

Pediatric Pharmacotherapy

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A Comparison of the Oral Cephalosporins

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Oral cephalosporins are the most commonly prescribed antibiotics in the United States. There are currently ten cephalosporins available for oral use, providing a variety of choices for the treatment of common infections. In general, these antibiotics are indicated for upper and lower respiratory tract infections (including otitis media, pharyngitis, and bronchitis), uncomplicated skin and soft tissue infections, and uncomplicated urinary tract infections.¹⁻³

Spectrum of Antibacterial Activity

Division of the cephalosporins into generations has been used for many years to help group them into easily recognizable categories (Table 1). Traditionally, the first generation agents are known to have greater activity against Gram-positive organisms with little Gram-negative activity. These agents are used most frequently for skin and soft tissue infections.

Second generation cephalosporins typically retain their Gram-positive activity and provide greater activity against Gram-negative organisms, including *Haemophilus influenzae*. Several new second generation agents have been introduced in the

last five years, targeted at the pediatric population for the treatment of otitis media and pharyngitis.

The third generation agents lose some Gram-positive activity, but demonstrate superior activity against Gram-negative organisms. Cefixime provides excellent coverage against Gram-negative bacteria, but is relatively ineffective against *Streptococcus pneumoniae*. Cefibutin, the newest of the oral cephalosporins, has a similar spectrum to cefixime. Cefpodoxime is usually considered a third generation agent due to its Gram-negative spectrum; however, it is sometimes listed with the second generation agents since it maintains activity against most *Staph.* and *Strep.* species.⁴

Table 1. Oral Cephalosporins

- **First Generation**
 - Cefadroxil (Duricef® or generic)
 - Cephalexin (Keflex® or generic)^a
 - Cephadrine (Velosef® or generic)
- **Second Generation**
 - Cefaclor (Ceclor® or generic)
 - Cefprozil (Cefzil®)
 - Cefuroxime axetil (Ceftin®)^a
 - Loracarbef (Lorabid®)
- **Third Generation**
 - Cefixime (Suprax®)
 - Cefpodoxime proxetil (Vantin®)^a
 - Cefibuten (Cedax®)

^a on formulary at UVA

Stability against hydrolysis by beta-lactamase producing bacterial strains increases from first to third generation. Many communities have high rates of resistant *Moraxella catarrhalis* and *H. influenzae*. The ability to overcome bacterial resistance has been suggested as one of the primary reasons for choosing the newer (second and third generation) oral cephalosporins over traditional, less expensive, therapies for otitis media and pharyngitis in these communities.²

The efficacy of these newer oral cephalosporins in treating common infections has been well established. There are numerous clinical trials demonstrating their equivalence to cefaclor, as the "gold standard," and to other oral antibiotics, such as amoxicillin-clavulanate and trimethoprim-sulfamethoxazole.⁵⁻¹¹

Pharmacokinetics

All of the oral cephalosporins are well absorbed from the gastrointestinal tract. While absorption may be delayed by food, the amount of drug absorbed is typically unaffected. In children experiencing drug-induced stomach upset, these medications should be administered with food. The absorption of cefuroxime axetil and cefpodoxime proxetil can actually be enhanced by administration with food. Both compounds are prodrugs and converted to their active forms in the intestinal epithelium; the presence of food may enhance release of the prodrug from the tablet dosage forms.^{1,11}

Cephalosporins distribute well into most tissues. The primary exception is cephalexin, which does not penetrate well into the middle ear and therefore, is not useful for treating otitis media.⁴ Cephalosporins are primarily eliminated unchanged in the urine. Elimination half-life varies among the agents, from only 30 to 60 minutes with cefaclor, up to three to four hours with cefixime. Children with significant renal dysfunction will require a dosing adjustment in order to avoid excessive drug accumulation. This is typically done by extending the dosing interval based on an estimated creatinine clearance.^{1,2}

Dosage Recommendations

In response to consumer demands for more convenient dosing regimens, pharmaceutical manufacturers have focused on producing new cephalosporins with long elimination half-lives. As a result, the newer second and third generation agents need to be taken only once or twice daily. For most parents, this is a significant benefit since it avoids the need to send medication to day-care or school.

Recommended pediatric dosages for the oral cephalosporins are provided in Table 2.^{1,12} All of the oral cephalosporins are available in both liquid (suspension) and solid dosage forms. Cefuroxime axetil, loracarbef, and cefixime offer the advantage of being stable at room temperature. The other liquids require refrigeration.¹ Palatability is very child-specific. Ceclor®, Cedax®, Cefitin®, and Suprax® are berry-flavored. Cefzil® is bubble-gum flavored. Lorabid® is strawberry-bubble gum; Duricef® is orange-pineapple; and Vantin® is lemon creme flavored.

Table 2. Cephalosporin Dosages

medication	dose	interval
	(mg/kg)	(hours)
Cefadroxil	15	12
Cephalexin	6.25 - 12.5	6

Cephadrine	12.5 - 25	6
Cefaclor	6 - 7	8
(for otitis media)	10	12
Cefprozil	7.5 - 10	12
Loracarbef	7.5 - 15	12
Cefixime	8	24
Cefpodoxime	5	12
(for otitis media)	10	24
Cefibuten	9	24

For uncomplicated infections, oral cephalosporins are typically given for a ten day treatment course. However, shorter regimens have been shown to provide equivalent bacterial eradication and clinical cure rates as longer, traditional treatment courses and may be more likely to result in improved patient compliance. Four days of cefuroxime axetil and five days of cefixime have both been found comparable to penicillin given for ten days to treat pharyngitis.^{13,14}

Adverse Effects

Oral cephalosporins are well tolerated by most children. Severe toxicities are rare; however, many children experience mild adverse effects. Approximately five to twenty percent of all patients will experience transient gastrointestinal effects, including abdominal pain, nausea, vomiting, or diarrhea.¹⁻⁴ Despite advertising claims, clinical studies have failed to demonstrate a significant, reproducible difference in the incidence of these side effects among the cephalosporins. Differences in study methodology and terminology prevent comparative analysis (meta-analysis) of multiple clinical trials. Allergic reactions are estimated to occur in one to four percent of all patients treated with cephalosporins. Most allergic patients develop a maculopapular rash, with or without eosinophilia. Severe dermatologic reactions, including Stevens-Johnson syndrome, have also been associated with cephalosporin use.^{1,2} Anaphylactic reactions to the cephalosporins have been reported, but appear to be rare. Although cross-reactivity with penicillins remains a concern when choosing therapy, only 3-7% of patients with documented penicillin allergies will also react to cephalosporins.^{1,4} A serum sickness-like illness has been associated with the use of cefaclor for many years.¹⁵ It has been estimated that 0.05 to 0.5% of children given cefaclor will experience this idiosyncratic drug reaction.^{4,16} Signs and symptoms include

rash, arthralgias, irritability, and fever, usually occurring within one week of starting therapy and continuing for several days to weeks after discontinuing the antibiotic. Antihistamines and corticosteroids may be used to minimize symptoms until resolution.² Recently, serum sickness-like reactions have been reported with cefprozil and loracarbef, two of the newer second generation agents.¹⁶ Rare adverse effects associated with cephalosporins include: pseudomembranous colitis, blood dyscrasias, elevations in liver function tests, acute interstitial nephritis, headache, dizziness, and lethargy.^{1,2,17}

Cost Comparison

The cost of therapy with oral cephalosporins varies among different communities. Frequently prescribed antibiotics can often be purchased at a reduced price due to volume discounts from manufacturers and wholesalers. In order to provide a reasonable comparison, Table 3 lists average wholesale prices (AWP) for a 10 day treatment course for a 10 kg child (using suspension dosage forms).¹⁸ These numbers represent the average cost for the pharmacy to obtain the product and do not reflect final cost to the patient. For products available as generics, a representative product was selected.

Table 3. Cost of Therapy for a 10 kg child

medication	cost (\$)
Cefadroxil (generic)	23.00
Cephalexin (generic)	5.00
Cephadrine (generic)	13.00
Cefaclor (generic)	27.00
Cefprozil (Cefzil®)	21.00
Cefuroxime (Ceftin®)	29.00
Loracarbef (Lorabid®)	24.00
Cefixime (Suprax®)	29.00
Cefpodoxime (Vantin®)	28.00
Ceftibuten (Cedax®)	30.00

When choosing among the oral cephalosporins, primary consideration must be given to the antibacterial spectrum of the agents as well as their stability against beta-lactamase

producing bacterial strains. However, clinicians must also consider factors which may influence patient and family compliance: frequency of dosing, duration of therapy, need for refrigeration, taste, and cost, before selecting the optimal therapy.

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Pharmacology Literature Review

Medications for Psychiatric Disorders

This brief review covers common treatments for attention deficit/hyperactivity disorder, depression, anxiety, and other psychiatric illnesses affecting children. The authors include pediatric dosage recommendations for the newest antidepressants, the selective serotonin reuptake inhibitors, and clomipramine for the treatment of obsessive-compulsive disorders. While it does not provide enough depth for prescribers, this article may be useful for other clinicians caring for patients being treated for a psychiatric illness. Carrey NJ, Wiggins DM, Milin RP. Pharmacological treatment of psychiatric disorders in children and adolescents: Focus on guidelines for the primary care practitioner. **Drugs 1996;51:750-9.**

Management of Acute Pain

In recent years, there has been tremendous growth in the number of publications on the treatment of pain in children. This review provides a good foundation for beginning clinicians who wish to learn the basic pharmacology of common analgesics. The author focuses much of her discussion on opioids, including a brief section on opioid tolerance and the need to prevent iatrogenic withdrawal. She has also included a useful table of common dosing and lockout regimens for patient controlled analgesia. Bhatt-Mehta V. Current guidelines for the treatment of acute pain in children. **Drugs 1995;51:760-76.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 5/24/96:

1. Cetirizine (Zyrtec®) was added to the formulary. This is the newest of the second generation antihistamines available in the United States. It is approved for adults and children over 12 years of age and is available in two tablet strengths, 5 and 10 mg. Cetirizine offers the advantage of once or twice daily dosing in adults and lacks significant drug interactions. Cetirizine has been used in Europe for many years, where it is also available in liquid form. A recent study from France evaluated the dosing requirements in children between two and six years of age. The authors recommend a starting dose of 5 mg twice daily (Inter J Clin Pharmacol Ther 1995;33:340-4).

2. In a related action, terfenadine (Seldane®) and astemizole (Hismanal®) were removed from the formulary. These antihistamines have been associated with an increased risk of cardiac arrhythmias when used concurrently with agents which block their metabolism, such as erythromycin. For more information, please refer to *Pediatric Pharmacotherapy*, Vol.1(No.9). Loratadine (Claritin®) remains on formulary. Like certirizine, it is not associated with significant drug interactions.
 3. A therapeutic class review of the long-acting dihydropyridine calcium channel blockers was also conducted. Amlodipine (Norvasc®) and isradipine (DynaCirc®) will remain on the formulary. A long-acting preparation of nifedipine, Procardia XL®, was removed from the formulary due to cost.
 4. The decision to add dexrazoxane (Zinecard®), a chelating agent designed to decrease the toxicity associated with doxorubicin, was tabled. This agent will continue to be available to prescribers through the non-formulary drug request system.
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If you have comments, questions, suggestions, or would like to be included on our mailing list, please send a note to Marcia Buck, Pharm.D., Box 274-11 Children's Medical Center at the University of Virginia, Charlottesville, VA 22908 or e-mail to mlb3u@virginia.edu
Fax: 804-982-1682 Office: 804-982-0921

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