Cephalosporins are a diverse group of beta-lactam antibiotics with a broad range of antibacterial activity and clinical applications. Since the initial discovery of the basic cephalosporin moiety in the 1940s, several cephalosporin compounds have been developed and approved for clinical use.1,2 At present, 24 cephalosporin compounds—more than half of the available beta-lactam antibiotics—are available in the United States.2,5 Although all cephalosporins exhibit some structural similarity, modifications of the basic cephalosporin nucleus have led to production of several unique cephalosporin compounds. Specific structure-activity relations account for clinically significant differences in pharmacokinetic profiles, spectrum of antibacterial activity (organism “coverage”), clinical applications, adverse reaction profiles, and modes of administration among many cephalosporins.2-7 As stated in a review of cephalosporins, “differences among the numerous cephalosporin antimicrobial agents are sometimes subtle; however, an understanding of these differences is essential for optimal use of these agents.”5

The continued popularity and worldwide use of both parenteral and oral cephalosporins relate predominantly to a proven track record of “broad-spectrum” antibacterial activity (against several gram-positive and gram-negative pathogens) and excellent safety during 30 years of cumulative clinical experience.2,3 Specific cephalosporins offer unique bacterial coverage advantages not found with most other cephalosporins. Examples include single-dose intramuscular ceftriaxone for treatment of uncomplicated gonorrhea or chancroid; parenteral cefoxitin or cefotetan for Bacteroides fragilis infection; and parenteral cefoperazone, cefazidime, or cefepime for Pseudomonas aeruginosa infection.2,7 In dermatology, cephalosporin use is primarily related to skin and soft-tissue infections such as folliculitis, cellulitis, impetigo, and wound infections including infected ulcers and perioperative infection.2,7 Other applications include treating some sexually transmitted bacterial diseases and early Lyme disease (erythema chronicum migrans stage).1,3,8

Eleven oral cephalosporins are available for clinical use in the United States (Table). In the following sections, I focus on oral cephalosporin use for dermatologic applications and review practical correlations of tissue pharmacokinetics, pharmacodynamic activity, clinical indications, and selected safety issues.

What is the significance of categorizing cephalosporins by generation?

Since the release of cephalixin in 1967, “four generations of cephalosporin antibiotics have emerged, based loosely on both the timing of development and..."
release, and their spectrum of antimicrobial activity. Each subsequent decade correlates loosely with the onset of a new generation of cephalosporin compounds. A common oversimplification is that, with the release of each new generation of cephalosporins, antibacterial activity decreases against gram-positive organisms and increases against gram-negative organisms. In fact, several important exceptions render this “rule” potentially misleading. Although most cephalosporins are clinically active against a variety of both gram-positive and gram-negative bacteria, the relative degree of inhibitory activity of individual cephalosporin compounds is irrespective of their categorized generation, both in vitro and in vivo. In one study involving several oral cephalosporin and macrolide antibiotics, investigators confirmed significant variability in inhibitory activity against community-acquired pathogens and concluded that the antistaphylococcal activity of oral cephalosporins “can be determined only by testing the individual agents.”

Differences in bacterial sensitivity profiles among cephalosporins may correlate at least partially with the susceptibility patterns of individual cephalosporins to specific types of β-lactamases produced by different bacterial organisms.

How do cephalosporins produce and sustain their antibacterial effect? Pharmacologically, cephalosporins bind to peptidase enzyme target sites (i.e., penicillin-binding proteins) in the outer cytoplasmic membrane of bacteria. This binding impairs integration of bacterial peptidoglycan into a lattice forming the structural support of the bacterial cell wall. Structural modifications of the basic cephalosporin nucleus—usually alterations in specific side chains—have produced differences in the spectrum of organism coverage and in pharmacokinetic profiles, and these differences significantly affect selection of antibiotics in clinical practice.

From a pharmacodynamic perspective, cephalosporin antibiotics exhibit time-dependent antibacterial activity. An antibacterial effect is exerted when the concentration of cephalosporin at the infection site exceeds the minimum inhibitory concentration (MIC). Raising the concentration more than 2- to 4-fold above the MIC provides no additional antibacterial benefit. Therefore, maintaining the concentration above the MIC for 50% to 70% of the dosing interval (period between doses) is needed to sustain antibacterial activity. Furthermore, maintaining the concentration above the MIC during the entire dosing interval maximizes efficacy and is less likely to result in the emergence of resistant bacterial strains. Time-dependent antibacterial activity demands close attention to pharmacokinetic differences among individual cephalosporins. Use of proper dosages and dosing intervals and patient adherence are vital to the success of therapy.

What are the most common uses of oral cephalosporins in dermatology? The majority of cephalosporin use in dermatology is for uncomplicated skin and soft-tissue infections such as folliculitis, furunculosis, superficial abscesses, impetigo, cellulitis, infected eczematous dermatoses, infected skin ulcers, erythema, and postsurgical wound infections. Most cutaneous infections, depending on clinical type and presentation, are caused by *Staphylococcus aureus* or *Staphylococcus pyogenes*. Responsive gram-negative pathogens may be causative in some cases of infected lower extremity ulcers or cellulitis and diabetic foot infections. Because *S. aureus* is the pathogen most commonly identified in studies of superficial diabetic foot infections, empiric antibiotic therapy should allow for appropriate

### Oral Cephalosporin Antibiotics Available in the United States*

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Brand Name(s)</th>
</tr>
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<tbody>
<tr>
<td>First generation</td>
<td></td>
</tr>
<tr>
<td>Cephalexin</td>
<td>Keflex®, Keftab®</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>Duricef®, Ultracef®</td>
</tr>
<tr>
<td>Cephradine</td>
<td>Velosef®</td>
</tr>
<tr>
<td>Second generation</td>
<td></td>
</tr>
<tr>
<td>Cefaclor</td>
<td>Cefclor®</td>
</tr>
<tr>
<td>Cefprozil</td>
<td>Cefzil®</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>Ceftin®</td>
</tr>
<tr>
<td>Loracarbef†</td>
<td>Lorabid®</td>
</tr>
<tr>
<td>Third generation</td>
<td></td>
</tr>
<tr>
<td>Cefdinir</td>
<td>Omnicef®</td>
</tr>
<tr>
<td>Cefixime</td>
<td>Suprax®</td>
</tr>
<tr>
<td>Cefditoben</td>
<td>Cefad®</td>
</tr>
<tr>
<td>Cefpodoxime proxetil</td>
<td>Vantin®</td>
</tr>
</tbody>
</table>

*All these antibiotics are available in both solid and liquid/suspension formulations, except cephadrine (solid only).
†Structurally a carbacephem derivative.
coverage of this pathogen, pending results from culture and sensitivity testing.17,19 Antibiotics from several medication classes (eg, semisynthetic penicillins, cephalosporins, macrolides, quinolones) may be selected for treatment of skin and soft-tissue infections based on specific clinical factors (eg, medication allergy history, potential medication interactions), clinical presentation, and the causative pathogen. For cephalosporin treatment of milder, superficial cutaneous infections, an oral agent with established clinical efficacy against commonly encountered gram-positive and gram-negative pathogens (eg, cefdinir, cefprozil) is a rational choice. Organisms resistant to available oral cephalosporins are methicillin-resistant S aureus; enterococci; Chlamydia species; and Pseudomonas species, including Pseudomonas aeruginosa.2,4,5,17,18,20

Cefuroxime axetil (500 mg twice daily for 14–21 days) has been reported to be an effective oral therapy alternative to doxycycline for adult patients presenting with early localized Lyme disease (erythema chronica migrans stage).3,4 Oral cefixime 400 mg, oral cefpodoxime proxetil 200 mg, and oral cefuroxime axetil 1000 mg may be used as singledose therapy for uncomplicated gonorrhea.2,4,5

What is the efficacy of oral cephalosporins in treating skin and soft-tissue infections?

Results of a collection of studies conducted between 1970 and 1998 showed clinical improvement or cure rates of 88% to 90% associated with use of cephalexin for uncomplicated skin and soft-tissue infections.22-25 The recommended adult dosage for cephalexin is 1 to 2 g daily, usually for 10 days; the suggested dosing frequency is 4 times daily.2-5,25 Less frequent dosing may not be optimal with cephalexin because of its short plasma half-life (<1 hour), the rapid (<8 hours) urinary excretion of 90% of cephalexin administered, and time-dependent antibacterial activity, though effective twice-daily dosing intervals have been suggested with first-generation oral cephalosporins.2,5,12-16 According to a retrospective data analysis regarding outpatient treatment for uncomplicated cellulitis, oral cephalexin had a failure rate of 40%, whereas other oral agents (eg, dicloxacillin, amoxicillin-clavulanate, clindamycin) had a failure rate of 20%.26 Cephalexin may be used in adult and pediatric populations.

Like cephalexin, cefdinir is active against S aureus, S pyogenes, and several gram-negative pathogens of the Enterobacteriaceae family. In addition, cefdinir is active against Haemophilus influenzae, erythromycin-resistant S aureus, and several cephalaxin-resistant pathogens.2,12-16 According to in vitro evaluations, including 2 comparative studies inclusive of 1069 clinical isolates, the activity of cefdinir against several gram-positive and gram-negative pathogens, including S aureus and S pyogenes, is superior to that of several other cephalosporins, including cephalexin and cefadroxil.2,10,20,23,27-32 In a study evaluating the clinical efficacy of using cefdinir versus cefalexin to treat uncomplicated cutaneous infections in adult patients, the eradication rate of S aureus was 92% in the group treated with cefdinir (n=143) versus 88% in the group treated with cefalexin (n=165).27 In the same study, cefdinir eradicated 88% of cephalexin-resistant gram-positive and gram-negative organisms. In a study of 231 pediatric patients with cutaneous bacterial infections (impetigo, infected eczema), the overall cure rate associated with cefdinir was 98.3%, and all cephalexin-resistant pathogens responded to cefdinir therapy.28 Cefdinir may be used in adult and pediatric populations. In the treatment of cutaneous infections, the recommended adult dosage regimen for cefdinir is 300 mg twice daily for 10 days.2,27,28

Cefprozil is active against S aureus and S pyogenes and has a moderate effect against some gram-negative pathogens (eg, Enterobacteriaceae, H influenzae).33-35 The recommended adult dosage for cefprozil is 250 mg twice daily.33-37 Its efficacy has been compared with that of cefaclor in the treatment of uncomplicated skin and soft-tissue infections. According to one study, cefprozil was more effective than cefaclor; results of another study showed similar efficacy.34,35 In other studies, involving mild to moderate skin and skin-structure infections, efficacy of cefprozil 250 mg twice daily was similar to that of erythromycin 400 mg 4 times daily and of amoxicillin 250 mg/clavulanate 125 mg 3 times daily.36,37

What is the risk of cross-reactivity reactions between penicillin and cephalosporins?

Cephalosporin therapy should not be used for patients with a history of immunoglobulin E–mediated hypersensitivity reactions (eg, anaphylaxis, urticaria, angioedema) to β-lactam antibiotics (penicillins, cephalosporins).5 Unfortunately, the true risk of allergic or hypersensitivity reactions secondary to cross-reactivity between penicillin and cephalosporins is poorly defined. Results of a 1995 study suggest that as much as 16.5% of patients with an allergy to a penicillin have cross-reactivity reactions to cephalosporins.38 More recent data suggest a lower incidence (1%–7%).2,5
Can cephalosporin antibiotics be used safely during pregnancy and breast-feeding?

Product labels and recognized compendia list several cephalosporins (including cephalexin, cefadroxil, cefdinir, cefaclor, cefprozil, and cefditoren) in pregnancy risk factor category B. The American Academy of Pediatrics indicates that several cephalosporins (including cefadroxil and cefprozil) are compatible with breast-feeding.

What are the major adverse reactions associated with cephalosporin therapy?

The most common adverse reactions associated with cephalosporin therapy are transient maculopapular or urticarial cutaneous eruptions, gastrointestinal reactions, and hypersensitivity reactions. Non-specific diarrhea may occur in as many as 5% of patients; pseudomembranous colitis associated with cephalosporins is rare, especially with oral therapy. Hepatotoxicity and nephrotoxicity are also very rare. Maculopapular skin eruption occurs in 1% to 3% of patients treated with cephalosporins; urticaria seems less common. Reports of a serum sickness–like reaction associated with use of cefaclor have been sporadic. This reaction presents as urticaria, fever, or arthralgia, with or without lymphadenopathy or eosinophilia, within the first 3 weeks of therapy. In contrast to true serum sickness, the reaction is not accompanied by circulating immune complexes, hypocomplementemia, vasculitis, or glomerulonephritis. According to an analysis of pediatric patients, the risk for developing this reaction is 0.024% to 0.2% per course of cefaclor administration. Eosinophilia, reported in 1% to 7% of patients as a possible association with cephalosporin therapy, is usually an isolated hematologic finding. Hemolytic anemia is rarely reported in association with cephalosporins, despite a reported incidence of 3% positivity on Coombs test.

What potentially significant medication interactions may occur with cephalosporin use?

Coadministration of agents suppressing gastric acidity (e.g., antacids, H-2 receptor antagonists) may reduce gastrointestinal absorption of cefuroxime and cefpodoxime. Concurrent ingestion of antacids also seems to decrease cefdinir absorption. Results of one study suggest that concomitant acid-suppression therapy is a risk factor for failure of cephalexin therapy for cellulitis. Given reports of reduction in cefdinir absorption, coadministration with ferrous sulfate and other iron salts should be avoided. Chelation of cefdinir by iron may be the mechanism of interaction. Case reports suggest a potential interaction between warfarin and cefixime or cefaclor.

REFERENCES