Drug Actions, Reactions, and Interactions

Cephalosporin Therapy in the Management of Uncomplicated Skin and Soft Tissue Infections

By James Q. Del Rosso, DO, FAOCD

Oral cephalosporins have proven to be effective and safe agents with broad-spectrum antibiotic effect. The pharmacokinetic and antimicrobial profiles of many cephalosporins allow for effective use for a wide variety of clinical infections, including respiratory, genitourinary, otologic, and dermatologic indications. Cephalosporins are often classified based on their generations. Currently, four generations are described based on the timing of their development. A common generalization made in relationship to the spectrum of antimicrobial activity (“coverage”) of cephalosporins is that as one moves from the first to the fourth generation, gram-positive “coverage” decreases coupled with an increase in coverage of gram-negative organisms. Close evaluation of the microbiologic profiles of available cephalosporins indicates several exceptions to this generalization. As discussed in more detail below, microbiologic studies from both adults and children demonstrate that cefdinir (Omnicef), which is a third-generation oral cephalosporin, exhibits the greatest degree of antimicrobial activity against several commonly encountered gram-positive bacteria (i.e., *Staphylococcus aureus, Streptococcus pyogenes,* *Streptococcus pneumoniae*) and many gram-negative organisms when compared to other available oral cephalosporins, including cephalexin (Keflex).

Differences among the numerous cephalosporin antimicrobial agents are sometimes subtle...an understanding of these differences is essential for optimal use of these agents.

History of Cephalosporin Antibiotic Development

The cephalosporin antibiotics were developed in the early 1940s by Professor Giuseppe Brotzu who discovered their natural production by the fungal organism *Cephalosporium acremonium.* His research was later expanded by investigators at Oxford leading to the discovery of cephalosporin C, the basic structural nucleus from which cephalosporin antibiotics are derived.1,2 With continued research and development, several cephalosporin antibiotics have been released since the 1960s, with 24 unique yet structurally similar compounds currently available for clinical use in the United States.2 For over four decades, due to a consistent track record of clinical efficacy and excellent safety, cephalosporins have sustained their position as a significant class of antibiotics worldwide, comprising over one-half of the available beta-lactam antibiotics.3,4 Cephalosporins are often categorized by generation, a terminology that many clinicians correlate with the overall antimicrobial spectrum of individ-
Antimicrobial Activity of Cephalosporin Antibiotics

Differences in spectrum of antibacterial coverage and pharmacokinetic properties among cephalosporins individually are dependent on specific structural modifications designed to alter the basic cephalosporin structure. “Tradeoffs” in spectrum of antibacterial activity are common consequences of modifications in antibiotic chemical structure.3,4 Regardless of their generation, cephalosporins are best evaluated and selected based on their individual characteristics and merits.3,4

From the pharmacological perspective, cephalosporins produce their antibiotic effects by inhibiting the integration of bacterial peptidoglycan, thereby reducing the structural integrity of the cell wall of susceptible organisms.3,4 As with several classes of antibiotics, including penicillins, tetracyclines, and macrolides, the pharmacodynamic activity of cephalosporin antibiotics is categorized as time-dependent bactericidal activity. Antimicrobial activity begins once drug concentration exceeds the minimum inhibitory concentration (MIC) and increases until achieving an upper threshold concentration (two- to four-fold higher than the MIC for the bacterial organism).3,4 To sustain antibacterial activity, it is preferable, but not mandatory, to exceed the MIC for the entire time period between dosing intervals; maintaining a level of antibiotic in excess of the MIC for 50 to 70 percent of the dosing interval is reported to be necessary for optimal efficacy and reduced emergence of antibiotic-resistant strains.3,4

Most cephalosporins exhibit at least some degree of antibiotic activity against individual gram-positive and gram-negative organisms, hence their reputation for being effective as single-dose treatments for uncomplicated gonorrhea.3,4

The observation of eradication of bacterial isolates resistant to cephalexin by cefdinir emphasizes that “all oral cephalosporins are not created equal…”

Comparative Antimicrobial Profiles

Microbiologic evaluations of cephalosporin antibacterial efficacy against S. aureus and S. pyogenes demonstrate that cefdinir (Omnicef) is superior to other cephalosporins, including cephalexin (Keflex) and cefadroxil (Duricef).3,4,13,15,23 Comparative studies of several cephalosporins, performed in 1,069 clinical isolates, confirmed the superior activity of cefdinir against S. aureus, S. pyogenes, and some gram-negative pathogens, including Escherichia coli, Klebsiella pneumoniae, and Hemophilus influenzae.13,15 Based on pharmacokinetic studies evaluating serum levels, half-life, and suction blister penetration, the current suggested frequency of administration for cefdinir is twice daily; the approved dosage for cutaneous infections is 300mg twice daily for 10 days.2,24

A study of 392 assessable adult patients with skin and skin-structure infections compared cefdinir 300mg twice daily and cephalexin 500mg four times daily administered for 10 days.25 Cefdinir produced bacterial eradication in 93 percent with clinical response in 88 percent, compared to 89 percent bacterial eradication and 87 percent clinical response in the cephalexin group. Cephalexin produced eradication of S. aureus in 88 percent of cases as compared to 92 percent eradication with cefdinir. In this same study, cefdinir effectively eradicated 88 percent of cephalaxin-resistant pathogens, including both gram-negative and gram-positive organisms, with clinical cure achieved in 84 percent. Cefdinir and cephalexin were also compared in 231 pediatric patients with impetigo, infected eczema, and other cutaneous infections.26 Cure was achieved in 98.3 percent of patients treated with cefdinir and 93.8 percent of patients treated with cephalexin; patients with cephalaxin-resistant pathogens responded to therapy with cefdinir. In this study, although both agents exhibited S. aureus susceptibility in vitro, cefdinir activity was superior to cephalexin based on an 8-fold lower MIC90 requirement. It is important to recognize that the dosing frequency in trials with cefdinir was twice daily versus four times daily with cephalexin. Cefdinir has also demonstrated activity against erythromycin-resistant S. aureus.15,23 Marked activity is noted against several aerobic gram-negative pathogens, such as H. influenzae (including beta-lactamase producing strains), K. pneumonia, E. coli, Citrobacter diversus, and Proteus mirabilis.3,4,13,23

The observation of eradication of bacterial isolates resistant to cephalexin by cefdinir emphasizes that “all oral cephalosporins are not created equal” and likely reflects the “upward creep in MICs” that is commonly experienced with antibiotic use over time.

Safety Profile of Oral Cephalosporins

The adverse reaction and drug interaction profiles of cephalosporin antibiotics are reviewed in detail elsewhere.3,4 The oral cephalosporins are
very well tolerated. Most reactions are mild to moderate and reversible. The most commonly encountered adverse effects reported in ≤5 percent of patients include morbilliform or urticarial drug eruptions and antibiotic-associated diarrhea. Hypersensitivity reactions are rare and are more likely to occur in patients with confirmed allergies to penicillin. Pseudomembranous colitis is rare with oral cephalosporin therapy. Among cephalosporin agents, serum sickness–like drug reactions are unique to cefaclor. Organotoxic reactions, such as hepatotoxicity, nephrotoxicity, or serious blood dyscrasias, are very rare with cephalosporin antibiotics.

Paradigm Shifts in Antibiotic Prescribing Habits

As many oral cephalosporins are available for clinical use, it often becomes difficult to make informed and rational selections among this diverse family of antibiotics. Literature review suggests relative disparity of activity among cephalosporins and other oral antibiotics in the treatment of skin and soft tissue infections.\(^{1,4,11,12,25–33}\) For example, one study evaluating the activity of multiple cephalosporins and three oral macrolide antibiotics demonstrated significant differences in antibacterial potency and spectrum of activity against community-acquired pathogens.\(^{14}\) The authors concluded that the antistaphylococcal activities of oral cephalosporins "can be determined only by testing the individual agents."\(^{14}\) Current reports indicate that the third-generation agent, cefdinir, appears to be the most active oral cephalosporin against S. aureus, S. pyogenes, and some gram-negative pathogens and is effective for treatment of skin infections in adults and children.\(^{3,4,15,25,26}\)

References

As with over a million cases of basal cell carcinoma (BCC) reported annually in the United States alone.1 As such, BCC is frequently seen in clinical practice. Surgical treatment of BCC is effective and a common approach, but cosmetic concerns, overall patient health, tumor size, location, age, worries about anesthesia, and other factors may rule out an operation for some patients. For some patients, two intriguing nonsurgical options for the treatment of BCC may be of interest: radiation therapy and photodynamic therapy.

Radiation Therapy
When a suitable match between patient and procedure can be made, radiation therapy (RT) has been shown to be a safe and effective treatment alternative to surgery. However, there are many factors to consider before selecting RT.

RT is not recommended in younger patients (<50 years), since late-onset changes of cutaneous atrophy and telangiectasia can occur over time,2 and there is also a risk of developing additional nonmelanoma skin cancers in the radiation field after 10 to 20 years.3 Furthermore, certain disorders contraindicate RT, because such patients are genetically predisposed to develop certain skin cancers. Patients with Gorlin's syndrome, xeroderma pigmentosum, or connective tissue diseases (e.g., lupus, scleroderma) should not receive RT.

Tumor location can play a role in the selection or exclusion of RT. Tumors in lower-risk areas, such as the trunk and extremities, are less likely to be treated with RT. Conversely, tumors in hard-to-treat locations, such as eyelids, are likely candidates for RT.

In general, RT should be considered for elderly patients or to treat tumors in locations that preclude other approaches. The total radiation dose and treatment regimen depends on tumor size, location, type, and depth.

Photodynamic Therapy
Photodynamic therapy (PDT) has not yet been approved by the Food and Drug Administration for the treatment of BCC, but it has been the subject of several promising clinical studies. PDT involves treating the skin topically with 5-aminolevulinic acid (ALA) or methyl ALA and then exposing the treated skin several hours later to oxygen and a light source. The mechanism of the treatment is believed to be the accumulation of heme precursors on the treated skin; these precursors start to appear several hours after the topical ALA application. When the precursors are exposed to oxygen and light, a cytotoxic reaction occurs via the oxygen radicals.

Still under investigation is the optimal number of treatments. Several studies have suggested that superficial BCC (sBCC) lesions do not clear with a single treatment of PDT. In a study of 95 patients with sBCC, the primary response rate with ALA PDT was 86 percent with a 44 percent recurrence rate after a median follow-up period of 19 months. The projected disease-free rate was only 50 percent.4 In a long-term study of 350 BCC lesions (both superficial and nodular) treated with methyl 5-ALA PDT, 89 percent of lesions cleared with an overall cure rate of 79 percent after a mean follow-up period of 35 months.5 While initial results show promise, PDT remains a relatively inconvenient treatment for both clinicians and patients. A single treatment involves a two-stage process that requires 14 to 18 hours after ALA is applied or three hours for methyl ALA. Since effective therapy seems to require more than one treatment, patients must return for treatment. PDT has been associated with localized adverse events, such as a stinging or burning sensation, erythema, and edema.6 Patients undergoing PDT also experience photosensitivity during treatment and must avoid exposure to the sun or even bright indoor lighting until the entire course of treatment is concluded.

PDT is not indicated for patients who have porphyria, known allergies to porphyrins, or photosensitivity to wavelengths of applied light sources.7 Because PDT is still in its infancy, it is possible that more practical forms of treatment will evolve. The potential promise of PDT is a safe and effective treatment option with improved cosmetic results versus certain conventional treatments.

In a European study that compared cryotherapy (double freeze-thaw cycles) to a single methyl ALA PDT treatment in a total of 118 patients with sBCC, no significant difference in clearance rates was observed. However, the PDT achieved a significantly higher number of “excellent” or “good” cosmetic results versus cryotherapy at three months post-treatment (89% versus 50%, respectively) with a similar pattern at 12 months post-treatment. Fewer lesions recurred at 12 months post-treatment with methyl ALA PDT compared to cryotherapy (8 percent versus 12 percent, respectively).7 In summary, this study suggests that methyl ALA PDT is as effective as cryotherapy at treating BCC but yields superior cosmetic results.

<table>
<thead>
<tr>
<th>Table 1: Selected Physical Modalities for BCC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>Radiation Therapy (RT)</td>
</tr>
<tr>
<td>Photodynamic Therapy (PDT)</td>
</tr>
</tbody>
</table>

By Roger I. Ceilley, MD, and James Q. Del Rosso, DO, FAOCD
Recurrence Rates for RT and PDT

The recurrence rate of BCC treated with “standardized” radiation (x-ray) therapy showed an overall five-year recurrence rate of 7.4 percent for primary BCC (n=862) and 9.5 percent for recurrent BCC (n=211).\(^2\)

PDT is so new that study data on recurrence rates is lacking. One major prospective randomized trial that compared methyl ALA PDT (52 patients) to surgery (49 patients) published recurrence data for 12 months post-treatment. In this study, the PDT patients received two treatments seven days apart for primary nodular BCC (nBCC), while the other arm of the study had the nBCC surgically excised. The clearance rates at three months post-treatment for the 105 lesions treated were statistically similar between treatment arms (91% of nBCC lesions were cleared with PDT versus 98% of lesions cleared with surgery.) At 12 months post-treatment, tumor-free rates were 83 percent for nBCC for the PDT group versus 96 percent for nBCC for the surgical group. Both patients \((p<0.05)\) and investigators \((p<0.001)\) reported significantly better cosmetic results for PDT at 12 months compared to surgical excision.\(^8\)

Conclusion

While surgical options for the treatment of BCC are a mainstay of modern dermatology practice, there are also nonsurgical treatment options for specific cases (see Table 1.) The most common nonsurgical approach remains RT, which has specific advantages for the treatment of older patients, very large tumors, or tumors in difficult-to-treat locations. A new and promising treatment, PDT is proving effective with superior cosmetic results versus certain conventional approaches but is not yet approved in the United States. Both RT and PDT are contraindicated for certain patients, and both are associated with certain disadvantages. RT, for example, is not recommended for patients predisposed to skin cancer or younger patients, while PDT is associated with localized adverse reactions, an inconvenient treatment modality, and contraindications for patients with porphyria. As a result, both RT and PDT appear to be useful in the treatment of BCC only in specific and, as yet, limited cases. • • •

References


Case of the Month

By Susan L. Epp, PA-C, and Roger I. Ceilley, MD

Case Study

A 48-year-old Asian female presented with a pruritic rash of six months duration on the buttock region. She tried topical treatment with triamcinolone cream, tretinoin, clotetasol, fluorocinide, pimecrolimus, and ammonium lactate creams with only slight relief of the itching. The rash persisted despite regular use of these medications. Examination revealed numerous discreet and coalescing reddish-brown annular papules and plaques with fine, papery, peripheral scale. The rash involved both buttocks but spared the perineum.

Diagnosis and Discussion

A biopsy confirmed the clinical diagnosis of disseminated superficial porokeratosis. Histologic changes revealed the characteristic “coronoid lamella,” a thin column of parakeratotic cells extending from a small invagination of epidermis.\(^1\) This corresponds with the thin hyperkeratotic border seen clinically.

Disseminated superficial porokeratosis is a condition that usually presents in the third or fourth decade of life. It is more common in females. Lesions can occur anywhere on the body, but the extremities are most commonly affected. There are several clinical variants of this condition, including porokeratosis of Mibelli (usually a solitary lesion), disseminated superficial actinic porokeratosis (DSAP), linear porokeratosis, and punctate porokeratosis. The differential diagnosis should include lichen planus and other lichenoid dermatoses, arsenical keratoses, and psoriasis.\(^2\)

continued on page 7
The Diameter of Melanomas

The Diameter of Melanomas

By Jo Ann LeQuang

This edition of litSCAN will review two original articles: a retrospective study on melanomas and a survey that provides the first quantitative data on premenstrual acne flares.


Since its formulation in 1985, the popular “ABCD” rule of melanoma diagnosis has been practiced by dermatologists and learned by their patients. ABCD stands for asymmetry, border irregularity, color variation, and diameter greater than 6mm. While these are clearly subjective judgments, the “D” in the acronym was matched with an arbitrary and specific measurement. The authors of this study sought to determine by retrospective analysis whether 6mm was a clinically appropriate dividing line in the diagnosis of melanomas.

Using a computerized database of pathology reports from the CoPath database at the Milton S. Hershey Medical Center, the authors obtained a total of 383 melanomas. Of that number, 137 were excluded, because they had been previously diagnosed elsewhere as melanomas and were referred to the facility for consultation only.

The pathology report contained the clinical diagnosis, a microscopic and gross description, and diagnosis comment on the depth of the lesion. Data was collected about each lesion’s diameter, depth, location on the body, as well as age and gender of the patient. The proportion of melanomas that were less than 6mm in diameter was analyzed using a 95 percent confidence interval (p=0.05). The trimmed mean was reported for Breslow’s thickness, which excluded the lowest and highest five percent of values.

Patients were almost exactly evenly divided by gender (50.4% male) with a mean age of 57 years. Most lesions appeared on the back (31%), upper extremities (24%), or on the head or neck (20%).

**Results.** The study found a significant number of melanomas that were smaller in diameter than 6mm. Of the 246 lesions analyzed, 94 (38.21%) were smaller than the “D” rule of the ABCD criteria. One hundred fifty-two (61.79%) of the lesions were larger than 6mm. The larger tumors occurred in slightly older patients (average age 59.16 years, p=0.002, versus 52.45 years for smaller tumors). Larger tumors tended to be deeper, at 0.4mm, than smaller tumors at 0.29mm (p=0.02) as well (see Table 1).

<table>
<thead>
<tr>
<th>Table 1: Melanomas Greater than 6mm Compared to Those Less than or Equal to 6mm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Average patient age, years</td>
</tr>
<tr>
<td>Average thickness (mm)</td>
</tr>
<tr>
<td>Trimmed Breslow’s thickness</td>
</tr>
</tbody>
</table>

**Clinical relevance.** This study found that larger melanomas were significantly deeper than the smaller melanomas, emphasizing that many melanomas begin as pinpoint lesions that grow over time. The arbitrary 6mm boundary for diameters may cause patients and dermatologists to miss lesions at their earliest and most treatable stages.

The ABCD slogan for diagnosing melanomas is catchy, but it requires some revision. Even before this study, some have proposed adding letters to the mnemonic to make it more useful. One suggestion was to add an E for elevation, but raised lesions are usually indicative of a later stage of the disease.

In truth, many melanomas have and will continue to defy our conventions. The issue in clinical practice is ensuring these “unconventional” melanomas do not evade diagnosis (most melanomas are detected first by the patient).

The authors found that the three most common diagnoses in lesions that were not expected to be melanomas were basal cell carcinoma, seborrheic keratosis, and nevus. Their findings are confirmed by other sources in the literature.

The ABCDs of melanoma detection are still important, and patients should continue to be educated in self-examination but with the caveat that there are no hard-and-fast rules to the ABCD slogan. These criteria, in particular the diameter, are not absolute values. Melanomas do not necessarily follow the rules and may, in fact, start out as small lesions. Patients should be encouraged to report any unusual marks or growths to their dermatologists, and dermatologists are well advised to biopsy any unusual lesions, even those that fall inside the 6mm boundary line.

Quantitative Documentation of a Premenstrual Flare of Facial Acne in Adult Women (Lucky AW. Quantitative documentation of a premenstrual flare of facial acne in adult women. Arch Dermatol 2004;140:423–4.)

The commonly observed phenomenon of premenstrual acne flares has yet to be rigorously studied or quantified. Although consensus exists that these flares can be attributed to hormonal fluctuations in women in the luteal phase of the menstrual cycle, the exact mechanisms have not yet been fully investigated.

The author reports results from a two-month nontreatment study at an investigational center. Women enrolled were nonpregnant, nonlactating women in good health, at least 18 years old,
with a regular menstrual cycle. Recent treatment of acne was an exclusionary criterion. Subjects had to have at least mild inflammatory acne to be enrolled, characterized by a minimum of three inflammatory lesions at least 2 mm in diameter and any number of comedones.

The patients were evaluated in five visits, occurring over the course of two menstrual cycles: one prestudy visit followed by two visits a cycle for two cycles. The appointments were scheduled to fall between Day 7 and Day 12 of the menstrual cycle or the late follicular phase and again between Day 22 and Day 28 during the late luteal or “premenstrual” phase.

Compliance with the nontreatment parameter was assured at each visit. The nontreatment aspect was particularly troublesome for some subjects; a total of 14 patients dropped out specifically for this reason.

The premenstrual flare was assessed as the percent change in mean nontreatment acne lesions from the late follicular to the late luteal stage of the menstrual cycle. It was measured as the change in the mean number of inflammatory acne lesions and the mean number of comedones.

Results. A total of 41 subjects enrolled in the study. Any patient who was available for both the late follicular and late luteal phase visits was considered for evaluation of premenstrual flare. In the first month, this amounted to 25 subjects. In the second month, there were 23 subjects. Of the 41 women enrolled, 18 did not complete the protocol for a variety of reasons; the most commonly stated reason was the patient’s unwillingness to leave her acne untreated. Thus, the study had a total of 48 evaluation points.

The mean number of inflammatory acne lesions increased from 9.5 to 11.9 or 25.3 percent, a statistically significant increase (p=0.02). The comedonal lesion count went from 9.2 to 11.1, another statistically significant increase of 21.2 percent (p=0.05) (see Table 2).

This is the first study to quantify what many female patients have long believed: acne flares are significant during the late luteal (premenstrual) phase of the menstrual cycle. In particular, the author found that 63 percent of 25 adult women had more acne during the late luteal phase of the menstrual cycle than during the late follicular phase. The author cites an earlier questionnaire-based study that estimated a 44 percent prevalence of premenstrual acne flares in women aged 20 to 33 years of age who had acne.

Study limitations. This was a small study, and it is unfortunate that 18 of 41 subjects (almost 44%) dropped out over the course of the study. (Two were excluded for irregular menses, two were lost to follow up, and 14 dropped out because they wanted to treat their acne.) However, the study is the first of its kind in that it quantified and objectively measured acne lesions, rather than relying on subjective assessments by the patients. In this particular case, the study’s objective data revealed more dramatic rates than the previous subjective data gathered.

Clinical relevance. Acne flares during the late luteal phase of the menstrual cycle have long been observed by both practicing dermatologists and their patients. Yet there was scant objective data on the phenomenon. This study was the first attempt to quantify acne flares over the course of the menstrual cycle, and this particular study confirms what many of us have “known” all along. The study found a 23.2 percent increase in total acne lesions (25.3% increase in inflammatory acne lesions and a 21.2% in comedones) during the late luteal phase of the menstrual cycle when compared to the late follicular phase. Of the 25 adult women involved in this study, 63 percent flared during the late luteal phase of their periods.

While this article will probably not change the behavior of practicing dermatologists, it does offer sound scientific data for a phenomenon that has long been observed but not thoroughly investigated.

### Table 2: Lesion Counts

<table>
<thead>
<tr>
<th>Inflammatory Comedones</th>
<th>Follicular</th>
<th>Luteal</th>
<th>Percent change</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9.5</td>
<td>11.9</td>
<td>25.3%</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>9.2</td>
<td>11.1</td>
<td>21.2%</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**References**


**Submission Instructions**

Do you have a case you would like to see published in this column? If so, please send a write-up (about 250 words) and a high-resolution image (at least 266 dpi) of the patient’s condition.

Please send materials to Larisa Hubbs, Extens, 83 General Warren Blvd., Suite 100, Malvern, PA 19355 or e-mail them to lhubbs@hmp-communications.com.
NOW YOU CAN
VIEW THE
TREATMENT OF
ACTINIC KERATOSIS
IN A WHOLE NEW LIGHT

A NEW RESPONSE TO
SUN-DISEASED SKIN


3M Pharmaceuticals