocci are noted on the Gram stain. The *best* choice for initial therapy is a combination of parenteral vancomycin and parenteral:

   A. Cefepime.
   B. Cefoxitin.
   C. Ceftazidime.
   D. Ceftriaxone.
   E. Cefuroxime axetil.

9. Ten days ago, a 4-year-old boy stepped on a nail that penetrated his tennis shoe and entered his heel. Over the last 2 days, he has developed a low-grade fever, warmth, swelling, and exquisite tenderness of his left heel. You are concerned about pseudomonal osteochondritis. In addition to surgical debridement, the *most* appropriate antibiotic among the following for monotherapy is:

   A. Cefdinir.
   B. Cefepime.
   C. Ceftriaxone.
   D. Cefuroxime axetil.
   E. Cephalexin.