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Update on Cephalosporins in Pediatrics

Updated and Revised June 2002

The cephalosporins have certain advantages that have made them a popular choice among physicians in the United States. These include a broad range of antimicrobial activity, concentration-independent bactericidal activity, and excellent tolerance in children, with almost no dose-related toxicity. These drugs also can be used safely in most infants and children with hepatic or renal failure. Serious adverse reactions are rare and consist primarily of hypersensitivity with urticaria, nonspecific rash and pruritis. The frequency of these cutaneous reactions is 0.9% to 3.2% (1, 2). Serious immediate hypersensitivity reactions, such as anaphylaxis and bronchospasm, are rare. Cross-reactivity in penicillin-allergic patients is reported to be 5-15%, but this figure is probably inflated (2). Still, a history of a serious immediate hypersensitivity reaction to penicillin is a contraindication for use of a cephalosporin.

Following the introduction of the first cephalosporin antibiotic in 1964, over 20 members of this antibiotic class have been released for use in pediatric patients. These agents have indications for several common infections, thus it is not surprising that they have emerged as the most commonly prescribed antibiotics in the United States (1). Due to the variety of formulations currently available, the selection of a particular cephalosporin may be a challenge for the practicing physician. This update will attempt to provide the reader with a review of the mechanism of action, spectrum of antimicrobial activity, and indications for use of the cephalosporins so that these agents may be used judiciously in pediatric patients. The relatively new agents, cefdinir and cefipime, will be highlighted.

MECHANISM OF ACTION AND RESISTANCE

The cephalosporins are derived from the parent compound cephalosporin C, a natural antibiotic produced by a strain of the mold *Cephalosporium acremonium* first isolated in 1948. Cephalosporins resemble penicillins in that they have a β -lactam structure, but the five-member thiazolidine ring characteristic of the penicillins is replaced by a six-member dihydrothiazine ring (Figure 1). This ring provides the molecule with the ability to resist bacterial enzymes; the antibacterial activity comes from the β -lactam ring. Two side chains in position 3 and 7 affect the pharmacokinetic and antibacterial spectrum of the cephalosporins.

The cephalosporins, like all β -lactams, act by inhibiting the enzymes that create the cross-linkage of the peptidoglycan polymer leading to interference with the cell wall structure. These enzymes are located beneath the cell wall and are known as "penicillin-binding proteins" (PBP). β -lactam antibiotics have different binding affinities to the various PBP. The effect of an antibiotic on a specific

FIGURE 1

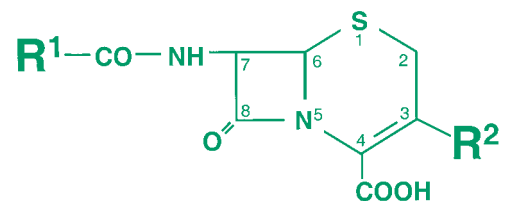


Figure 1: The basic cephalosporin molecule. Modifications at positions R1, R2, C7 and position 1 of the dihydrothiazine ring dictate pharmacokinetics and antibacterial properties of these compounds.

microorganism depends on which PBP is bound and inactivated.

Bacterial resistance to cephalosporins is achieved by distinct mechanisms. These include the inability of the drug to reach its site of action (decreased permeability through the outer membrane of gram-negative organisms), alterations in the PBP's (low affinity of binding as in cephalosporin-resistant pneumococci), or by β -lactamases that hydrolyze the β -lactam ring (the most common mechanism of resistance). Cephalosporins are variably susceptible to β -lactamases; a good example is the relative resistance of second and third-generation agents to hydrolysis by β -lactamases produced by gram-negative organisms compared to the first-generation agents. However, the exception is the extended-spectrum β -lactamases (ESBLs) that hydrolyze the oxyimino side chain of cefotaxime, ceftriaxone, ceftazidime and cefepime. This plasmid-mediated trait is most often associated with *Klebsiella pneumoniae*, but it can transfer to other genera, including *Escherichia coli* and other enteric bacilli.

SPECTRUM OF ACTIVITY

When considering use of a cephalosporin, physicians must remember that many of these agents are not reliably active against penicillin nonsusceptible pneumococci (minimal inhibitory concentration [MIC] $\geq 0.1 \mu\text{g/ml}$). Another limitation of this class of antibiotics, is that none of the currently available cephalosporins has good activity against the following organisms: methicillin-resistant *Staphylococcus aureus* (MRSA), *S. epidermidis*, *Enterococcus*, *Legionella*, *Mycoplasma*, *Campylobacter*, *Listeria*, and *Clostridium difficile*.

CLASSIFICATION

The cephalosporins are classified into generations (Table 1) based on general features of their antimicrobial activity. The first-generation agents have good activity against gram-positive bacteria (methicillin-susceptible *S. aureus* (MSSA), group A streptococci, penicillin-susceptible *Streptococcus pneumoniae*) and relatively modest activity against gram-negative organisms. The second-generation

TABLE 1
Currently Available Cephalosporins for Pediatric Use

Generic Name (Trade Name)	Usual Dose* (mg/kg/day)	Route(s)	No. Doses per Day	Cost†
First generation				
Cephalexin (Keflex®)	25-50	Oral	4	\$†
Cephadrine (Velosef®)	25-50	Oral	4	\$
Cefadroxil (Duricef®)	30	Oral	2	\$\$
Cefazolin (Ancef®)	50-100	IM, IV	3	\$
Cephalothin (Keflin®)	75-125	IM, IV	4	\$
Second generation				
Cefaclor (Ceclor®)	40	Oral	2 or 3	\$
Cefprozil (Cefzil®)	30	Oral	2	\$
Cefuroxime axetil (Ceftin®)	30	Oral	2	\$\$
Loracarbef (Lorabid®)	30	Oral	2	\$\$
Cefuroxime (Zinacef®)	150	IM, IV	3	\$\$
Cefamandole (Mandol®)	100-150	IM, IV	4 to 6	—
Cefoxitin (Mefoxin®)	80-150	IM, IV	3 or 4	\$\$\$
Cefotetan (Cefotan®)**	40-80	IM, IV	2	\$\$
Third generation				
Cefixime (Suprax®)	8	Oral	1	\$\$
Cefpodoxime (Vantin®)	10	Oral	2	\$\$
Ceftibuten (Cedax®)	9	Oral	1	\$\$
Cefdinir (Omnicef®)	14	Oral	1 or 2	\$\$
Cefditoren (Spectracef®)	9	Oral	2	\$\$
Cefotaxime (Claforan®)	100-300	IM, IV	3	\$\$
Ceftriaxone (Rocephin®)	50-100	IM, IV	1 or 2	\$\$
Ceftazidime (Fortaz®)	90-150	IM, IV	3	\$\$\$
Cefoperazone (Cefobid®)**	100-150	IM, IV	2 or 3	\$\$\$
Ceftizoxime (Cefizox®)	100-200	IM, IV	3 or 4	\$\$
Fourth generation				
Cefepime (Maxipime®)	100-150	IM, IV	2 or 3	\$\$

* Assumes normal renal function. Consult manufacturer's recommendation for dosage adjustment in renal insufficiency. In general, when a dosing range is given, the lower dosage is for mild-to-moderate infections.

† Assumes generic, if available.

\$ = modest; \$\$ = moderate; \$\$\$ = expensive.

cephalosporins have increased activity against certain gram-negative pathogens (including *Haemophilus influenzae*, *Neisseria meningitidis* and *Moraxella catarrhalis*) and, for cefoxitin and cefotetan *only*, against bowel anaerobes. The third-generation cephalosporins are somewhat less active against gram-positive cocci, but much more active against enteric gram-negative organisms. The new fourth-generation agents have an extended spectrum of activity against both gram-positive (including MSSA) and gram-negative organisms (including *Pseudomonas*).

FIRST GENERATION CEPHALOSPORINS

The first generation cephalosporins for oral use include cephalexin, cefadroxil and cephadrine. These agents have a similar antibacterial spectrum. **Cephalexin** (Keflex®) and **cephadrine** (Velocef®) are well absorbed but their short half-life requires QID dosing. **Cefadroxil** (Duricef®, Ultracef®) has a longer half-life that allows for BID administration. The first generation oral cephalosporins are approved for use in the treatment of skin and soft tissue infections and streptococcal pharyngitis. The recent emergence of community-acquired methicillin-resistant strains of *S. aureus* (MRSA) in some regions of the United States (primarily as a cause of skin and soft tissue infections) may limit their usefulness as an alternative to penicillins for treatment of skin and soft tissue infections. Because they have some activity against *E. coli*, *K. pneumoniae* and *Proteus mirabilis*, these agents can be used to treat urinary tract infections caused by susceptible strains of these organisms.

The parenteral first-generation cephalosporins are the drugs of choice for perioperative prophylaxis before

orthopedic, vascular, cardiac and neurosurgical procedures (3). **Cefazolin** (Ancef®, Kefzol®) is widely used for this purpose, and also is an alternative to penicillins for treatment of serious soft tissue infections as well as for bone and joint infections caused by group A streptococci or MSSA. The other parenteral agent in this class, **cephalothin** (Keflin®), is seldomly used.

SECOND GENERATION CEPHALOSPORINS

The oral second-generation cephalosporins have increased activity against gram-negative bacteria, including *H. influenzae*, *N. meningitidis* and *M. catarrhalis*. Thus they have been widely used for the treatment of upper and lower respiratory tract infections, acute otitis media (AOM) and sinusitis. However, the only reliably effective second generation agent for AOM caused by penicillin nonsusceptible pneumococci or β -lactamase producing *H. influenzae* is cefuroxime axetil (Figure 2). As with the first-generation agents, the spectrum of activity also includes *E. coli*, *K. pneumoniae* and *P. mirabilis*, making them potential alternatives in the treatment of urinary tract infections.

Cefaclor (Ceclor®) has a spectrum of activity similar to other second-generation agents, except for its somewhat limited activity against *S. aureus* (4) and poor activity against penicillin-nonsusceptible pneumococci. Cefaclor has been associated with an unusual serum-sickness like reaction that appears to be due to an inherited defect in the handling of metabolic products of cefaclor. This adverse effect, the requirement for TID dosing and the limited spectrum of activity make cefaclor a poor choice for the treatment of most pediatric infections.

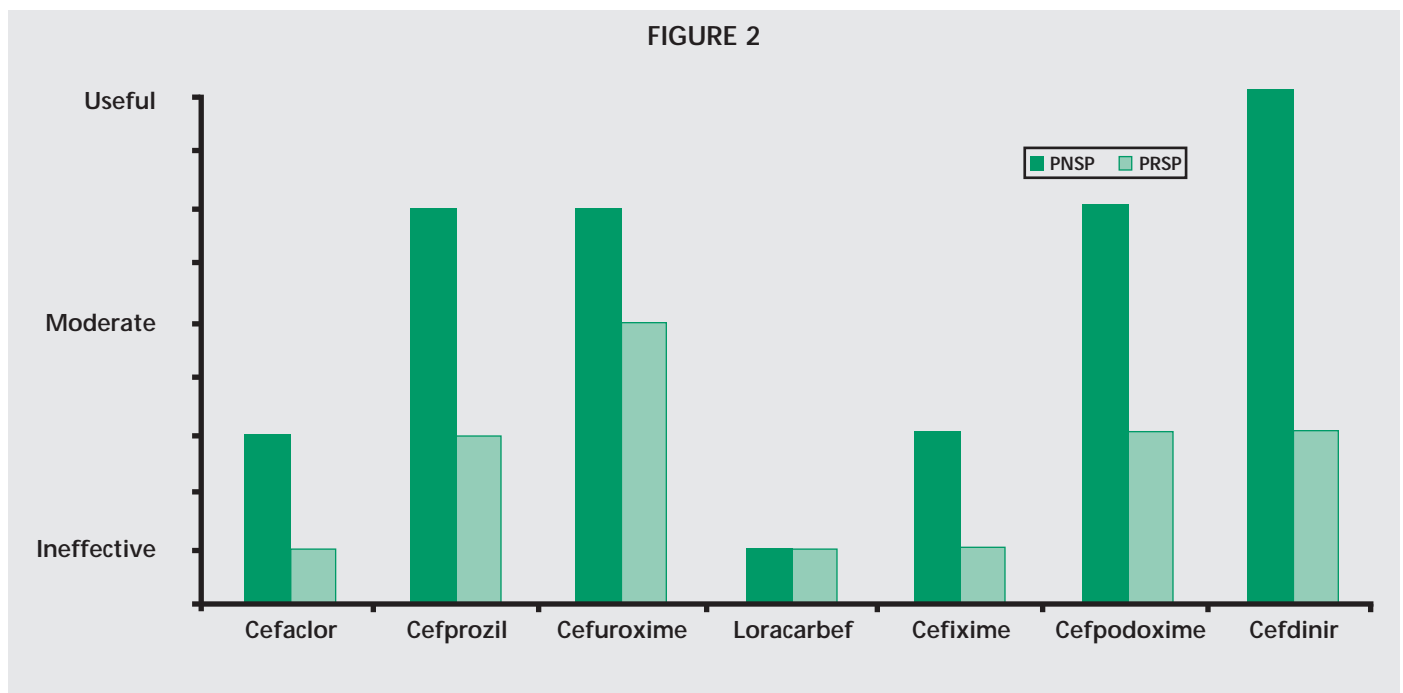


Figure 2: Relative activity of oral cephalosporins for AOM caused by penicillin-nonsusceptible (PNSP) and penicillin-resistant (PRSP) strains of *S. pneumoniae* based on MIC₉₀ data from several published studies.

Cefprozil (Cefzil®) has a similar spectrum to that of the other second-generation cephalosporins, with the convenience of BID dosing. Its activity against β -lactamase producing strains of *H. influenzae* is not ideal, but cefprozil does have moderate activity against many penicillin nonsusceptible strains of *S. pneumoniae*.

Cefuroxime axetil (Ceftin®) is available in a pediatric suspension with a BID dosing schedule. This compound is an ester prodrug to facilitate its absorption, but this characteristic causes an unpleasant metallic aftertaste. The antimicrobial activity is identical to the parenteral cefuroxime formulation, thus it is quite active against most penicillin nonsusceptible pneumococci as well as β -lactamase producing *H. influenzae*.

Loracarbef (Lorabid®), although chemically a carbacephem, has a spectrum of activity similar to that of the second-generation cephalosporins, but it is not reliably active against penicillin-nonsusceptible pneumococci. Structurally it is identical to cefaclor except for a sulfur atom that has been replaced by a methylene group. The serum sickness-like reaction associated with cefaclor does not appear to be as common for loracarbef.

Of the parenteral second-generation cephalosporins, **cefuroxime** (Zinacef®, Kefurox®) remains a frequent first choice for the treatment of community-acquired pneumonia in children, as its spectrum includes penicillin nonsusceptible pneumococci and MSSA. An alternative regime is cefotaxime or ceftriaxone (plus nafcillin or oxacillin if MSSA is suspected). Because of the need for more frequent dosing, and a tendency to cause bleeding, **cefamandole** (Mandole®) is rarely used in pediatrics (5). **Cefonicid** (Monocid®) is a parenteral second-generation cephalosporin that does not have a pediatric indication.

Although **cefoxitin** (Mefoxin®) and **cefotetan** (Cefotan®) are cephamycins, they usually are included with the parenteral second-generation cephalosporins. Their spectrum of activity includes enteric gram-negative organisms (but not *Pseudomonas*) as well as bowel anaerobes, including *Bacteroides fragilis*. Thus, they are appropriate agents for prophylaxis in colorectal surgery and appendectomy (3), and for the treatment of mixed aerobic-anaerobic infections, such as intra-abdominal abscess and pelvic inflammatory disease. In addition, a unique property of cefoxitin is its activity against several strains of rapid-growing mycobacteria (*Mycobacterium fortuitum*, *M. chelonae* and *M. abscessus*). Whereas cefoxitin has been approved for use in children 3 months of age and older, cefotetan has not.

THIRD GENERATION CEPHALOSPORINS

The currently available oral third generation cephalosporins are cefixime, cefitibuten, cefpodoxime, and cefdinir, are very active against many enteric gram-negative organisms, including β -lactamase producing *H. influenzae* and *M. catarrhalis*, *Salmonella* and *Shigella*,

but they have poor activity against *S. aureus* compared the first-generation agents. Strains of *Enterobacter*, *Pseudomonas* and *Serratia* often are resistant. Cefixime and cefpodoxime are alternatives in the treatment of uncomplicated urethral or cervical infections due to *N. gonorrhoeae*, and are administered as single oral doses.

Cefixime (Suprax®) has poor activity against *S. aureus* and penicillin-nonsusceptible *S. pneumoniae* precluding its use for treatment of AOM or soft tissue infections. It is useful in the treatment of urinary tract infections caused by strains resistant to ampicillin, trimethoprim-sulfamethoxazole and other cephalosporins, and although some physicians select cefixime to treat ambulatory patients with antibiotic-resistant *Shigella* infections, its use for that indication is controversial (5).

Cefpodoxime proxetil (Vantin®), unlike cefixime, is very active against *S. aureus* and some penicillin-nonsusceptible pneumococci, but because it is an ester prodrug, it causes an unpleasant metallic aftertaste.

Cefitibuten (Cedax®) is a once-a-day oral cephalosporin with excellent activity against gram-negative organisms, but not against *S. aureus*, and its use is limited by poor clinical efficacy against pneumococci.

Cefdinir (Omnicef®) is one of the newest members of this group and is the most frequently prescribed cephalosporin in Japan. It has a broad spectrum of antimicrobial activity, including MSSA and *S. pneumoniae*, including many penicillin nonsusceptible strains. Because of its superior palatability to amoxicillin-clavulanate, cefprozil, and cefuroxime, and activity comparable to cefuroxime against penicillin nonsusceptible pneumococci, it quickly has become a frequently prescribed oral cephalosporin for the treatment of AOM that fails to respond to initial amoxicillin therapy (6).

In children cefdinir is absorbed rapidly after oral administration with peak plasma concentrations being achieved in about 2 hours. Food does not alter absorption, but ferrous sulfate in infant formula does. Cefdinir is excreted principally through the kidneys, and according to studies in adults, dosage does not need to be modified until the creatinine clearance is <30 mL/min. Cefdinir is comparable in AOM treatment efficacy to cefprozil when each agent is used for 10 days in children <2 years of age. In AOM studies where cure was defined by tympanocentesis cultures, cefdinir was comparable to cefuroxime axetil. Other pediatric indications include streptococcal pharyngitis (5-day course), skin and soft tissue infections, and uncomplicated urinary tract infection. Adverse effects are much like those of the other oral cephalosporins.

Cefditoren (Spectracef®) is another new third generation cephalosporin that has been widely used in Japan and is now approved for the treatment of bronchitis, pharyngitis, and uncomplicated skin and soft tissue

infections. It is similar to cefdinir in antibacterial activity, being highly active against penicillin susceptible *S. pneumoniae* and MSSA. Like all broad-spectrum oral cephalosporins, cefditoren is active against *H. influenzae*, *M. catarrhalis* and many gram-negative bacilli. It is not active against MRSA, *Pseudomonas aeruginosa*, *Enterococcus* or many anaerobes.

In adults ceditoren is well absorbed from the gastrointestinal tract after oral administration, with peak plasma concentrations in 2 to 3 hours. It is excreted primarily by the kidneys. Its long half-life allows for dosing every 12 hours, and currently it is formulated only as a tablet. It is equivalent to penicillin in efficacy for the treatment of group A streptococcal pharyngitis and to clarithromycin for bronchitis in adults. It offers no advantage over cefdinir, except for slightly less cost, and is not approved for use in children less than 12 years of age.

Cefotaxime (Claforan®) and **ceftriaxone** (Rocephin®) are the most frequently prescribed parenteral third-generation cephalosporins for pediatric patients. Their microbiologic spectrum is very similar, and includes many β -lactamase producing gram-negatives (excluding *Pseudomonas*) and most penicillin nonsusceptible *S. pneumoniae*. Their excellent penetration into the cerebrospinal fluid makes them drugs of choice in the treatment of bacterial meningitis. Due to the dramatic increase in the incidence of penicillin-nonsusceptible pneumococci—some of which have also exhibited decreased susceptibility to third-generation cephalosporins—empiric vancomycin should be added until culture results are available. Other common indications for these cephalosporins include bacteremia, community-acquired pneumonia, mastoiditis, pyelonephritis, gonorrhea and enteric fever. The activity of these two agents against *S. aureus* is poor and they should not be used for serious infections when this pathogen is suspected.

A unique attribute of **ceftazidime** (Ceftaz®, Tazidime®) is its activity against *Pseudomonas aeruginosa*. However, ceftazidime is significantly less active than either cefotaxime or ceftriaxone against penicillin-nonsusceptible pneumococci, limiting its use for treatment of nosocomial pneumonia unless combined with another agent. **Cefoperazone** (Cefobid®) also has some activity against *P. aeruginosa*, but has not been approved for use in children. Although not approved for pediatric use, this agent is occasionally used in children with cholangitis because it is excreted in the biliary tract. **Ceftizoxime** (Ceftizox®) is approved for use in children, but is seldom indicated.

FOURTH GENERATION CEPHALOSPORINS

The most recently released parenterally administered agent, **cefepime** (Maxipime®), is considered a fourth-generation agent because of its extended spectrum of activity against both gram-positive (including MSSA) and gram-negative organisms (including

P. aeruginosa) (7). However, it does *not* have activity against most bowel anaerobes including *B. fragilis*. It has comparable activity to cefotaxime and ceftriaxone against penicillin-nonsusceptible pneumococci and to ceftazidime against *P. aeruginosa*. Cefepime penetrates the outer membrane of gram-negative bacteria more rapidly than older generation compounds, and has a greater affinity for certain PBPs (PBP3 and PBP2). A unique microbiologic feature of cefepime is its frequent resistance to the hydrolysis of the inducible and derepressed β -lactamases that are responsible for the emergence of resistance during therapy (8).

Cefepime appears to be a safe agent with adverse effects similar to those observed with other cephalosporins in pediatric patients. Because of its enhanced activity against certain gram-negative enteric bacteria that are frequent causes of nosocomial infections, the primary use of cefepime will be for healthcare associated infections and for febrile neutropenia in cancer patients. Current indications for cefepime in pediatric patients include urinary tract infection (including pyelonephritis), hospital- and community-acquired pneumonia (for which it is administered BID) and for febrile neutropenia in immunocompromised patients (administered TID). Cefepime has good activity against most penicillin-nonsusceptible strains of *S. pneumoniae*, and its potential use in the treatment of bacterial meningitis is under investigation. **Cefpirome** is another fourth-generation agent in that it is undergoing clinical testing.

PRACTICAL USE OF CEPHALOSPORINS

Cephalosporins are useful agents because of their spectrum of activity against many pediatric pathogens and their excellent safety record. However, these agents should be prescribed judiciously or the development of resistance will limit their usefulness. The physician must be familiar with only a handful of cephalosporins to exploit their potential for the treatment of pediatric patients. Table 2 summarizes the overall taste properties of the oral suspensions. Palatability is a factor that should be taken into account in choosing an antimicrobial agent, because if the administration of some agents to infants and young children is difficult or unsuccessful, efficacy will be limited. Tables 3 and 4 suggest some useful oral and parenteral formulations of the cephalosporins based on antimicrobial activity, dosing convenience, patient tolerance and cost. In the past 5 years, two new cephalosporins have been approved for use in children: cefepime (parenteral) and cefdinir (oral). Each should be useful in children more than 6 months of age. The taste and smell properties and once a day dosing of cefdinir make it an especially attractive therapy in the child with AOM failing current therapy or known to be caused by penicillin-nonsusceptible pneumococci.

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TABLE 2
Taste Ratings for Oral Cephalosporin Suspensions*

Antibiotic	Rating
Loracarbef	++++
Cefdinir	++++
Cefixime	+++
Cephalexin	+++
Cefaclor	+++
Amoxicillin*	+++
Trimethoprim-sulfamethoxazole*	++
Cefprozil	++
Amoxicillin/clavulanate*	++
Cefpodoxime	+
Cefuroxime axetil	+

* Data modified from references 9-11

+ Comparative commonly prescribed agent in pediatric patients

++++, best overall taste; +++ above average;

++, below average; + poorly palatable

TABLE 3
Suggested Uses of Some Oral Cephalosporins*

Name	Generation	Doses/Day	Indications
Cephalexin	1 st	3-4	Alternative to penicillins in treating streptococcal and MSSA infections of throat, skin and soft tissues; UTI caused by susceptible <i>E. coli</i> or <i>K. pneumoniae</i>
Cefuroxime axetil	2 nd	2	AOM that fails to respond to amoxicillin; lower respiratory tract infections after hospital discharge
Cefixime	3 rd	1	UTI caused by susceptible strains of <i>E. coli</i> and <i>K. pneumoniae</i> ; acute shigellosis
Cefdinir	3 rd	2	AOM that fails to respond to amoxicillin

* Selection based on spectrum of activity, frequency of dosing, tolerability and cost

TABLE 4
Suggested Uses of Some Parenteral Cephalosporins*

Name	Generation	Doses/Day	Indications
Cefazolin	1 st	3	Surgical prophylaxis excluding bowel surgery or appendectomy Alternative to penicillins for less frequent dosing in soft tissue, bone and joint infections due to susceptible strains
Cefuroxime	2 nd	3	Lower respiratory tract, bone and joint infections if MRSA not suspected
Cefoxitin	2 nd	4	Treatment of intraabdominal infections
Cefotaxime	3 rd	3	Bacterial meningitis; gram negative sepsis; <i>Salmonella</i> and gonococcal infections
Ceftriaxone	3 rd	1-2	Same as for cefotaxime
Ceftazidime	3 rd	3	Febrile neutropenia; septicemia if <i>P. aeruginosa</i> is suspected
Cefepime	4 th	2 or 3	Nosocomial pneumonia; febrile neutropenia; pyelonephritis

* Selection based on spectrum of activity, frequency of dosing, tolerability and cost

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Educational Objectives After reading this publication, the reader should be able to:

- Enumerate two (2) oral and two (2) parenteral cephalosporins in the first, second, and third generation of cephalosporins and give the indications for each.
- List three (3) oral cephalosporins with above average palatability and give the indications for each.
- Identify one cephalosporin with good clinical activity against each of the following class of bacteria:
 - a) Enterobacteriaceae b) *Pseudomonas aeruginosa* c) Anaerobes

CME Self-Assessment Examination

1-4. Rank order the following oral antimicrobials on the basis of palatability, with one (1) being the best and four (4) being the worst:

<u>Antimicrobial</u>	<u>Rank Order</u>
1. Amoxicillin	_____
2. Amoxicillin/clavulanate	_____
3. Cefdinir	_____
4. Cefuroxime axetil	_____

5. Which of the following antimicrobials has good anti-pseudomonal coverage?

- a. Cephalothin
- b. Ceftazidime
- c. Cefuroxime axetil
- d. Ceftriaxone

6. Which of the following antimicrobials has good anti-anaerobic coverage?

- a. Cefepine
- b. Ceftazidime
- c. Cefoxitin
- d. Cephalothin

7. Which of the following antimicrobials would be an acceptable alternative for the outpatient treatment of acute otitis media that fails to respond to amoxicillin?

- a. Cefuroxime axetil
- b. Cefepime
- c. Cefdinir
- d. a and c

8-10. Match each indication numbered 8-10 with the best antimicrobial choice (from the antimicrobial list: a, b, or c). Use each antimicrobial choice only once.

<u>Indication</u>	<u>Antimicrobial Choice</u>
8. Treatment of intraabdominal infections	8. _____
9. Gonococcal infections	9. _____
10. Surgical prophylaxis (excluding bowel)	10. _____

Antimicrobial List

- a. Cefotaxime
- b. Cefazolin
- c. Cefoxitin

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