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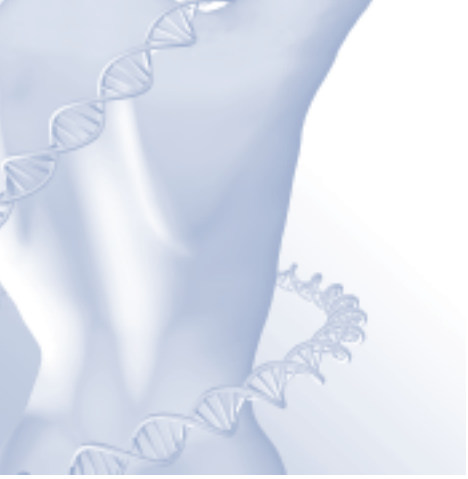
New Methods and Techniques

Supplement

The Management of Skin and Skin Structure Infections: Guidelines for Prophylaxis and Treatment

A Report from a Symposium at the
American Academy of Dermatology Summer Meeting
Chicago, Illinois
July 20-24, 2005



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INTRODUCTION

ORIGINAL ARTICLES

Supported by an educational grant from Medicis Pharmaceutical Corp.

Introduction

Mark S. Nestor MD PhD

The most common skin and skin structure infections (SSSIs) seen by dermatologists are cellulitis, impetigo, and folliculitis. Without prompt antibiotic treatment, these types of infection can lead to skin and skin structure destruction and scarring and eventually to systemic sequelae such as nephritis, carditis, arthritis, septicemia, and death.[1] Among pediatric clinic consultations, up to 17% of dermatologic complaints result from bacterial skin infections.[2]

To treat patients with uncomplicated (u) SSSIs, dermatologists typically initiate empiric antibiotic therapy against the most probable pathogens, *Staphylococcus aureus* and *Streptococcus pyogenes*. Dermatologists must also decide whether to use incision and drainage, whether to obtain a culture, which antibiotic(s) to prescribe, and whether to refer a patient to an infectious disease specialist. They must also consider the risk for community-acquired methicillin-resistant *S. aureus* (MRSA), the risk for complications, and comorbidities.[1] Empiric treatment should take all of the above into account, as well as the possibilities of infection by Gram-negative organisms and potential cross reactivity in penicillin-allergic patients.

To guide primary care physicians in the initial empiric antibiotic treatment of uSSSIs, a panel of dermatology experts convened in a roundtable discussion to develop an algorithm based on the most recent evidence-based data.[1] The algorithm offers guidance in the differential diagnosis of uSSSI and complicated SSSI (cSSSI), initial empiric therapy, and treatment of high-risk patients. The algorithm recommends the use of cephalosporins, penicillinase-resistant penicillins, and β-lactam/β-lactamase inhibitor combinations for initial empiric therapy. Specifically, an extended-spectrum cephalosporin such as cefdinir provides excellent coverage of infections by Gram-positive and common Gram-negative organisms and may be used in patients who have a history of penicillin allergy.

Dermatologists soon found that the specific use of this algorithm was somewhat limited in a variety of clinical situations that frequently occur. A new treatment algorithm was therefore developed and used as the basis for the treatment of a variety of clinical concerns.

A panel of 7 dermatology experts in the treatment of uSSSIs participated in a symposium held in Chicago at the American Academy of Dermatology meeting of July 20-24, 2005. These experts discussed modifications of the current algorithm and the use of the new algorithm (Dirk M. Elston, MD); pharmacokinetic and pharmacodynamic effects, antimicrobial resistance, and MRSA (Thomas R. Fritsche, MD, PhD); updates on treating uSSSIs (Theodore Rosen, MD); preventing and treating perioperative infections (Mary E. Maloney, MD); prophylaxis for and treatment of uSSSIs in laser and cosmetic surgery (Mark S. Nestor, MD, PhD); treatment of uSSSIs in the diabetic patient (Phoebe Rich, MD); and treatment of uSSSIs in pediatric and adolescents (Lawrence A. Schachner, MD).

The content of this supplement is based on the presentations of these experts and the new algorithm.

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IMPORTANCE OF UNDERSTANDING PHARMACOKINETIC/PHARMACODYNAMIC PRINCIPLES IN THE EMERGENCE OF RESISTANCES, INCLUDING COMMUNITY-ASSOCIATED *STAPHYLOCOCCUS AUREUS*

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Abstract
Pharmacologic parameters have been defined to predict efficacy in antimicrobial selection for the treatment of uncomplicated skin and skin structure infections (uSSSIs). Pharmacokinetics (PK) and pharmacodynamics (PD) are the bases for describing the *in vivo* behavior of antimicrobial agents. T>MIC is the duration of time that a pathogen is exposed to concentrations of antimicrobial agents that exceed the MIC of that particular organism. For antimicrobials with time-dependent activity (eg, penicillin and cephalosporins), the T>MIC needed to eradicate bacteria is generally 40% to 50% of the dosing interval. The most frequently prescribed oral antimicrobials for uSSSI are oral cephalosporins, amoxicillin/clavulanic acid, macrolides, anti-staphylococcal penicillins, and fluoroquinolones. The selected oral agent should display a broad spectrum of antimicrobial coverage, be able to be dosed once, or at most twice, a day, and show high levels of target attainment (≥90%) for eradicating the key pathogens associated with uSSSI. The recent emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the community setting (CA-MRSA) is especially troublesome in that oral cephalosporins (and all other β-lactam agents) are contraindicated, requiring alternative therapeutic approaches. While a common cause of cutaneous disease, including abscess formation, CA-MRSA has caused life-threatening necrotizing fasciitis and pneumonia. Treatment of abscesses produced by this pathogen consists of incision and drainage followed by an appropriate oral antimicrobial, based upon knowledge on the local resistance prevalence rates or as directed by culture and susceptibility testing.

Introduction

When penicillin was introduced in 1942, dosage schedules of antibiotics were based upon animal infection models and empirical results obtained on patients. It was not until 1950 that Eagle and colleagues[1] established the basis for pharmacologic indices now used to compare activities of different antimicrobial agents and develop optimal dosing regimens.[2]

Eagle and colleagues noticed that in animals that had been given penicillin, killing of pathogens stopped when the serum concentration of penicillin dropped to levels below the minimum inhibitory concentration (MIC). They also noted that penicillin's therapeutic effects (on a specific dosage schedule) were related to how long the drug concentration remained above the bactericidal level, and that cure rates of animals did not increase with penicillin concentrations above this "effective" level. In other words, increasing the penicillin concentration above the therapeutic level did not produce greater efficacy. These observations laid the foundation for the understanding that T>MIC, the cumulative percentage of time over the dosing interval that the drug concentration exceeded MIC of the pathogen, is the key target parameter.[2-4]

For antimicrobials with time-dependent activity (eg, penicillin and cephalosporins), the T>MIC needed to eradicate bacteria is generally 40% to 50% of the dosing interval.[5,6] For example, the relationship between efficacy and T>MIC has been evaluated in patients with acute otitis media caused by *Hemophilus influenzae* and *Streptococcus pneumoniae*. Cure rates of 80% to 85% were regularly achieved when T>MIC values for β-lactams were 40% to 50% of the dosing interval for β-lactams.[7,8]

The MIC is defined as the lowest concentration of antimicrobial agent that inhibits the growth of pathogen.[9] It is an *in vitro* measurement of which antimicrobials display the greatest activity against a target pathogen. The MIC_{50} is the lowest concentration of drug that inhibits growth of one-half of isolates tested, whereas the MIC_{90} is the lowest concentration that inhibits 90% of isolates tested.[4] MIC has limited usefulness because it is an *in vitro* test. Less frequently used and applied to more serious or intractable deep-seated infections, the minimum bactericidal concentration (MBC) is an *in vitro* test that is defined as the lowest drug concentration reducing the viable bacterial count by 99.9% or more over 24 hours compared to the initial inoculum.

To obtain clinically useful information, additional pharmacologic indices have been defined to describe antimicrobial efficacy. Pharmacokinetics (PK) and pharmacodynamics (PD) are the bases for describing the *in vivo* drug behavior. PK refers to the absorption, distribution, and elimination of antimicrobial agents; it describes the concentration-time profile of drugs in the patient. The peak serum concentration (C_{max}) of a drug is a PK parameter. PD describes the relationship

between antimicrobial effect (MIC) and the drug concentrations (PK parameters).[6] The product of drug concentration and time of exposure to the drug over the dosing interval is expressed as the AUC (area under the curve). C_{max}/MIC and AUC/MIC are useful indices for determining efficacy of concentration-dependent (as opposed to time-dependent) antimicrobial agents (eg, macrolides and fluoroquinolones). Target T>MIC or AUC/MIC values necessary for optimal therapy differ by pathogen species (shorter for Gram-positive organisms and longer for Gram-negative organisms).

The purposes of this overview are to (1) show how PK/PD indices are used to select appropriate antimicrobials and dosing regimens that will optimize outcomes of patients with uncomplicated skin and skin structure infections (uSSSIs) and (2) present an update on the recent emergence of infections produced by community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA).

Treatment of uSSSI

The pathogens most commonly associated with uSSSIs are Gram-positive pathogens such as *S. aureus*, coagulase-negative staphylococci (*S. epidermidis*), *Streptococcus pyogenes* (Group A), *Streptococcus agalactiae* (Group B), other β-hemolytic streptococci (Groups C, F, G), and enteric bacilli such as *Escherichia coli* and *Klebsiella* species. The most frequently prescribed oral antimicrobials for uSSSI are oral cephalosporins, amoxicillin/clavulanic acid, macrolides, antistaphylococcal penicillins, and fluoroquinolones. When selecting an antimicrobial agent, physicians should consider PK, PD, antimicrobial spectrum and potency, resistance patterns, drug safety profile, and probability of patient compliance. Compliance is heavily influenced by factors such as drug tolerability and dosing schedule.

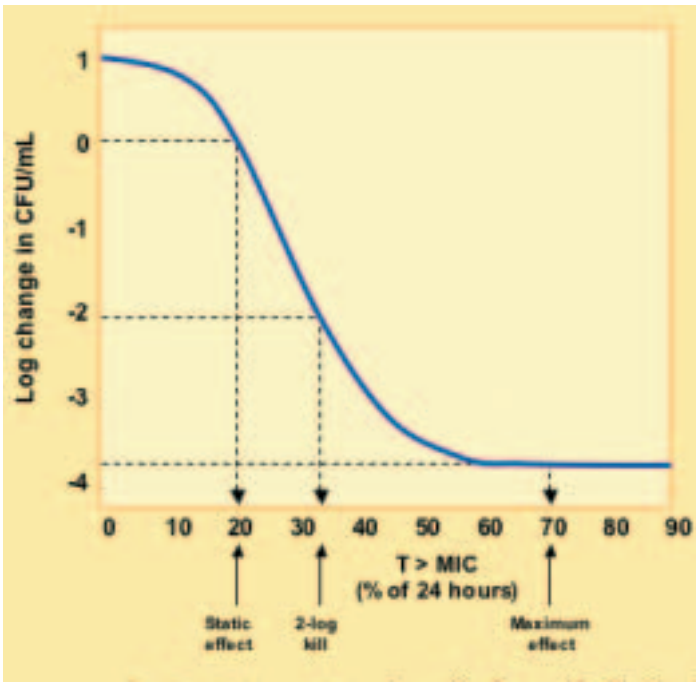
Pharmacokinetic/Pharmacodynamic (PK/PD) Considerations

The relationship between T>MIC and organism eradication is shown in Figure 1. Static inhibition occurs at shorter T>MIC (eg, 20% of the dosing interval) compared to maximal killing which usually requires approximately 50% of the dosing interval. For cephalosporins used in the outpatient setting, T>MIC values ranging from 20% to 30% are associated with optimal outcomes in the treatment of uSSSIs because of the preponderance of Gram-positive isolates and the unnecessary requirements for maximal, bactericidal actions.

Categorical breakpoints (susceptible, intermediate, and resistant) are used when testing bacterial isolates to characterize the activity of antimicrobial agents that may be considered for use against a demonstrated or presumed infecting pathogen. These *in vitro* criteria have been promulgated by professional organizations including the US Food and Drug Administration, the Clinical Laboratory Standards Institute (CLSI; formerly the National Committee on Clinical Laboratory Standards), and various European national standards organizations such as the European Society of Clinical Microbiology and Infectious Diseases (EUCAST). For a given antimicrobial agent, a pathogen is deemed susceptible when the MIC is at or below a designated breakpoint concentration and resistant when the MIC is above another breakpoint for the designated antimicrobial agent and bacterial species.[9]

Breakpoints based upon characteristics of PK and PD (PK/PD breakpoints) can be used to reliably predict antimicrobial efficacy by integrating pharmacologic and microbiologic data. Use of such PK/PD breakpoints can, for example, predict efficacy of an agent such as amoxicillin/clavulanate against enteric bacilli, *S. aureus*, and *S. pyogenes* with usual twice-daily dosing (Figure 2). Amoxicillin/clavulanate will predictably display activity against *S. pyogenes* because the MIC_{90} (0.06 µg/mL) for this species is below the PK/PD breakpoint of 2 µg/mL where 90% of infections would respond to the usually prescribed dose. Coverage of *S. aureus* is less optimal (for methicillin-susceptible strains only) because the MIC_{90} of this pathogen is higher and the antimicrobial is present at concentrations above the PK/PD breakpoint for a smaller, suboptimal percentage of the dosing interval. Enteric bacilli are poorly covered because the peak drug concentration does not reach the MIC_{90} for these organisms.

Figure 1. Graphical representation of the relationship between the β-lactam T>MIC and killing of a potential pathogen. At T>MIC = 20%, growth has stopped and there is little change in the bacterial population; at T>MIC of approximately 30% to 40%, a 2-log kill (99% of bacterial cells) is achieved. Increasing T>MIC beyond 70% (maximum effect) produces no additional benefit.



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Comparison of the PK/PD relationships for two dosing regimens of cefdinir (an oral suspension) in children demonstrates consistently high levels of target attainment (T>MIC at 20% to 30%; Figure 3). More than 90% of key pathogen isolates associated with uSSSI can be expected to respond to cefdinir.

Bacterial Resistance Among SSSI Pathogens

Community-acquired uSSSIs are rarely cultured by primary care physicians. Even when they are, orally administered antimicrobials—cephalosporins, new macrolides, and fluoroquinolones—are seldom tested *in vitro* against SSSI-associated pathogens. As a result, physicians are unaware of prevailing resistance rates and may prescribe inappropriate empiric antimicrobial therapy that further selects for bacterial resistance. If available, local susceptibility data from strains of uSSSI are helpful in selecting agents for empiric therapy. As resistance rates change over time, utilization of culture and susceptibility testing should be routinely performed.

Two emerging resistance problems are currently altering prescribing habits for uSSSI. Resistance to macrolides (erythromycin, azithromycin, clarithromycin) among β-hemolytic (10% to 30%) or viridans group streptococci (8%) is achieving a threshold whereby adequate coverage can no longer be reliably predicted. Likewise, the emergence of CA-MRSA, which can also display resistance to macrolides and other commonly prescribed drug classes such as the fluoroquinolones, is of even greater clinical concern.[10]

Characterization and Treatment of CA-MRSA

While the occurrence of MRSA in the hospital environment has been known for decades, the emergence of CA-MRSA is a recent phenomenon that is now being documented worldwide.[11] Risk factors include intravenous drug use, previous use of antimicrobials, diabetes, chronic skin disease, and malignancy. Persons without these risk factors are, however, found to be commonly infected. Outbreaks have occurred in a variety of settings in which individuals are in close physical contact—universities, schools, daycare centers, cruise ships, athletic groups, and prisons.[12] A careful patient history to exclude previous health care contacts helps to differentiate between community-associated and hospital-acquired MRSA (which tend to be more multidrug-resistant).

The genetic backgrounds of CA-MRSA strains from different parts of the world can be unique to their respective regions.[13] Genetic features common to CA-MRSA include the Panton-Valentine leukocidin (PVL) gene, the staphylococcal-cassette-chromosome *mec* type IVa (SCC*mec*IVa) gene, plus

Figure 2. Use of PK/PD to predict efficacy of amoxicillin/clavulanate against streptococci, staphylococci and enteric bacilli. The MIC_{90} for enteric bacilli exceeds achievable serum concentrations and such strains would not predictably be inhibited by this agent.

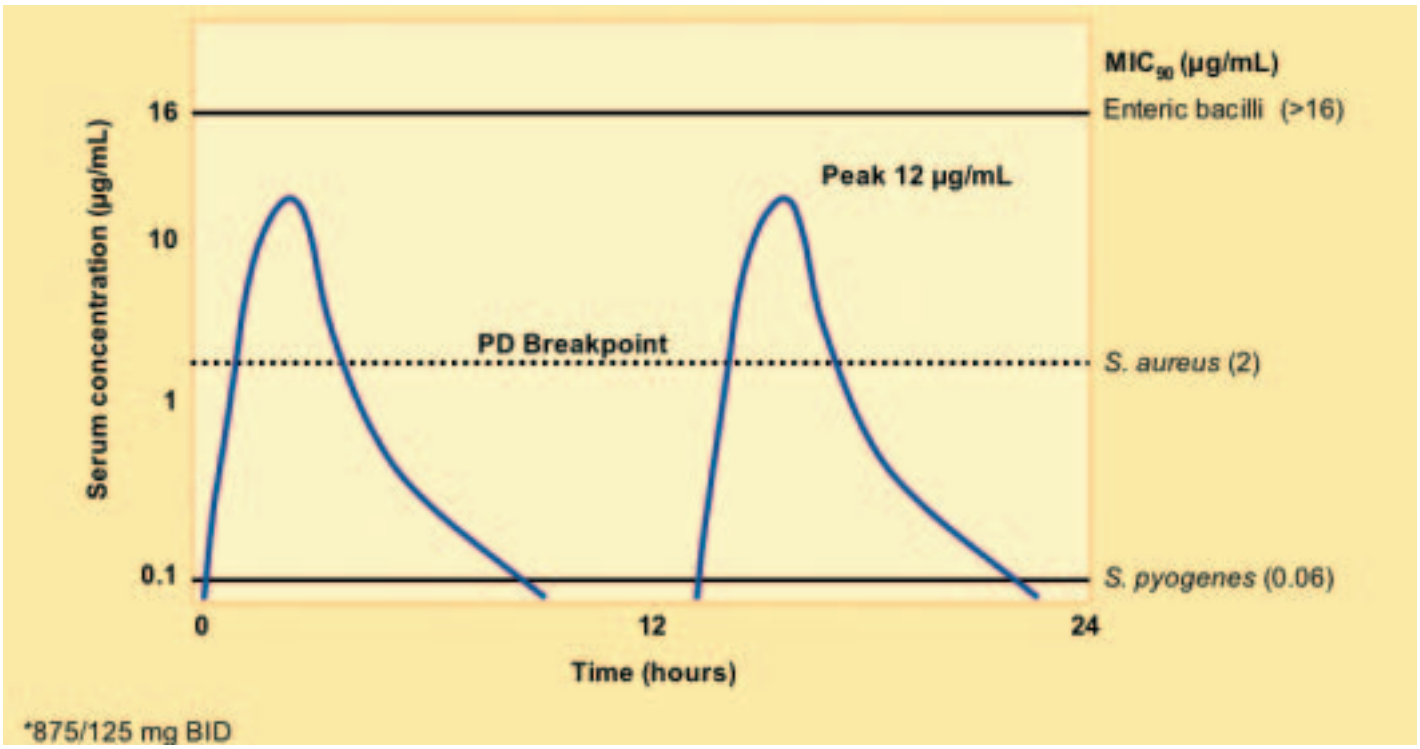

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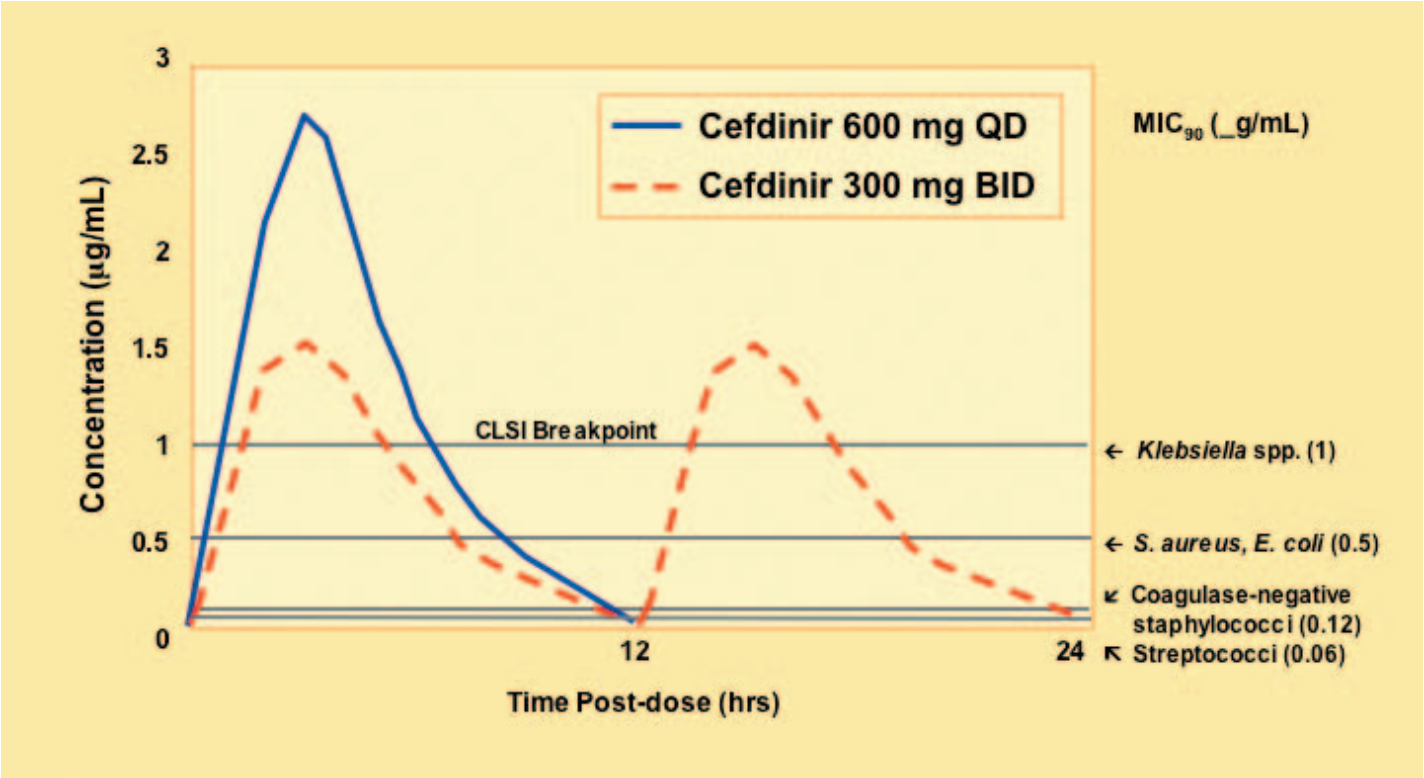
Figure 3. The PK/PD relationships for cefdinir at two dosing intervals in children over 24 hours against selected pathogens. Target attainment is predictably reached for the usual pathogens.



(Data on file, Abbott Laboratories)

distinct components of local endemic/epidemic clones.[14] PVL is a cytotoxin that destroys leucocytes and causes tissue necrosis; this cytotoxin has been detected in a small percentage (<5%) of *S. aureus* strains overall, but is predominant in some CA-MRSA clones, especially those that produce infections with poor outcomes.[15]

CA-MRSA is usually associated with cutaneous infections—furuncles (40%), carbuncles (28%), abscess (14%), and folliculitis (5%).[16] These organisms are often resistant *in vitro* to both macrolide and β-lactam agents, but not other antimicrobial classes.[17,18] These clones are recognized, however, to also produce life-threatening fasciitis and necrotizing pneumonia.[19,20] Treatment of cutaneous CA-MRSA abscess-related disease consists primarily of incision and drainage followed by administration of oral antimicrobials.

An example of one such outbreak was reported in 2005, where skin abscesses caused by CA-MRSA were observed among members of a professional football team and determined to have spread to members of an opposing team during competitive play.[17] Eight cutaneous infections—all developed at turf-abrasions sites—were found among five of the 58 players (9%). *S. aureus* isolates were found to contain the genes for PVL and SCC*mec*IVa resistance, and were found to be clonal type USA300-0114 (a wide-spread clone) when analyzed by pulsed-field gel electrophoresis (PFGE). Infections resolved after abscesses were drained and players were given oral antimicrobial therapy. Unlike MRSA strains found in health care settings, this community-associated clone, and others like it, caused skin infection in healthy individuals, was susceptible to most commonly used agents other than β-lactams and macrolides, and displayed typical genotypic characteristics.

Conclusions

Advancements in our understanding of PK/PD parameters now permit physicians to better predict efficacy of antimicrobial agents when treating the usual pathogens associated with uSSSIs. For oral cephalosporins used in the outpatient setting, T>MIC values ranging from 20% to 30% are associated with optimal outcomes in the treatment of uSSSIs because of the preponderance of Gram-positive isolates and the unnecessary requirements for maximal bactericidal PD action. However, emergence of resistance to many of the commonly utilized classes of agents (β-lactams, macrolides, and fluoroquinolones) is changing our perception of empiric therapeutic approaches. The recommendation has recently been made to consider MRSA as a potential pathogen wherever *S. aureus* infections occur in the community setting,[21] necessitating the need for routine incorporation of culture and susceptibility testing into the initial outpatient visit. Because CA-MRSA

are to be considered resistant to β-lactams and usually macrolides, incision and drainage followed by appropriate oral antimicrobic therapy (as directed by *in vitro* testing) can be expected to resolve most uncomplicated cutaneous infections.

Disclosure: Drs. Fritsche and Jones are consultants to Abbott Laboratories.

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UPDATE ON TREATING UNCOMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS

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Abstract
Dermatologists treat a variety of uncomplicated skin and skin structure infections (uSSSIs) such as folliculitis, impetigo, erysipelas, cellulitis, furuncles, carbuncles, and non-perirectal abscesses. Most uSSSIs are caused by *Staphylococcus aureus* and *Streptococcus pyogenes*. The new extended-spectrum cephalosporins (cefdinir, cefpodoxime) offer efficacy against most Gram-positive and Gram-negative pathogens.

Despite recently published guidelines, many physicians do not prescribe cephalosporins for uSSSIs out of concern that these agents will produce a hypersensitivity reaction in patients allergic to penicillin. Although the rate of cephalosporin reaction in penicillin-allergic patients is often quoted as up to 10%, this rate does not take into account the 1% to 3% risk for allergy to cephalosporin alone and the nonspecific increased risk of penicillin-allergic patients to develop hypersensitivity to other drugs. When these additional risks are considered, the likelihood of a reaction in known penicillin-allergic patients, especially to most third-generation and extended spectrum cephalosporins, becomes less than 1%.

Cephalosporins with side chains unlike those of penicillin or ampicillin side chains are less likely to result in an allergic reaction in penicillin or ampicillin-allergic patients than cephalosporins with similar side chains. Although both cefdinir and cefpodoxime are considered to carry a very low risk of cross reactivity with penicillin or ampicillin, the former demonstrates better activity against *S. aureus*. Among the late-generation cephalosporins, cefdinir is the most potent oral agent when tested against oxacillin-susceptible staphylococci, 4- to16-fold more active than cefprozil and cephalexin, respectively.

Introduction

Skin and skin structure infections (SSSIs) comprise a large component of cutaneous diseases treated by dermatologists in community practice. SSSIs are treated according to whether they are uncomplicated or complicated.[1] Uncomplicated infections include folliculitis, impetigo, erysipelas, cellulitis, furuncles, carbuncles, and non-perirectal abscesses. Complicated infections involve deeper tissue as well as skin; include infected ulcers and infected burns; may include systemic confounders such as neutropenia and immunosuppression; and may occur at high-risk sites (eg, near the anus).

In both pediatric and adult patients, most uncomplicated skin and skin structure infections (uSSSIs) are caused by *Staphylococcus aureus* and *Streptococcus pyogenes*.[2] *S. aureus* is found in 85% and *S. pyogenes* in 30% of lesions associated with impetigo, the most common superficial skin infection in children.[3,4] Due to the high prevalence of these organisms in pyogenic skin infections, empiric therapy is usually directed against them unless the infection is known to be caused by another pathogen.

When treating bacterial uSSSIs, a variety of antibiotic agents are available from which to choose (Table 1). Efficacy and safety are prime factors, but antibiotic resistance, potential litigation due to unexpected adverse drug reactions, and cost must also be considered. Choices are also based on spectrum of activity, pharmacologic properties, and the potential for complicating pregnancy discovered after antibiotic administration.[5]

Categorized by generation, cephalosporins are the most widely prescribed class of orally administered antibiotics for SSSIs. First-generation members (cephalexin, cefadroxil) have good activity against *S. pyogenes* and methicillin-susceptible *S. aureus* (MSSA) and are given once or four times daily. Second-generation members (cefaclor, cefuroxime, cefprozil) have expanded activity against Gram-negative pathogens while retaining good activity against Gram-positive organisms. Their longer half-lives permit less frequent (twice daily) dosing. Third-generation cephalosporins

Table 1. Antibiotics for Uncomplicated Skin and Skin Structure Infections.

- Cephalosporins
- Penicillins
- Macrolides
- Tetracyclines
- Fluoroquinolones
- Lincosamides
- Trimethoprim/sulfamethoxazole

(cefixime, ceftibuten, cefditoren) are effective against Gram-negative pathogens but less effective against Gram-positive organisms when compared with earlier cephalosporins. They are given once or twice daily.

The new extended-spectrum agents (cefdinir, cefpodoxime) offer advantages of broader activity spectrum, showing efficacy against both common Gram-positive and Gram-negative pathogens. These agents are administered twice daily.

The American Academy of Pediatrics (AAP) has issued evidence-based practice guidelines for the use of cephalosporins for certain indications in patients allergic to penicillin. These guidelines were formulated with the assumption that the frequently quoted rates of cross-sensitivity to cephalosporins among patients allergic to penicillin (8%-18%) require revision.[6] The AAP guidelines support (1) the use of cefuroxime, cefpodoxime, and cefdinir in the management of acute bacterial sinusitis for patients with allergy to penicillin, providing the allergic reaction is not severe,[7] and (2) the use of cefuroxime, cefpodoxime, and cefdinir for patients with "non-type I allergy," and parenteral ceftriaxone as a treatment alternative.[8] The types of immunopathologic drug reactions are shown in Table 2.[6,9] Type I reactions may be acutely life threatening, while the others are not. All four types have occurred with penicillin and penicillin derviatives.[10]

Despite these updated guidelines, many physicians hesitate to prescribe cephalosporins due to confusion regarding the definition of a reaction due specifically to penicillin allergy.[6]

This report explores the issue of prescribing cephalosporins to patients with allergies to penicillin, provides updated information on the potency and spectrum of various antibiotics used to treat community-acquired skin and soft-tissue infections (CA-SSTIs), and summarizes the sensitivities of various antibiotics used to treat SSSIs.

Cephalosporins and Penicillin Allergy

When a known penicillin-sensitive patient has an allergic reaction after receiving a cephalosporin, the reaction may not be due to the established allergy to penicillin; it may be caused by an allergy to cephalosporin, which occurs in 1% to 3% of patients regardless of penicillin-allergy status. In addition, penicillin-allergic patients have an increased risk for allergic reaction to *any* drug. The reported rate of cephalosporin reaction in penicillin-allergic patients is 0.7% to 8.1%,[11,12] but the actual rate is much lower when the generalized risks enumerated above are considered. First- and second-generation cephalosporins have approximately 2% risk and third-generation cephalosporins carry about a 0.6% risk.[6] A detailed review of data on the relationship between penicillin allergy and cephalosporins showed that most penicillin-allergic patients could be given cephalosporin antibiotics safely.[13] This is especially true if one pre-selects the cephalosporin based upon chemical structural considerations (see below).

The Role of Side Chains

Cephalosporins and penicillin are both of low molecular weight, are highly substituted, and possess a ß-lactam ring.[14] Representative structures are shown in Figure 1. As the primary antigenic determinant, the ß-lactam ring is responsible for antimicrobial activity.[14,15] However, it is not this ring structure which is primarily the determinant of hypersensitivity, but rather the side chains. The cross reactivity between penicillin or ampicillin and cephalosporins with a different side chain appears to be less than that between penicillin/ampicillin and cephalosporins with similar side chains.[15]

Table 2. Types of Allergic Reactions and Clinical Characteristics.

Type	Characteristics
IgE-mediated (type 1)	Onset <1 hour after exposure
	Immediate hypersensitivity
	Includes urticaria, hypotension, angioedema, anaphylaxis
	Fatal in 1 per 50,000-100,000 persons
IgG & complement (type II)	Cytotoxic reaction
	Onset < 72 hours after exposure
	Hemolytic anemia, thrombocytopenia, neutropenia
IgG or IgM immune complexes (type III)	Onset > 72 hours after exposure
	Serum sickness, nephritis, pneumonitis, morbilliform rash
T-lymphocytes (type IV)	Onset 48-72+ hours after exposure
	Delayed hypersensitivity
	Contact dermatitis

Ig = immunoglobulin

Therefore, it is important to recognize which cephalosporins "resemble" penicillin or ampicillin in side-chain structure to make logical decisions about potential problems and permissible drug usage despite a history of penicillin allergy.

Figures 2 to 5 illustrate the role of side chains in cross reactivity between penicillins and cephalosporins. The safety of prescribing cephalosporins with side chains dissimilar to those of penicillin is supported by the study of Novalbos and colleagues.[15] In this study, 41 penicillin-allergic patients were challenged with three cephalosporins (cephazoline, cefuroxime, and ceftriaxone) with a side chain unlike that of the specific penicillin derivative that induced the known allergy. When therapeutic doses of the aforementioned cephalosporins were given to these patients, no ill affects were observed. These results are consistent with those of other studies[13,16,17] that suggest markedly reduced cross-reactivity between penicillin and cephalosporins with dissimilar side chains.

Cephalosporins with side chains that are structurally similar to penicillin include cephaloridine, cephalothin, and cefoxitin. The former two agents are no longer available in the US for human use, and thus have no clinical relevance. By contrast, many widely available cephalosporins are structurally similar to, and therefore potentially cross-reactive with, ampicillin (and amoxicillin). Such drugs include cefaclor, cephalexin, cefprozil, cephradine, and cefadroxil. Notably absent from both penicillin and ampicillin structural analogues are the following, presumed safer agents: cefdinir, cefpodoxime, cefditoren, and cefuroxime (oral), as well as ceftriaxone (parenteral).

Clinical Basis for Selecting Antibiotics

A comprehensive study of the comparative potencies and spectra of cefdinir with those of various antibiotics used to treat community-acquired SSSIs has been reported.[18] The data from this study were used to establish a clinical basis for selecting empiric antibiotic therapy for the treatment of uSSSIs.[1] The data are shown in Tables 3 and 4.

Among cephalosporins, cefdinir was the most potent oral cephalosporin (MIC_{90} 0.5 µg/mL) tested against oxacillin-susceptible staphylococci, 4- to 16-fold more active than cefprozil and cephalexin, respectively. Cefuroxime (MIC90 4 µg/mL) and amoxicillin/clavulanate (MIC_{90} 2 µg/ml) also showed excellent activity. Cefpodoxime was notably less effective *in vitro* against pathogenic staphylococci than cefdinir. With the exceptions of erythromycin and ciprofloxacin, all Group A and B streptococci were 100% susceptible to all tested agents.

Against *S. pyogenes*, cefdinir (MIC_{90} ≤0.03 µg/mL) and cefpodoxime (MIC_{90} ≤0.03 µg/mL) were the most active cephalosporins. Cefuroxime (MIC_{90} ≤0.06 µg/mL) and amoxicillin clavulanate (MIC_{90} ≤0.06 µg/mL) also showed excellent activity.

Figure 1. Structures of Penicillin Prototype and Cephalosporin Showing the β-Lactam Ring Common to both Structures.

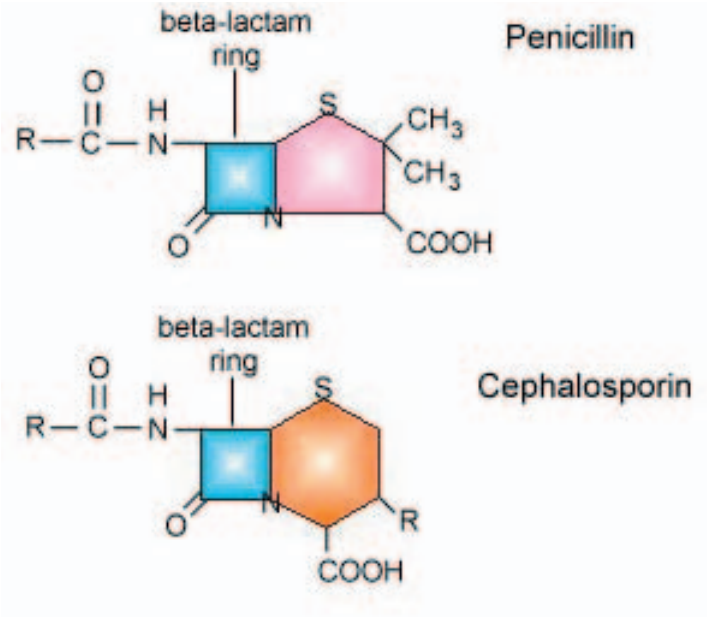


Figure 2. The Difference in Side Chains of Penicillin G (Gray) and Ampicillin (Blue).

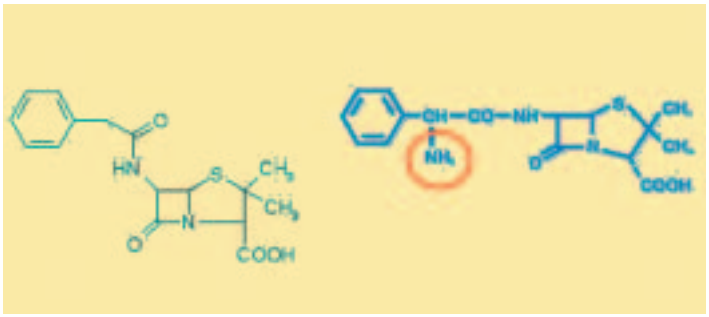


Figure 3. Because the Side Chains of Cefoxitin and Cephalothin are Similar to the Side Chain of Penicillin G, Cross Reactivity is Highly Probable.

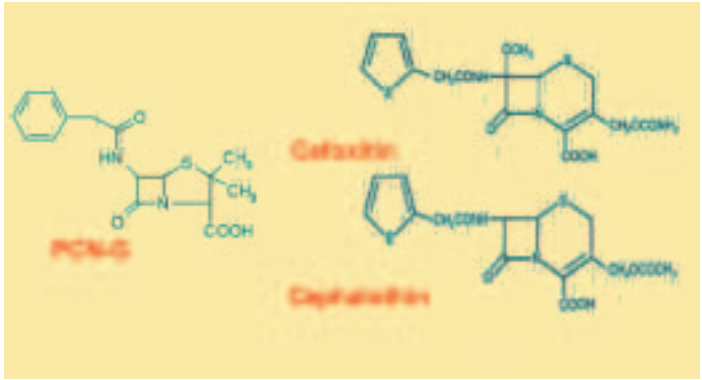


Figure 4. The Side Chains of Cefaclor and Cephalexin are Similar to the Side Chain of Ampicillin, so Cross Reactivity is Likely to Occur.

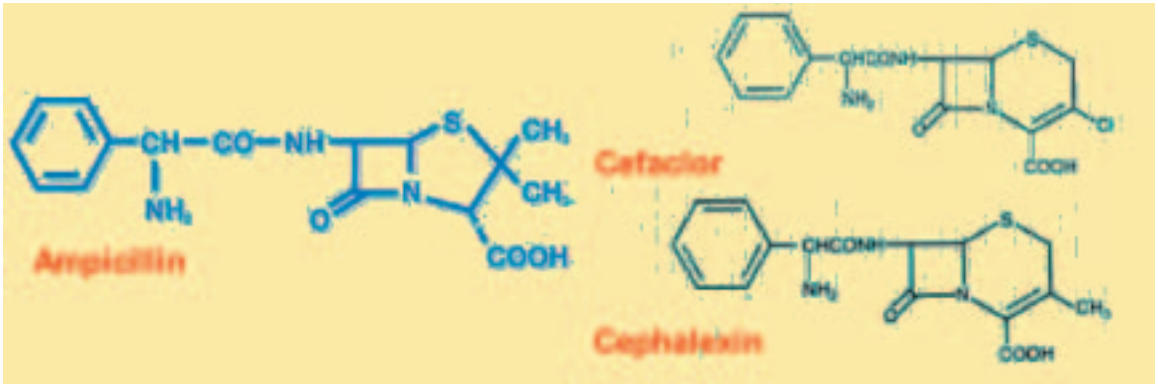
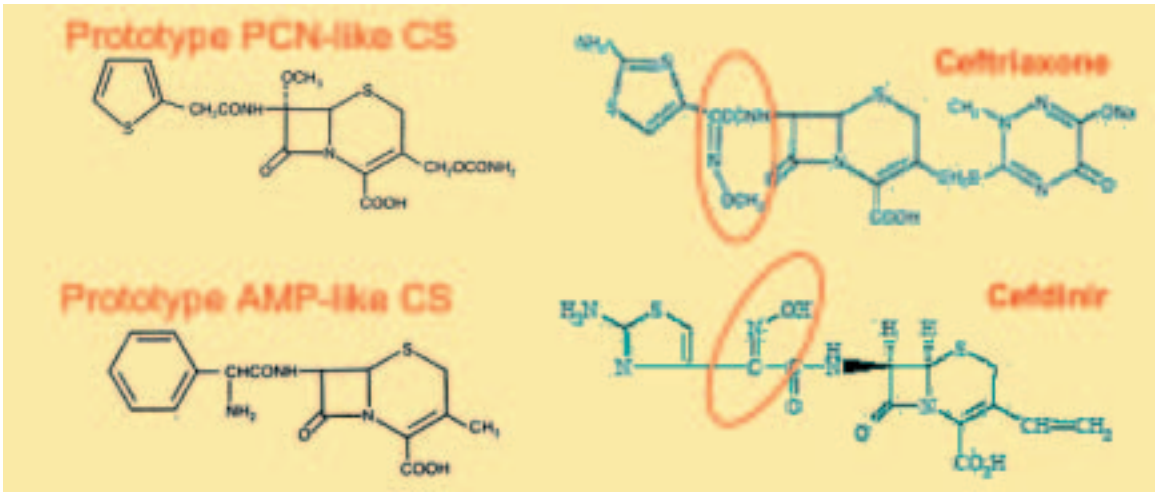


Figure 5. The Side Chains of Ceftriaxone and Cefdinir are not Similar to the Side Chain of a Prototype Penicillin or Ampicillin, so Cross Reactivity is Unlikely.



In some situations, one may encounter Gram-negative pathogens as etiologic for uSSSIs, particularly *Escherichia coli* and *Klebsiella* species. Against these most common Gram-negative etiologies of uSSSIs, cefdinir (MIC_{90} 0.5 µg/mL) and cefpodoxime (MIC_{90} 0.5 µg/mL) are the most active cephalosporins, while cefuroxime is considerably less effective against these microbes.

Taking these recent microbiological data together, one might attempt to identify a cephalosporin which is: (1) easy to administer (orally), (2) considered safe to use in allegedly penicillin or ampicillin allergic patients, (3) expected to be effective against the Gram-positive organisms which typically cause uSSSIs, and (4) expected to be effective against the few Gram-negative organisms which may cause or confound uSSSIs. Cefdinir and cefditoren seem the logical candidates to fulfill these criteria based upon current MIC patterns and our better understanding of the role of chemical structure in penicillin cross-reactivity. It should be noted that the latter drug is not indicated in patients less than 12 years of age.

Updated Uses and Limitations of Antibiotic Classes

Penicillins

S. pyogenes is generally sensitive to penicillins. *S. aureus* is no longer routinely sensitive due to widespread resistance. β-Lactamase-stable penicillins exhibit good anti-staphylococcal activity and good tissue penetration, but are not effective against Gram-negative organisms. Most penicillins and penicillin derivatives are given twice or four times a day.

Macrolides

Erythromycin is less useful because of selected properties, including frequent gastrointestinal (GI) intolerance, short half-life, increasing resistance of organisms associated with uSSSI, and lack of utility if Gram-negative pathogens cause or complicate the infection. Clarithromycin and azithromycin have fewer GI side effects and longer half-lives but activities against staphylococci and streptococci are largely similar to erythromycin. Cross-resistance will limit utility.[19]

Lincosamides

Lincosamides, clindamycin in particular, have good activity against *S. pyogenes* and MSSA. They are active against many

Table 3. Antimicrobial Potency and Spectrum Results.

Organism (no. tested)	MIC (µg/mL) 50%	MIC (µg/mL) 90%	% by category Susceptible	% by category Resistant
S. aureus (242)				
Cefdinir	0.5	0.5	99.6	0.0
Cephalexin	4	8	93.8*	-
Cefprozil	1	2	100.0	0.0
Cefuroxime	2	4	100.0	0.0
Cefpodoxime	4	4	43.4	0.8
Amoxicillin/clavulanate	1	2	99.6	0.4
Ciprofloxacin	0.25	0.5	95.5	4.5
Levofloxacin	0.12	0.25	96.3	2.9
Trimethoprim/sulfa	≤0.5	≤0.5	98.8	1.2
Erythromycin	0.25	>8	78.5	21.1
S. pyogenes (57)				
Cefdinir	≤0.03	≤0.03	100.0	0.0
Cephalexin	1	1	100.0*	-
Cefprozil	≤0.12	≤0.12	100.0	0.0
Cefuroxime	≤0.06	≤0.06	100.0	0.0
Cefpodoxime	≤0.03	≤0.03	100.0	0.0
Amoxicillin/clavulanate	≤0.06	≤0.06	100.0	0.0
Ciprofloxacin	0.5	1	-	-
Levofloxacin	≤0.5	1	100.0	0.0
Trimethoprim/sulfa	≤0.5	≤0.5	100.0	0.0
Erythromycin	≤0.25	1	87.7	10.6
Klebsiella spp (21)				
Cefdinir	0.12	1	95.2	4.8
Cephalexin	8	16	81.0	-
Cefprozil	2	8	90.5	9.5
Cefuroxime	4	>8	66.7	14.3
Cefpodoxime	0.12	1	95.2	4.8
Escherichia coli (21)				
Cefdinir	0.25	0.5	95.2	4.8
Cephalexin	8	32	66.7	-
Cefprozil	2	4	90.5	9.5
Cefuroxime	4	8	57.1	42.9
Cefpodoxime	0.25	0.5	95.2	4.8

(Adapted with permission from: Sader HS, Streit JM, Fritsche TR, Jones RN. Potency and spectrum reevaluation of cefdinir tested against pathogens causing skin and soft tissue infections: a sample of North American isolates. *Diagn Microbiol Infect Dis*. 2004;49:283-287.)

Table 4. Cefdinir Potency and Spectrum Results.

Organism (no. tested)	MIC (µg/mL) 50%	MIC (µg/mL) 90%	% by category Susceptible	% by category Resistant
CoNS (21)a	0.06	0.12(4)b	100.0	0.0
S. agalactiae (28)	0.06	0.06(4)	100.0	0.0
viridans grp strep. (25)	0.25	2(16)	<c	-
E. coli (21)	0.25	0.5(32)	95.2	4.8
Klebsiella spp. (21)	0.12	1(16)	95.2	4.8

a CoNS = coagulase-negative staphylococci, oxacillin-susceptible strains only.
b Cephalexin MIC_{90} in parenthesis.
c No criteria by NCCLS (2004).

(Adapted with permission from: Sader HS, Streit JM, Fritsche TR, Jones RN. Potency and spectrum reevaluation of cefdinir tested against pathogens causing skin and soft tissue infections: a sample of North American isolates. *Diagn Microbiol Infect Dis*. 2004;49:283-287.)

community-acquired MRSA strains. A resistance to erythromycin may signal inducible resistance to clindamycin. There is, however, an increased risk of gastrointestinal overgrowth of *Clostridium difficile*, which is associated with pseudomembranous colitis. Although almost any antibiotic can induce pseudomembranous colitis, it appears that clindamycin is particularly likely to cause this severe adverse event. Lincosamides are given twice or four times daily.[19]

Tetracyclines

Tetracycline, doxycycline, and minocycline have also been studied in the management of uSSSIs. Some resistance exists to all three variations. Minocycline covers some MRSA, for example. However, MRSA susceptibility to minocycline may vary from locale to locale, and it is imperative for the clinician to be familiar with resistance patterns inherent to his or her region. Timing is an issue, as both food and cationic minerals may bind tetracyclines. There is a risk of GI intolerance and yeast infections, as well as some concern about administration to a female of child-bearing potential who might become (or might be) pregnant. Studies and clinical experience also suggest variable degrees of photosensitivity; the latter is most severe with the parent molecule (tetracycline) and least severe with minocycline. Doxycycline induces a dose-dependent photosensitivity (none at 40 mg/day and increasing photosensitivity up to the standard 100 mg twice-daily dose).

Fluoroquinolones

Despite a long half-life and efficacy comparable to ß-lactams for erysipelas, cellulitis, impetigo, surgical wounds, and diabetic foot infections, fluoroquinolones should be reserved as alternatives to ß-lactams. Due to widespread use, resistance among staphylococci, streptococci, and Gram-negative bacilli is increasing.[20] MRSA develops rapid resistance to fluoroquinolones, and for this reason this class has not proven satisfactory for this indication.[21] Animal data suggest some degree of fetal risk should drugs of this class be inadvertently given to a pregnant female. Agitation, nightmares, and insomnia also may rarely complicate fluoroquinolone administration.

Trimethoprim/Sulfamethoxazole

This combination is effective against CA-MRSA but resistance occurs among staphylococci. There is also significant risk of severe hypersensitivity reactions such as erythema multiforme major and toxic epidermal necrolysis. For this reason, this agent is not a first-line therapy for most uSSSIs. Photosensitivity has occurred in rare cases. Trimethoprim/sulfamethoxazole continues as a popular choice for CA-MRSA, however, as most strains will be susceptible throughout the US.

Conclusion

The safety of treating penicillin-allergic patients with cephalosporins with side chains not similar to those of penicillin is supported by numerous studies, as is the superior potency, broad spectrum, and tolerability of later-generation agents (such as cefdinir) in the treatment of uSSSIs. While other classes of antibiotics may be effective, they all manifest some suboptimal properties. Thus, cephalosporins remain an excellent choice for the empiric therapy of most uSSSIs in both adults and children.

Disclosure: Dr. Rosen is a member of the Speakers Bureau of Abbott Laboratories.

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OPTIMAL ANTIBACTERIAL TREATMENT OF UNCOMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS: APPLYING A NOVEL TREATMENT ALGORITHM

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Abstract
Incision and drainage combined with antibiotic therapies form the backbone of managing uncomplicated skin and skin structure infections (uSSSIs). An algorithm has been developed to guide the treatment of uSSSIs in the primary care setting in situations where initial empiric therapy is appropriate. This includes instances when a culture is taken, but it is deemed appropriate to begin an antibiotic empirically pending the results of the culture. The panel that developed the algorithm was chaired by Dr. Richard Scher of Columbia University and included thought leaders in the fields of clinical dermatology, dermatologic surgery, infectious disease, pediatric infectious disease, podiatry, and HIV infection.

The panel acknowledged that the initial choice of antibiotic is generally determined by tolerability, ease of administration, cost, and efficacy. The usual choices for initial empiric therapy include cephalosporins, penicillinase-resistant penicillins, and ß-lactam/ß-lactamase inhibitor combinations. Currently marketed cephalosporins, penicillinase-resistant penicillins, and ß-lactam/ß-lactamase inhibitor combinations lack activity against methicillin-resistant *Staphylococcus aureus* (MRSA), and the increasing prevalence of community-acquired MRSA (CA-MRSA) was a major consideration when designing the treatment algorithm. Many CA-MRSA skin infections present as abscess, and drainage is the most important component of therapy in this setting. When the history and physical exam suggest CA-MRSA infection, and there is no fluctuant collection of purulent material to be drained, a sulfa drug or tetracycline is generally the best choice for initial empiric therapy.

Introduction

Up to 17% of dermatology-related clinic consultations involve bacterial skin infections.[1] When skin and skin structure infections (SSSIs) are not complicated, therapy is most often directed against *Staphylococcus aureus* and *Streptococcus pyogenes*, the most likely causative organisms. Incision and drainage combined with antibiotic therapies form the backbone of managing uncomplicated (u) SSSIs.[2] When selecting the most appropriate antimicrobial agent, decisions must take into account spectrum of activity, pharmacokinetics, patient characteristics, new treatment options, bacterial resistance, history of allergy, and the risk that the infection is due to methicillin-resistant *S. aureus* (MRSA).

USSSIs can often be managed successfully in the office setting. A treatment algorithm for initial empiric therapy of uSSSIs has been developed (Figure 1).[3] In some patients, empiric treatment may be initiated without a culture, or it may be initiated while awaiting the results of culture.

The purpose of this paper is to summarize current concepts in the initial empiric treatment of uSSSIs in the ambulatory care setting and to present the initial draft of a treatment algorithm modified for dermatologists who treat uSSSIs.

Therapy

The goals of therapy for uSSSIs are to (1) promptly eradicate the pathogen to obtain early resolution and a low recurrence rate of the infection, (2) minimize the emergence of resistant organisms, and (3) treat the infection safely with well-tolerated agents. Patient history, physical examination data, and (readily available) laboratory data form the basis for diagnosis as well as the decision as to whether the infection is complicated or uncomplicated (Figure 1). Some patients who are immunocompromised, diabetic, or who have significant comorbidities are considered high risk, but it is important to note that skin and skin structure infections in most well-controlled diabetics and most patients with HIV behave no differently than in patients without these disorders.

To Culture or Not To Culture

Results of culture tests confirm the presence of an organism, but the diagnosis of infection remains a clinical assessment. Since most uSSSIs are caused by *S. aureus* or *S. pyogenes*, some have questioned whether every infection requires a culture. Generally, physicians weigh the expected benefits of culture and sensitivity testing against the cost to obtain this information. Cultures are not recommended when lesions are not clinically infected and may not be practical when an organism is difficult to isolate. They are generally appropriate when pus is present or when the risk is high for complications, methicillin-resistant *S. aureus*, or both. Even when a culture is obtained, it may be in the best interest of a given patient to start empiric therapy while awaiting culture results. It is then appropriate to begin empiric therapy on the basis of clinical data and reevaluate the patient when culture results become available.[3] If the culture demonstrates a resistant

organism, but the patient is improving clinically, the isolated organism may not be the true pathogen. Alternatively, other interventions such as drainage may result in cure with or without antibiotic therapy to which the organism is sensitive. In either case, it is the patient who is ultimately treated, not the lab result.

Antibiotic Therapy

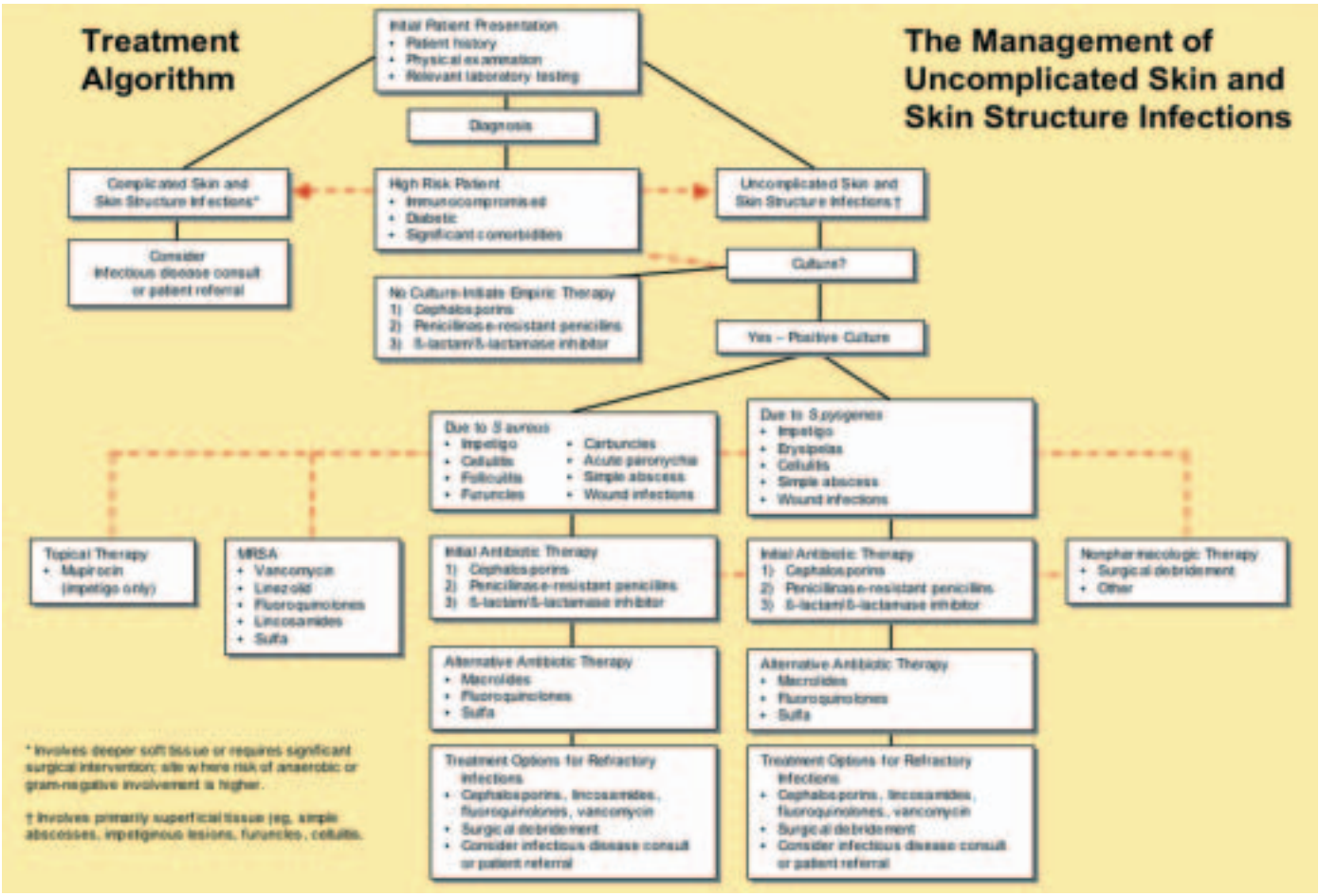
The recent susceptibility data reported by Sader and colleagues[4] provide a clinical basis for recommending cephalosporins, penicillinase-resistant penicillins, and ß-lactam/ß-lactamase inhibitor combinations as first choices for the initial empiric treatment of SSSI (Figure 1). Due to their broad-spectrum activity, ease of use, and tolerability, cephalosporins have dominant market share as first-line therapies for uSSSIs. Amoxicillin/clavulanate, though effective, is associated with a higher incidence of gastrointestinal side effects.[3] Semisynthetic penicillins are typically dosed 4 times daily, which may limit compliance.

First generation cephalosporins provide good Gram-positive coverage. Although most third generation cephalosporins are noted for their efficacy against Gram-negative pathogens, cefdinir—an extended-spectrum cephalosporin—is also quite active against gram-positive bacteria such as methicillin-sensitive *S. aureus* and *S. pyogenes*.[3] Cefdinir has shown greater potency than older cephalosporins (16-fold better than cephalexin when the MIC_{90} is measured).[4] Since cefdinir, cefixime, ceftibuten, and cefuroxime have no side chains in common with penicillins, they would not be expected to cross react in patients with allergy to penicillin or amoxicillin.[3]

For children, cefdinir shows comparable efficacy, less likelihood of diarrhea, and better taste than amoxicillin/clavulanate.[5,6]

All antibiotics have some limitations. Fluoroquinolone use is limited by emergent resistance, association with arthropathies in children, increased risk for emergence of MRSA (levofloxacin and ciprofloxacin), and increased risk for Achilles tendon rupture in older adults.[3] Lincosamides (eg, clindamycin) are associated with a significant incidence of diarrhea and have been associated with pseudomembranous colitis. They are commonly reserved for patients with allergy to penicillin or those for whom other antibiotics are unsuitable. It is important to note that erythromycin resistance may be a

Figure 1. Current Algorithm for Primary Care Physicians.



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marker for inducible lincosamide resistance. The trimethoprim/sulfamethoxazole combination is not as effective against streptococci and its use may be limited because of allergy to sulfa drugs. A new oxazolidinedione, linezolid, is best suited for oxacillin-resistant staphylococci, vancomycin-resistant enterococci, and severe cases of MRSA. Some data have suggested that outcomes may be better than with vancomycin in some settings, but the drug is very expensive. Topical antibiotics such as mupirocin are useful for elimination of nasal staphylococcal colonization and the treatment of superficial pyodermias. Some topical antibiotics have been associated with allergic contact dermatitis.[3]

Incision and drainage remains the most important intervention in the treatment of abscesses.[2] A recent study[7] suggests that for pediatric patients with community-acquired (CA) MRSA, incision and drainage was associated with clinical improvement in most of 69 pediatric patients, even those who did not receive MRSA-active antibiotics. (Skin and soft-tissue abscesses were less than 5 cm in diameter.)

Methicillin-Resistant S. Aureus

A major factor in deciding whether to culture is the risk of MRSA. Since MRSA was first identified in the 1960s as a nosocomial pathogen, these organisms—which are not susceptible to ß-lactam antibiotics as a class[8]—have been found among hospitals worldwide and risk factors have been identified (Table 1). Since the 1990s, reports have described regional outbreaks of CA-MRSA among wrestlers,[9] child care centers,[10] children without known risk factors,[11] injected-drug users,[12-14] prison inmates,[15] men who have had sex with men,[15] adults aboard a naval ship,[16] professional football players,[17] and healthy people not associated with health care institutions.[2,8,11,18-24]

Unlike nosocomial MRSA infections, CA-MRSA infections are resistant to both ß-lactam and macrolide antibiotics, and those with skin infections usually present with abscesses or cellulitis.[17,23] Outside of the skin, MRSA may also cause necrotizing fasciitis and pneumonitis, life-threatening conditions requiring immediate treatment.[18] When the risk of MRSA is high and there is no pus to drain, empiric therapy should be directed toward MRSA. In the setting of skin infections, sulfa and tetracyclines are most commonly chosen. Other options for the treatment of MRSA infections include vancomycin, linezolid, lincosamides, and fluoroquinolones (Figure 1). Emerging resistance has been associated with fluoroquinolones.

New Treatment Algorithm

The current algorithm for the ambulatory care setting (Figure 1) offers guidance for initial empiric antibiotic therapy for uSSSIs, recommends nonpharmacologic therapy such as drainage, and topical antibiotic agents when appropriate, and includes suggestions for treating refractory infections. New algorithms are being developed that include pathways important to dermatologists and podiatrists who treat a wide range of skin infections. Important topics to be addressed include antibiotic prophylaxis of wound infections and bacterial endocarditis, the choice of therapy in patients with a history of penicillin or first generation cephalosporin allergy, and the treatment of foot ulcers in the diabetic patient. An initial draft of one new algorithm is shown in Figure 2.

Table 1. Risk Factors for Methicillin-Resistant *Staphylococcus Aureus*.

Hospital Acquired
Previous hospitalization
Intensive care unit
Surgery/abdominal surgery
Total parenteral nutrition/enteral feedings
Mechanical ventilation
Previous antibiotic therapy (eg, fluoroquinolones, ß-lactams, vancomycin)
Endotracheal/tracheostomy/nasogastric tube
Previous MRSA infection leading to long-term colonization
Nursing home resident
Dialysis patient
Community acquired
Recent contact with healthcare-providing environment
Parenteral substance abuse
Race (eg, American Indian)

MRSA indicates methicillin-resistant *Staphylococcus aureus*

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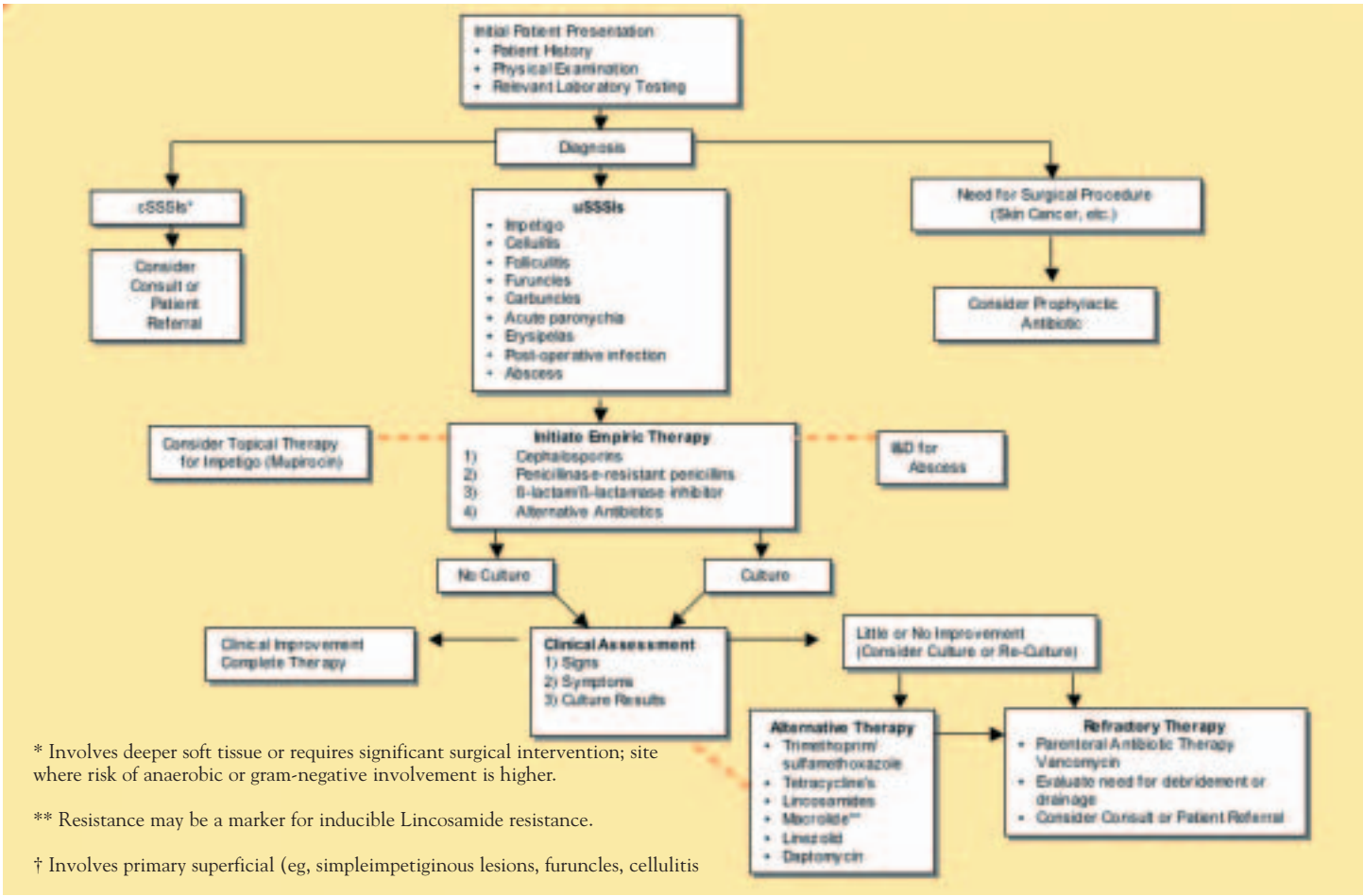
It must be emphasized that collections of purulent material—abscesses—must be drained. Drainage is the single most important aspect of treatment in these patients, and antibiotic therapy is secondary. For SSSI without collections of purulent material, antibiotics become the primary intervention.

The importance of drainage in the setting of MRSA infection is suggested by the results of Lee and colleagues[7] in which pediatric patients with community-acquired MRSA showed clinical improvement with abscess drainage, even without effective antibiotic therapy. In a more recent analysis of patients with confirmed community-acquired MRSA, Fridkin and colleagues[8,25] found that, counter-intuitively, outcomes of most patients started on an MRSA-resistant antibiotic were more favorable than patients started on other therapies. The authors attributed this surprising result to the fact that most patients receiving MRSA-resistant agents had abscesses that had been incised and drained, indicating that drainage takes precedence over antibiotic therapy in patients with CA-MRSA.

Figure 2. Draft of Revised Algorithm for Dermatologists and Podiatrists.



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An algorithm for dermatologists should take into account that dermatologists are more likely than primary care physicians to (1) treat complicated (c) SSSIs as well as uSSSIs, (2) drain complex abscesses by surgery, (3) treat refractory infections and MRSA infections, and (4) prescribe perioperative antibiotic therapy.

An algorithm for dermatologists should reference guidance for preventing bacterial endocarditis.[26] Prophylaxis for cutaneous surgery and for endocarditis are discussed in detail by Mark S. Nestor, MD, PhD in this supplement.

Conclusions

The treatment of SSSIs—uncomplicated and complicated—remains a challenge, particularly with the increasing prevalence of MRSA and the development of new therapeutic choices. New algorithms should be developed and current algorithms revised to reflect changes in resistance patterns and new treatment options for both primary care physicians and specialists treating SSSIs.

Dr. Elston is a consultant for and serves on the Speakers Bureau of Abbott Laboratories.

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PROPHYLAXIS FOR AND TREATMENT OF UNCOMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS IN LASER AND COSMETIC SURGERY

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Abstract
Complications of laser resurfacing include infections, scarring, hyperpigmentation, hypopigmentation, and delayed healing. Postoperative infections cause pain, prolonged healing, and can result in scarring. Ablative laser techniques cause partial- or full-thickness wounds, whereas so-called "nonablative procedures" may cause "spotty" epidermal wounds. Antibiotic prophylaxis is necessary when the risk for postoperative infection is significant or when the risk of infection is moderate but the consequences of infection are significant. Prophylactic antibiotic agents should have a broad spectrum of activity, be well-tolerated and be safe. The most appropriate choice is a broad-spectrum agent such as cefdinir, even for patients allergic to penicillin. Additionally, all patients should be treated prospectively with antivirals to prevent activation and dissemination of herpes simplex virus type I. Treatment of infections in patients who have and have not received prophylactic antibiotics requires identification of the causative factor and appropriate treatment. Nonablative treatments such as photodynamic therapy do not usually require antibiotic prophylaxis, although a few patients treated for acne may acquire a secondary bacterial infection that should be treated.

Introduction

As people age, they accumulate significant exposure to ultraviolet light, leading to sun damage, wrinkles, and skin cancer. To meet the demands of our patients to "turn back the clock," we continue to improve the effectiveness and safety of our cosmetic surgical techniques.

For each patient, our general approach is to (1) evaluate the degree of photoaging, expectations for improvement, downtime, risks (eg, infections), and need for anesthesia; (2) consider treatment options; and (3) educate the patient on the efficacy and safety of various treatment modalities. Although improvement in deep wrinkles and scars is greatest with ablative procedures, nonablative procedures minimize downtime and the risks of infection and scarring. For these reasons nonablative procedures have been applied to skin diseases, especially those with cosmetic overlap—rosacea, melasma, acne, and actinic damage. Current treatments for cosmetic enhancement are shown in Table 1.

Complications of laser resurfacing, the most common ablative procedure, can include infections, scarring, hyperpigmentation, hypopigmentation and delayed healing syndromes. Healing problems may lead to permanent scarring 8 to 10 months after resurfacing.[1-3] Postoperative infections cause pain, prolong healing, and can result in scarring.[4] Most laser surgeons choose antibiotic and antiviral prophylaxis in laser resurfacing although to some the use remains controversial.

An algorithm for the treatment of uncomplicated skin and skin structure infections has been prepared for use by primary care physicians.[5] This algorithm is being revised to more closely fit the medical and surgical practices of dermatologists. The new algorithm will include the appropriate use of antibiotics (eg, prophylaxis) in dermatologic and laser surgery. An initial draft of the new algorithm appears in Figure 1.

This report discusses the current use of antibiotic and antiviral agents to prevent and treat postoperative infections in patients treated with both ablative and nonablative laser procedures.

Table 1. Types of Cosmetic Skin Treatment.

Treatment
Facelift, blepharoplasty, endoscopic procedures, deep peels, dermabrasion
Ablative laser resurfacing (CO_2, Er:YAG)
Nonablative treatments (peels, particle resurfacing, laser, pulsed light, ALA PDT, radiofrequency, fractional photothermolysis)
Removal of vascular lesions, unwanted hair; repigmentation
Botulinum toxin type A, fillers (eg, human collagen, non-animal-based hyaluronic acid)
Pharmaceutical-cosmetic combinations (eg, fluocinolone acetonide-hydroquinone-tretinoin, metronidazole, retinoids, or imiquimod)
OTC cosmeceuticals (eg, alpha-hydroxy acid, retinol)

Er:YAG = Erbium:yttrium-aluminum-garnet
ALA PDT = photodynamic therapy with 5-aminolevulinic acid

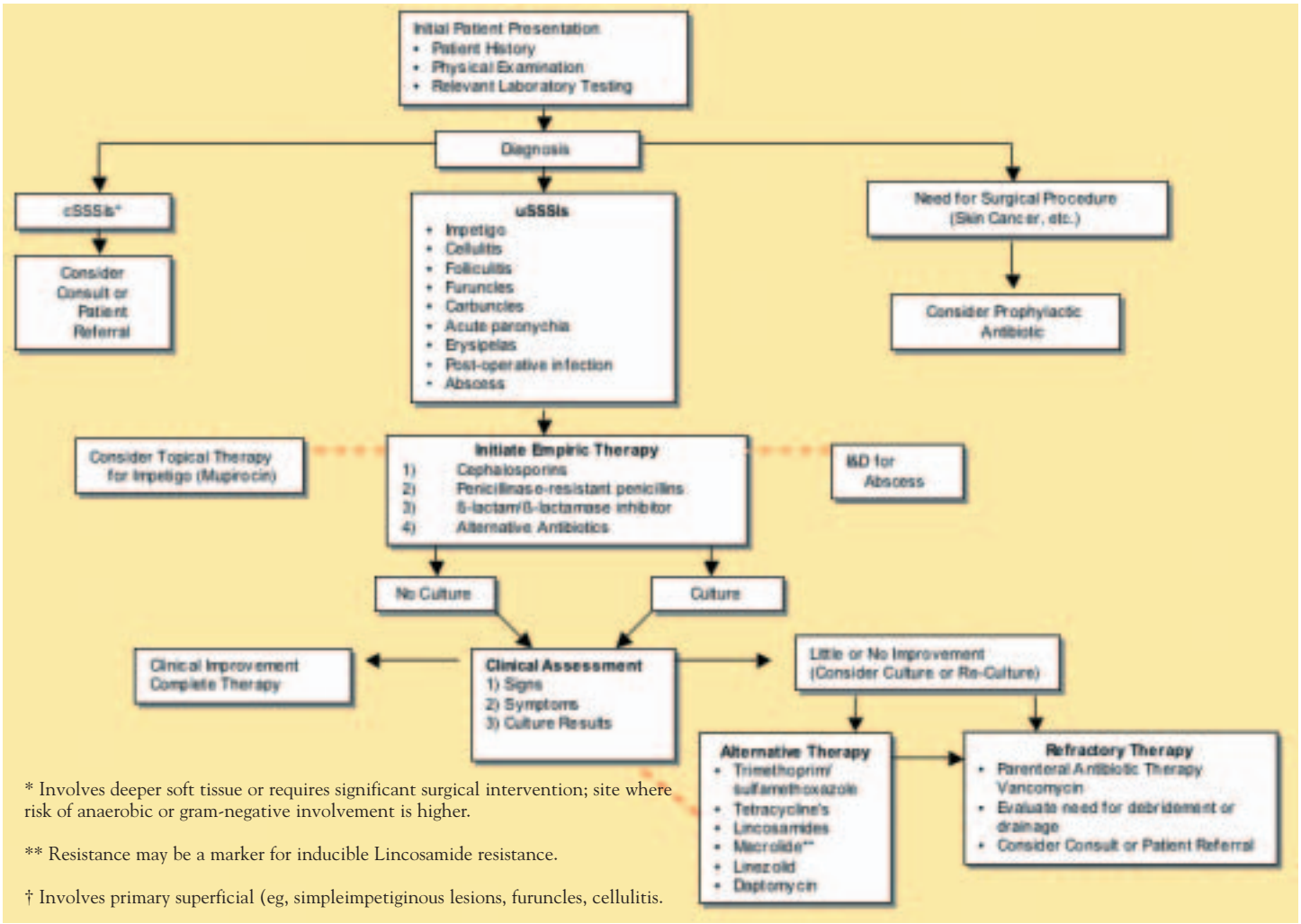
Figure 1. Draft of Treatment Algorithm for Dermatologists and Podiatrists.

History and physical examination are critical to diagnosis. The location of the infection and the patient's signs and symptoms allow the physician to classify the skin infection as uncomplicated or complicated. Since complicated skin and skin structure infections may be severe, an infectious disease consult may be indicated. If so, the algorithm stops. If not, the algorithm proceeds in another direction.

Special consideration is given to "high risk" patients, those with known risk factors (eg, diabetes, immunosuppression, significant comorbidities) for more severe, complicated infections. Such patients may have an uncomplicated infection, but their risk factors may complicate the selection of therapy. If the physician considers the infection complicated, then the algorithm recommends referral unless the physician decides to do a culture and continue with treatment, pending culture results. If the physician considers the infection uncomplicated and elects to forego culture, the algorithm recommends empiric therapy with cephalosporins.

Positive culture results typically indicate the presence of 1 or 2 pathogens. Fortunately, recommended initial therapy consists of cephalosporins, whether due to *S. aureus* and *S. pyogenes*. Penicillinase-resistant penicillins (eg, dicloxacillin) and ß-lactam/ß-lactamase inhibitor combinations (amoxicillin-clavulanate) are also appropriate for initial therapy. When ß-lactam agents (cephalosporins, penicillins) cannot be used (due to history of hypersensitivity or intolerability), alternatives include macrolides (erythromycin, clarithromycin, and azithromycin), fluoroquinolones (levofloxacin, gatifloxacin, ciprofloxacin, and ofloxacin) and trimethoprim/sulfamethoxazole.

With refractory infections, interventions typically involve surgical procedures, parenteral administration of antibiotic agents, or both.



* Involves deeper soft tissue or requires significant surgical intervention; site where risk of anaerobic or gram-negative involvement is higher.

** Resistance may be a marker for inducible Lincosamide resistance.

† Involves primary superficial (eg, simpleimpetiginous lesions, furuncles, cellulitis.

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Postoperative Infection

Any wound can become infected, even when a procedure is performed by the most skilled professional. Ablative laser techniques cause partial- or full-thickness wounds (epidermal and dermal), whereas newer nonablative procedures may cause "spotty" epidermal wounds. Regarding infection, physicians must decide whether to prescribe antibiotics or antiviral agents as a prophylactic measure or to prescribe these agents only when an infection actually occurs.

Postoperative infection with ablative (CO_2) laser resurfacing (discussed below) is well documented.[6-10] Occluded wounds are more likely to become infected than open wounds.[11] The risk of postoperative cutaneous colonization, infection, or both—which may cause scarring—may be higher in patients with preoperative staphylococcal colonies in their anterior nares.[6] Methicillin-resistant *Staphylococcus aureus*,[6,12] *Mycobacterium fortuitum*,[8] herpes simplex virus (HSV),[7,12,13-15] fungal,[12,15] and yeast[15] infections have been associated with CO_2 laser resurfacing.

In surgery, antibiotic prophylaxis is the use of antimicrobial agents in surgical patients with no established infection.[16] Antibiotic prophylaxis is considered necessary when the risk for postoperative infection is significant (as in diabetic or immunosuppressed patients) and when the risk of infection is moderate but the consequences of infection are significant. Prophylactic antibiotic agents should have a broad spectrum of activity, be well-tolerated, and be safe.

Anti-HSV prophylaxis has been recommended[17] with CO_2 laser resurfacing, even in patients with no history of HSV.[12-15] In a 500-patient study, postoperative infection with HSV occurred in 14 patients (7.4%), half without history of perioral "fever blisters" or "cold sores."[15]

Antiviral prophylaxis is necessary when the risk for reactivation of HSV is significant and when the risk for reactivation is moderate but the consequences of reactivation are significant (eg, simple outbreak vs. an open wound). HSV can be reactivated by trauma[15] and proliferates in an open wound. Immunosuppression, tolerability, and safety are primary considerations in selecting a prophylactic antiviral agent.

Antibiotic agents, antiviral agents, or both are indicated when wounds become clinically infected or *de novo* infection (eg, HSV) occurs and requires evaluation and treatment. Early signs of infection include increasing redness, increasing pain, and new ulcerations that emerge as a wound heals.[18] Empiric therapy with antivirals and broad-spectrum antibiotics is initiated and, when culture results become available, the initial therapy may be modified. When patients fail broad-spectrum antibiotics and experience a chronic unyielding course, HSV, a fungal infection, or atypical bacteria may be present.[8]

Ablative Laser Resurfacing

With proper technique, patient selection, and care (preoperative and postoperative), ablative resurfacing with CO_2 and erbium:yttrium-aluminum-garnet (Er:YAG) laser devices can be safe and effective.[19,20] Significant complications can be minimized when they are recognized and treated quickly. Ablative resurfacing procedures may be used alone or in combination with nonablative procedures.[21]

Classically, the high-energy, short-pulsed, CO_2 laser device has been the standard in ablative resurfacing because its rapid pulsing and computer-controlled scanning permit consistent levels of ablative damage to the skin.[21] The UltraPulse CO_2 laser (Lumenis, Santa Clara, CA)[22] and the Silk and FeatherTouch scanned lasers (Lumenis)[23] are examples of devices with these technologies. While results are certainly impressive, the use of these devices can be associated with significant side effects and complications. Virtually all patients treated with the CO_2 laser device have an open wound for 1 week and erythema that lasts at least 8 to 12 weeks. Complications can include infections, scarring, hyperpigmentation, hypopigmentation, and delayed healing. Because of these drawbacks, the number of CO_2 procedures performed has dropped dramatically.

Introduced in the late 1990s, the gentler Er:YAG laser device can achieve similar results with reduced healing times, duration of erythema, and adverse effects.[24] Long-pulsed Er:YAG laser devices offer homeostasis and improved tightening of the skin. Complications (including infection) still occur, however, and physicians must still exercise care in technique, patient selection, and preoperative and postoperative care.

When treating patients with the Er:YAG laser device, most physicians prescribe both oral antibiotics and oral antiviral agents for prophylactic reasons, and some also believe that topical retinoids and bleaching creams improve healing attributes of the skin as well as enhance the final result.

Prophylaxis or Not?

The use of antibiotic prophylaxis in full-face CO_2 laser resurfacing has been debated. In a prospective study,[25] Ross and colleagues found that infection with *S. aureus* occurred in 2 of 4 consecutive patients who had not received antibiotics before full-face treatment with a CO_2 laser device. The next 4 consecutive patients were given oral antibiotic for Gram-positive organisms 2 days before the same laser treatment. Culture of these 4 patients showed no staphylococcus colonies or infection after 2 days. Culture of another non-study patient receiving the same pretreatment (plus an antiviral agent) showed only Gram-negative organisms after laser treatment. The authors concluded that narrow-spectrum, Gram-positive oral antibiotic prophylaxis was appropriate for patients receiving full-face and regional laser resurfacing.

In a retrospective study,[26] 133 consecutive patients who had received cutaneous CO_2 laser resurfacing were placed into 4 categories: (1) no antibiotic prophylaxis, (2) single-dose intraoperative cephalexin given intravenously, (3) postoperative oral azithromycin, and (4) intraoperative intravenous cephalexin with postoperative oral azithromycin. The authors found a significantly higher infection rate in patients of categories 2 and 4 and Gram-negative organisms in patients with antibiotic prophylaxis.

The authors concluded that antibiotic prophylaxis appears to be unnecessary in class 1 clean wounds (wounds made in uncontaminated skin with sterile surgical technique and an infection rate less than 5%[27]), given that patients receive appropriate postoperative care, for which two methods exist: open techniques, which use topical emollients, and closed techniques, which use artificial dressing materials. Open techniques require patients to apply emollient multiple times daily and provide more visibility while the wound heals. Closed techniques, though they may require less of patients, appear to be associated with a high risk of infection. Leaving closed bandages in place for no longer than 48 hours may minimize the risk of infection with closed techniques.[18,28]

Antibiotic Prophylaxis

Despite these opposing views, most laser surgeons feel that antibiotic prophylaxis is necessary and the most appropriate choice for antibiotic infection prophylaxis is a broad-spectrum agent effective against Gram-positive pathogens (eg, *S. aureus* and *Streptococcus pyogenes*) and, to some degree, Gram-negative pathogens. An excellent choice would be an extended spectrum cephalosporin such as cefdinir which provides coverage of Gram-positive bacteria and appropriate coverage of Gram-negative bacteria. In addition, since cefdinir does not cross react with penicillin, it can be used in patients allergic to penicillin. Another option is to start with a broad-spectrum antibiotic and add a complementary agent. Patients preparing for ablative cutaneous CO_2 surgery should start the antibiotic during the evening before the procedure or on the morning just before the procedure. They should continue therapy until reepithelialization is complete.[12]

Antiviral Prophylaxis

As for antiviral infection prophylaxis, patients should take the antiviral twice daily beginning 2 days before laser surgery and continue the treatment until reepithelialization is complete (10 days). Susceptible patients should take moderate doses of the antivirals. When infection occurs during prophylaxis, a culture should be performed to guide therapy. A patient who received deep Er:YAG laser resurfacing with prophylaxis is shown in Figure 2.

Complications

In addition to infection, ablative laser resurfacing may result in hyperpigmentation, hypopigmentation, and scarring. A small number of patients have significant difficulty in healing after laser resurfacing.[29] These patients are generally of skin type I or II and are treated by closed-dressing type procedures. Although the etiology of this complication is unclear, a combination of infection and autoimmunity phenomena are thought to impede reepithelialization. The most success in treating this rare complication has been with (1) combinations of oral antibiotics, antivirals, and gentle topical treatment; (2) open-dressing type procedures; and (3) judicious use of topical corticosteroids (eg, betamethasone dipropionate ointment). Healing may require up to 10 months and result in scarring.[21]

Nonablative Procedures

Photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) has been used to treat actinic damage, acne, and nonmelanoma skin cancers. In this relatively new nonablative technique, topical ALA, a precursor in the biosynthesis of heme, is selectively taken up by rapidly proliferating cells and converted to protoporphyrin IX (PpIX), a potent photosensitizer.[30] Exposure to intense light of the appropriate wavelength activates PpIX, leading to the formation of singlet oxygen and ultimate cell death. Depending on the indication, PpIX may be activated by lasers, pulsed light, or continuous light (blue, red).[31,32]

In the author's experience, secondary bacterial infections have not occurred in more than 500 patients treated for actinic damage, rosacea, or photorejuvenation by ALA PDT. Antibiotic prophylaxis is therefore unnecessary, although antiviral prophylaxis may be appropriate in some patients.

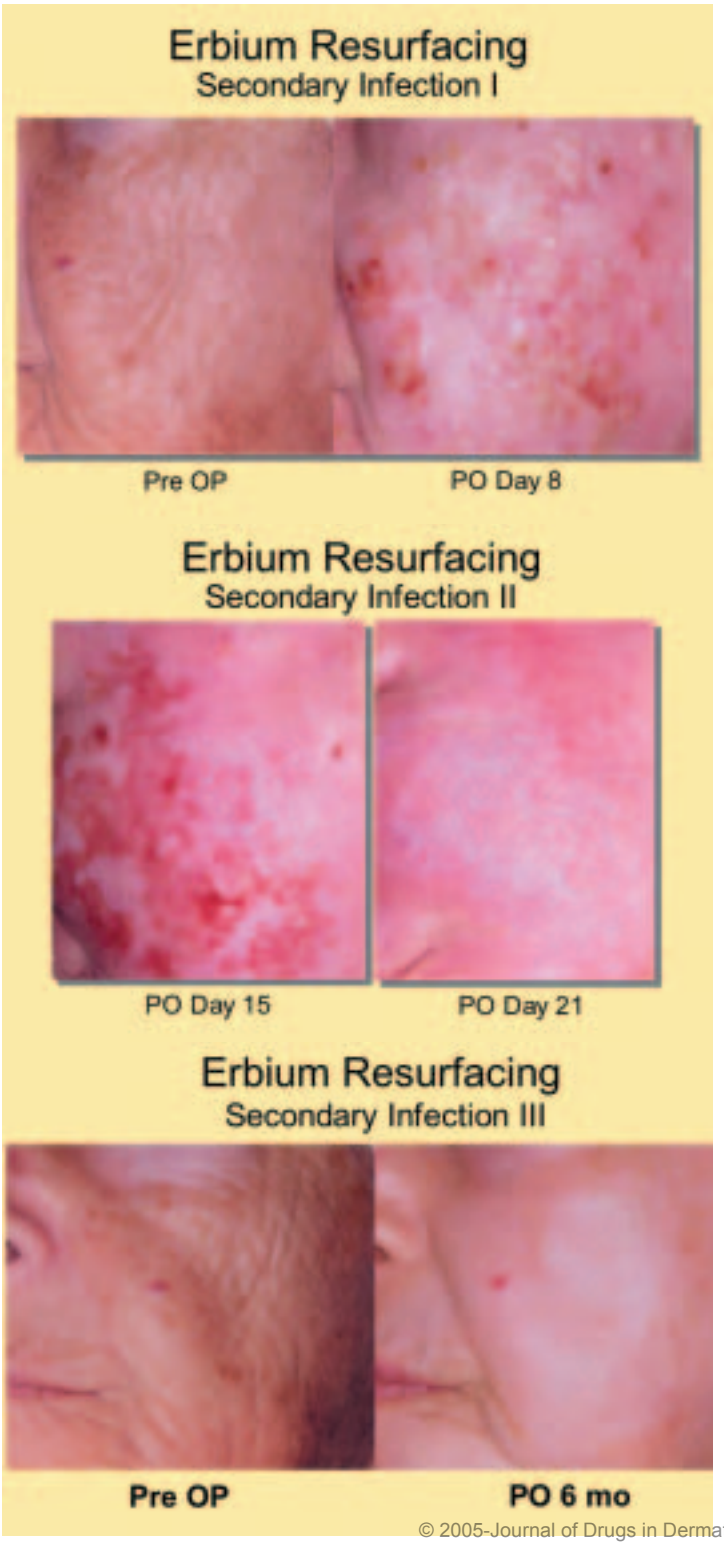
Since ALA also penetrates sebaceous glands, ALA PDT has been applied to the treatment of popular, pustular, and severe cystic acne. PpIX activation leads to the destruction of sebaceous glands and, by other mechanisms, *Propionibacterium acnes*. Three of the author's patients have acquired secondary bacterial infections (Gram-negative enteric) with this treatment, so antibiotic prophylaxis may be necessary at times in this patient population.

In general, prophylaxis with antibiotics and antivirals is unnecessary with nonablative procedures. Aggressive treatments can cause superficial wounds lasting 2 to 7 days and judicious use of broad-spectrum antibiotics (eg, cefdinir) may be indicated in these cases. Antiviral prophylaxis should be considered in susceptible patients. When infections occur in patients not on prophylactic antibiotics or receiving prophylaxis treatment, culture and appropriate antibiotic or antiviral regimens are required to guide therapy. Guidelines for antibiotic and antiviral prophylaxis are shown in Table 2.

Summary and Conclusions

Ablative laser resurfacing continues to have significant clinical benefits in patients with deep wrinkles and scars. When prophylaxis is indicated, patients should be treated with broad-spectrum antibiotics (eg, cefdinir) and antivirals. Nonablative treatments such as ALA PDT do not usually

Figure 2. An 84-year-old woman who received deep Er:YAG laser resurfacing. The patient was given azithromycin and famciclovir before treatment. Increased redness, pain, and crusting indicated infection and culture showed the presence of *Staphylococcus aureus* and *Pseudomonas* species. The patient was given ciprofloxacin, valacyclovir, and levofloxacin for 14 days and betamethasone ointment for 5 days.



require antibiotic prophylaxis, although a few patients treated for acne may acquire a secondary bacterial infection that should be treated.

Dr. Nestor is a member of the Speakers Bureau of Abbott Laboratories.

Table 2. Guide for Antibiotic and Antiviral Prophylaxis in Cosmetic Procedures.

Procedure	Antibiotic	Antiviral
CO_2 laser	Yes	Yes
Er:YAG laser	Yes	Yes
ALA PDT	No	Yes/No
ALA PDT (acne)	Yes/No	Yes/No
Photorejuvenation	No	Yes/No
Radiofrequency (Thermacool™)	No	Yes/No
Fractional photothermolysis (Fraxel™ Laser)	Yes/No	Yes/No
Microdermabrasion	No	No
Botulinum toxin type A	No	No
Dermal fillers	No	No

Er:YAG = Erbium:yttrium-aluminum-garnet
ALA PDT = photodynamic therapy with 5-aminolevulinic acid.

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TREATMENT OF UNCOMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS IN THE DIABETIC PATIENT

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Abstract
Diabetic neuropathy can lead to the development of ulcers on the lower extremities. Prompt treatment lowers the likelihood of infection and reduces the probability that an established infection will lead to amputation. Antibiotics are selected on the basis of the suspected organism and the level of infection. Unnecessary antibiotic prophylaxis is discouraged because it increases the likelihood that bacterial resistance to the antibiotic agent will develop. Culture samples must be taken by curettage of biopsy rather than by swabbing to assure detection of pathogens.

Introduction

In the United States, foot infection is the leading cause of both diabetes-related hospitalization[1] and lower-extremity amputation.[2-4] More than 90% of cases of osteomyelitis of the foot are associated with infected foot ulcers. The American Diabetes Association estimates that almost 90,000 lower extremity amputations secondary to diabetes are performed each year. In 85% of amputations, ulceration is a pre-disposing factor. The 5-year survival rate of unilateral diabetic amputees is 50%; for bilateral amputees, the rate drops to 0%.

Lower-extremity neuropathy associated with diabetes mellitus often leads to the development of uncomplicated skin and skin structure infections (uSSSIs) (Figure 1). Untreated, uSSSIs may develop into complicated infections (Figure 2). Long-term survival of diabetic patients depends on the recognition and proper treatment of uSSSIs before they develop into more serious conditions that warrant amputation. This article focuses on the treatment of uSSSIs in diabetic patients.

Classifying the Diabetic Wound

Proper classification of the diabetic wound is essential before selecting treatment. Diabetic foot infections are divided into 4 categories of severity: non-infected, mild, moderate, and severe.[5]

Non-infected ulcers are characterized by granulation of the tissue base, shallow tract, the absence of cellulitis and pus, and normal serous drainage. The wound is likely to be contaminated or colonized by bacteria but there are no signs of infection.

Mildly infected ulcers have 2 or more manifestations of inflammation (purulence, erythema, tenderness, pain, induration, warmth) and cellulitis or erythema that extends 2 cm or less around the ulcer. The infection is restricted to skin and superficial subcutaneous tissues. This type of wound is usually local and patients have no systemic illness or other complications.

Moderately infected ulcers have one or more of the following characteristics: cellulitis greater than 2 cm, lymphangitic streaking, location beneath superficial fascia; gangrene; abscess of deep tissue; and muscle, tendon, bone, or joint involvement. The patient is metabolically stable and systemically well, although white blood cell counts or glucose levels may change and require treatment. If located in the foot or limb, wounds of this type may eventually lead to amputation.

Severely infected ulcers have the characteristics of moderate infection plus one or more additional factors—signs or symptoms of sepsis, significant metabolic imbalance, severe peripheral vascular disease, or combinations of these. Severe diabetic infections are life-threatening. In diabetic patients, uSSSIs comprise only non-infected and mildly infected wounds.

Treatment of Diabetes-Related uSSSIs

Diabetic wound treatment requires debridement, offloading, and antibiotics in that order. Antibiotics alone will not heal a diabetic wound. Debridement (Figure 3) promotes healing by creating an acute wound. By removing necrotic tissue and bacteria, debridement establishes a basis for wound healing, allows more accurate visual assessment, promotes the influx of growth factors and platelets, and reduces the level of matrix metalloproteinases (MMPs). MMPs have been shown to degrade growth factors.

Offloading the pressure causing the wound inhibits inflammatory stimuli and allows the wound to heal. Chronic inflammatory stimuli (ie, pressure and infection) delay wound healing by increasing MMPs and decreasing the entry of endogenous growth factors. The inflammatory cascade begins with the causative pressure and may continue when infecting agents are introduced. This leads to increased activity of neutrophils and macrophages, increased production of TNF-α and IL-1b, and increased MMP production.

Wound care products can be used to interrupt the inflammatory cascade (Regranex Gel, 0.01%) or reduce MMPs (Promogran) in the chronic wound environment. If infection is present, the appropriate administration of antibiotics in important. The use of prophylactic antibiotics, however, is not based on scientific data and does not accelerate healing.

Figure 1. An Uncomplicated Skin Infection of the Great Toe in a Diabetic Patient.

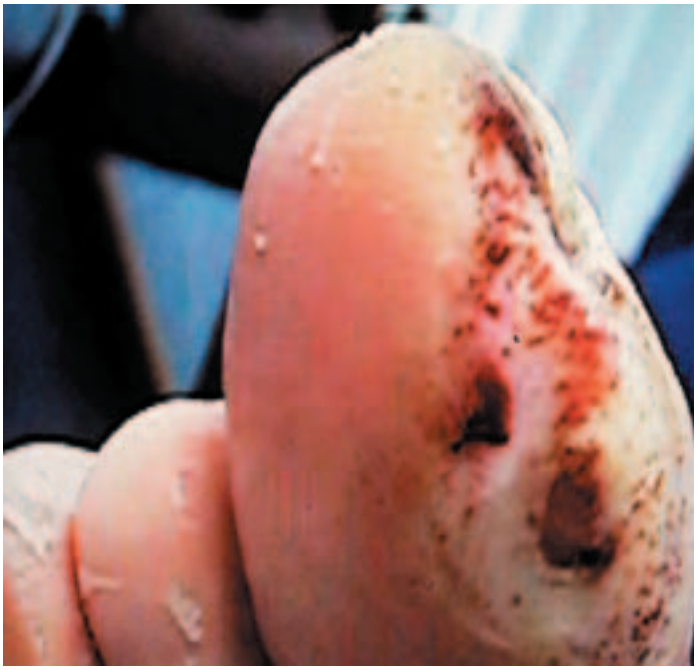


Figure 2. A Complicated Foot Infection in a Diabetic Patient.

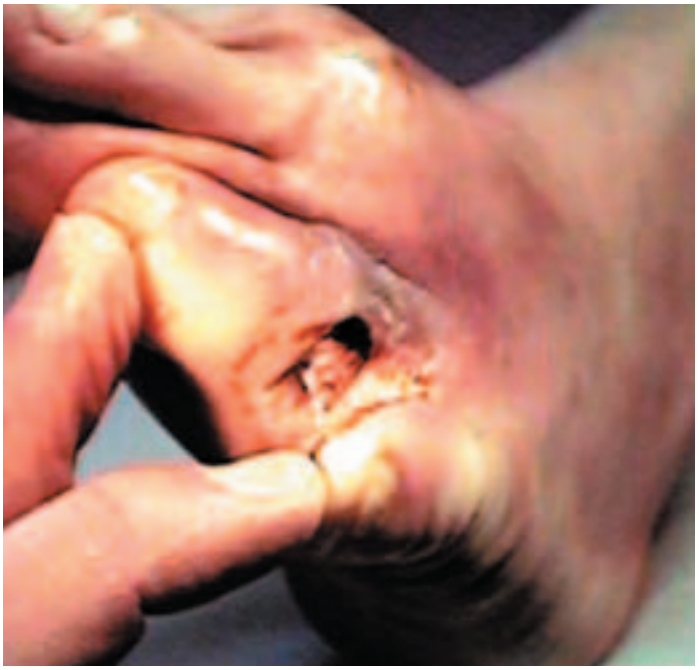
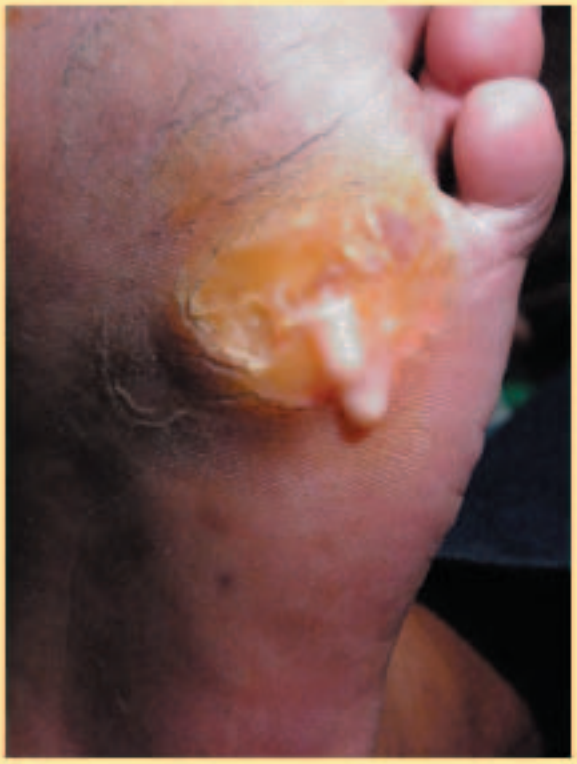
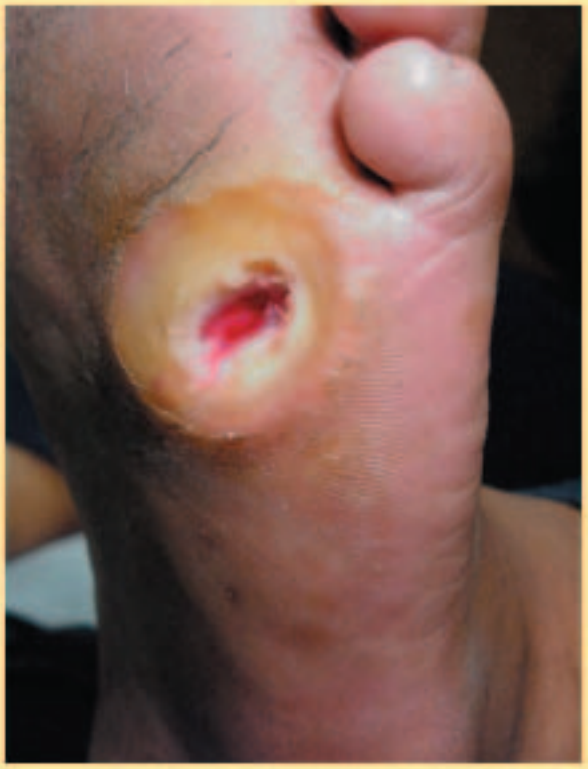


Figure 3. Debridement of this hyperkeratotic lesion revealed a superficial collection and a clean, non-infected ulcer. Note the absence of the cardinal signs of infection. This ulcer does not require antibiotics, but will require debridement and offloading to heal.





Antibiotics for the Infected Ulcer

Diabetic wound infections are often not polymicrobial as was previously thought. The responsible organisms are usually Gram-positive pathogens such as *Staphylococcus aureus* or group *B* streptococci.[6-9] In diabetic ulcers, *S. aureus* may occur as methicillin-susceptible *S. aureus* (MSSA) or methicillin-resistant *S. aureus* (MRSA). Community-acquired MRSA is becoming more common. Isolates in mild diabetic infections are shown in Figure 4.

Because virtually all strains of *S. aureus* found in lower extremity infections produce ß-lactamase, empiric treatment of suspected *S. aureus* infections always includes a ß-lactamase-stable antibiotic (eg, a cephalosporin).

Mild diabetic infections are caused most often by staphylococci and streptococci. ß-Lactamase-stable antibiotics are appropriate empiric choices for these infections. In moderate to severe infections, causative agents include *S. aureus* (MSSA or MRSA), group B streptococci, Gram-negative organisms (*Pseudomonas* species are still uncommon), anaerobic bacteria (Gram-positive and Gram-negative), and *Enterococcus* species.

More severe infections are best treated with β-lactamase inhibitors (eg, ampicillin/sulbactam with or without a quinolone), clindamycin plus an agent effective against Gram-negative pathogens, broad-spectrum quinolones, or linezolid.

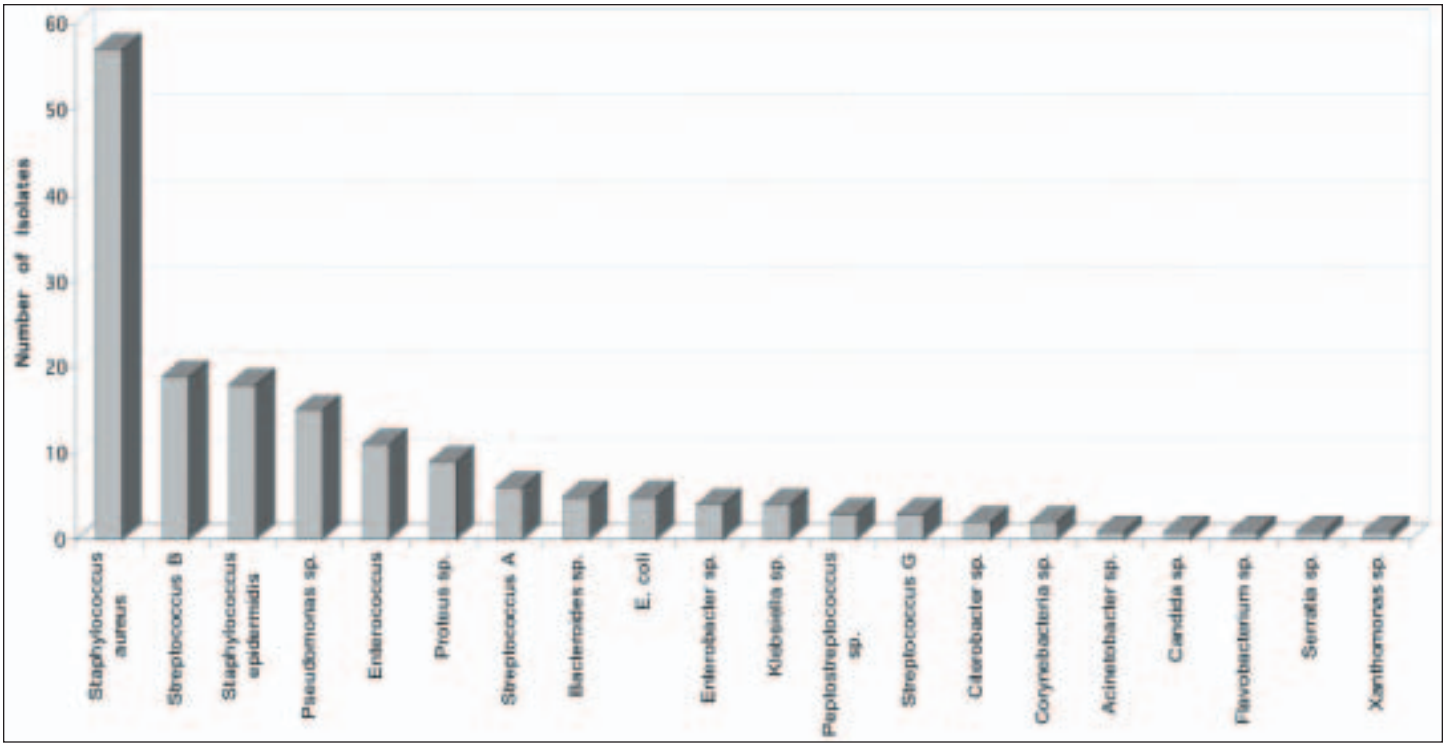
A Note About Culturing

Bacteria exist in wounds at 3 levels: contamination, colonization, and infection. A wound is contaminated when bacteria are present but not multiplying. In colonization, bacteria are present and multiplying. In infected wounds, bacteria are present, multiplying, and eliciting a host response.

Because all diabetic ulcers are colonized by a variety of bacterial species, cultures of superficial swabs usually reveal multiple species[10] that may or may not be pathogenic. There is little compelling evidence that this bioload inhibits wound healing.

Evidence exists that ulcers may heal without antibiotics.[11] When physicians receive positive culture results from an ulcer lacking overt signs of infection, they may nevertheless prescribe antibiotics as a supplement to standard wound therapy. This issue was addressed in a 1996 study of Chantelau and colleagues.[11] Forty-four diabetic patients with uncomplicated neuropathic foot ulcers were given standard treatment consisting of pressure relief, daily wound cleansing, and sterile dressings. All but one ulcer was infected. Patients were randomized to receive either amoxicillin and clavulanic acid or placebo. The results indicated no significant difference in

Figure 4. *Staphylococcus* sp and *Streptococcus B* sp were the most frequently isolated organisms in a 1995 study of mild diabetic foot infections.[9]



(Reprinted with permission from: Armstrong DG, Liswood PJ, Todd WF. 1995 William J. Stickel Bronze Award. Prevalence of mixed infections in the diabetic pedal wound. A retrospective review of 112 infections. *J Am Podiatr Med Assoc*. 1995;85:533-537.)

healing between the 2 groups. The authors concluded that antibiotic treatment with amoxicillin and clavulanic acid in addition to standard wound care provided no additional benefit in uncomplicated neuropathic foot ulcers of diabetic patients.

Physicians may be concerned about the medico-legal implications associated with not prescribing antibiotics when positive culture results appear on the chart of a patient with a clinically non-infected wound. If they prescribe an inappropriate antibiotic to avoid potential litigation, however, the cost of treatment will increase and the possibility of adverse events (eg, development of resistant strains) will be introduced.

If culturing is necessary, the area is first cleansed thoroughly with antiseptic (eg, Betadine) and rinsed with sterile saline or water. Of critical importance is that culture samples be taken by curette or biopsy from the ulcer base where infectious agents reside, rather than by swabbing the surface.[7,8]

Topical Antimicrobials

Although studies show the topical antimicrobials in diabetic foot ulcerations lack efficacy, most clinicians prescribe them regularly. Commonly used agents include mupirocin, silver compounds, povidone-iodine, gentamicin-triple antibiotic preparations, and fusidic acid.

Mupirocin is FDA-cleared for the treatment of impetigo and pyoderms, but is often used off label to treat ulcers because of its effectiveness against Gram-positive organisms. Silver compounds (eg, silver sulfadiazine) are broad-spectrum antimicrobials whose usage in wound healing is increasing rapidly, especially in the treatment of venous stasis ulcers. Usage of silver compounds is supported by anecdotal case studies.

In vitro culture studies suggest that povidone-iodine antiseptic may be toxic to tissue, but *in vivo* toxicity in wounded tissue has not been shown. Fusidic acid is a potent anti-staphylococcal drug available in both topical and oral preparations. It is available only in Europe and Canada.

Conclusions

Antibiotics for diabetic foot infections are chosen on the basis of suspected pathogens and class of infection. Since mild infections are most often caused by staphylococci and streptococci, cephalosporins are the treatment of choice for initial therapy. To optimize compliance, antibiotic dosing should be as infrequent as possible, especially in patients taking multiple medications. Antibiotics should be changed or continued on the basis of culture and sensitivity test results.

Disclosure: Dr. Rich received an honorarium from Abbott Laboratories for her presentation.

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TREATMENT OF UNCOMPLICATED SKIN AND SKIN INFECTIONS IN THE PEDIATRIC AND ADOLESCENT PATIENT POPULATIONS

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Abstract
Before 1980, superficial pyodermas in the US were caused primarily by streptococci. Studies conducted in Miami show that during the early 1980s, the predominant pathogen associated with impetigo in pediatric patients shifted from *Streptococcus pyogenes* to *Staphylococcus aureus*. Subsequent reports revealed a trend of increasing resistance of *S. aureus* to penicillins. By regular monitoring of local sensitivity patterns physicians are more likely to select the appropriate antibiotic. The current recommendation for the treatment of pediatric skin disease is cephalosporins due to their low likelihood of resistance by *S. aureus*.

Introduction

When diagnosed early and treated with a suitable antibiotic, bacterial skin infections in children can usually be cured. If not treated promptly, nephritis, septicemia, carditis, or arthritis may result.[1] For example, streptococcus infections have been associated with glomerulonephritis[2-6] during the 1960s and 1970s in Jamaica, Trinidad, and Red Lake, Minnesota. Until the early 1980s, therapy for mixed skin infections in children was usually directed at streptococci (group A ß-hemolytic *Streptococcus pyogenes*), the primary causative organism, and staphylococci, the secondary invader.[7-9]

Impetigo

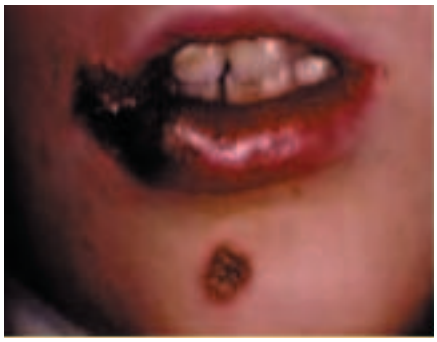
Impetigo is a common skin infection in pre-school and school-aged children. It occurs most frequently in geographic areas with long, hot summers and high humidity.[1,10] Poor hygiene, crowded living conditions, minor skin trauma, and pre-existing infections are also associated with impetigo.[1]

Impetigo contagiosa is caused by *Staphylococcus aureus*, *Streptococcus pyogenes*, or both. This highly infectious form is characterized by vesicular lesions that may be preceded by micro or macro trauma. Lesions become thick with honey-colored crust. (Figure 1). Bullous Impetigo is caused by coagulase-positive *S. aureus* and is more common among infants (Figure 2). Vesicular lesions and superficial flaccid pustules may be present as well as a collarette of scale, often on covered areas of the skin. The exfoliative toxin is produced by phage group II *S. aureus*.

The Shifting Trend

Before 1980, superficial pyodermas in the US were caused primarily by streptococci. A Miami study reported in 1983,[9] however, uncovered a change. The authors evaluated 101 children (aged 6 months to 3 years) with pyoderma. Samples for culture and sensitivity testing were taken on the initial visit and after 1 week of treatment. After the initial visit, patients randomly received either penicillin V potassium (pen VK) or cloxacillin sodium. Patients not responding after 1 week of treatment were switched to another antibiotic and evaluated 2 weeks later.

Figure 1. Pre-School Children with Vesicular Facial Lesions of Impetigo Contagiosa.



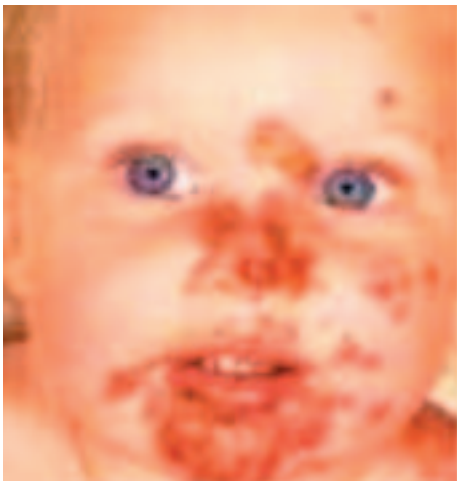
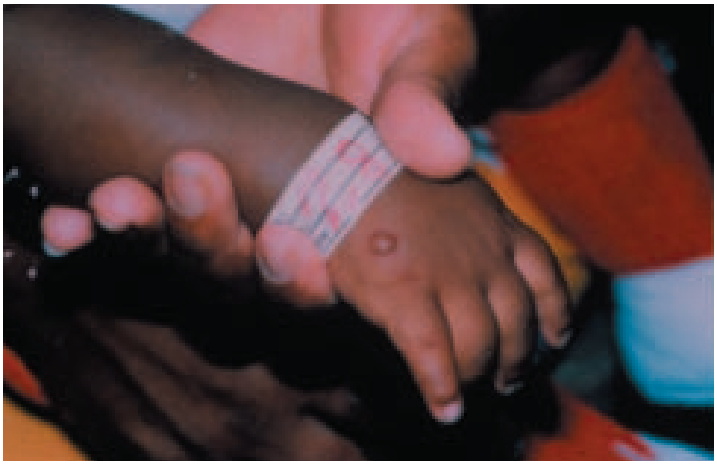


Figure 2. Vesicular, Pustular Lesion of Pre-School Child with Bullous Impetigo.



In patients presenting with staphylococcal bullous impetigo, most had vesicular bullous lesions but the predominant lesions were pustules, and most were on the extremities (Figure 4). Conventional expectation at the time was that most lesions of staphylococcus bullous impetigo would appear on the face and genitalia.

Culture revealed *S. aureus* in 29 patients receiving cloxacillin and *S. aureus in* 38 patients receiving pen VK. Treatment was successful in all cloxacillin recipients but failed in 47% of pen VK recipients. Nine patients had mixed infections in which both *S. aureus* and *S. pyogenes* were isolated. Four had received cloxacillin and 5 had received pen VK. Treatment was successful in all 4 cloxacillin recipients and treatment failed in 2 of the 5 pen VK recipients (40%).

These results showed that the primary invader was no longer *S. pyogenes;* otherwise the response rate to pen VK would have been higher. The principal pathogen now appeared to be *S. aureus*, as shown in Figure 3. Two other studies have corroborated these findings.[8,11]

At the University of Miami where this study was conducted, *in vitro* studies showed resistance of *S. aureus* against Pen VK at ≥98%, against cloxacillin at ≤2 %, and against erythromycin at 10%.

The authors concluded that (1) cloxacillin was effective and pen VK was not; (2) erythromycin was a fair choice but not ideal due to lower efficacy, potential resistance, and GI intolerance; (3) dicloxacillin could also be effective but was not ideal due to its bad taste; and (4) cephalosporins were an ideal alternative because of their efficacy, palatability, and tolerability.

A Decade Later

Later studies in Miami showed a continuing pattern of resistance development. In a retrospective analysis conducted from August 1990 to November 1991,[12] *S. aureus* was isolated from impetiginized lesions of 111 patients with atopic dermatitis and 23 patients without atopic dermatitis. Antibiotic sensitivity testing revealed pen VK resistance of *S. aureus* at ≥90%, as in 1983; cloxacillin resistance at 21% compared to ≤2% in 1983; and erythromycin resistance at 42% compared to 10% in 1983.

The authors concluded that (1) cloxacillin and/or erythromycin-resistant *S. aureus* may become a widespread trend, (2) clinical response to *in vitro* antibiotic susceptibilities needed to be studied, and (3) impetigo patients should also be spot-cultured before antibiotic treatments. The authors also recommended the use of first-generation cephalosporins with consideration of topical agents such as mupirocin as the ideal treatment option.

The Turn of the Century

In a 1999 retrospective study[13] conducted in Miami, bacterial resistance was studied in 105 patients aged 6 months to 12 years. Calcium alginate swabs from skin and asymptomatic nares were plated on trypticase soy agar with 5% sheep blood. Antibiotic susceptibility testing was performed using the Microscan method. The results are shown in Figure 5. Resistance is clearly highest for penicillin.

These studies[9,12,13] show that antibiotic sensitivities are constantly changing (Table 1) and that local monitoring of antibiotic sensitivities is crucial to selecting the appropriate antibiotic for a bacterial skin infection. Jegasothy and colleagues[13] recommend oral cephalosporins and/or topical mupirocin for the treatment of impetigo, and add that clinicians should watch for increasing utility of other antibiotics.

Table 2 shows the current sensitivities of *S. aureus* to frequently used antibiotics.

The 2003 *Red Book* Treatment Guidelines of *Staphylococcus aureus* and GABHS Skin Infection[15] recommend mupirocin to treat superficial localized skin infection. For deeper skin infection, first- and second-generation cephalosporins, cloxacillin, and dicloxacillin are recommended with macrolides, and clindamycin for penicillin-allergic patients. Serious invasive skin infections require IV antibiotic treatment barrage (ie, vancomycin and oxacillin, with gentamicin and clindamycin if necessary).

The increasing prevalence of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) is an important development. Lee and colleagues[15] showed that in most of 69 pediatric patients, incision and drainage resulted in clinical improvement, even in patients who did not receive MRSA-active antibiotics. The reports by Fritsche and Jones and by Elston in this supplement provide more detail on MRSA.

Figure 3. Results of Cultures at the Initial Visit. *Staphylococcus aureus* was isolated in 77% of patients, indicating a shift in the predominant pathogen associated with impetigo.

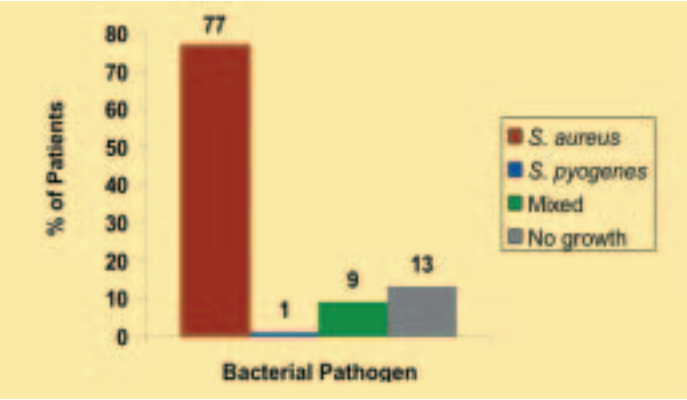


Figure 4. Lesions of Bullous Impetigo Appearing on the Legs rather than the Face and Genitalia.

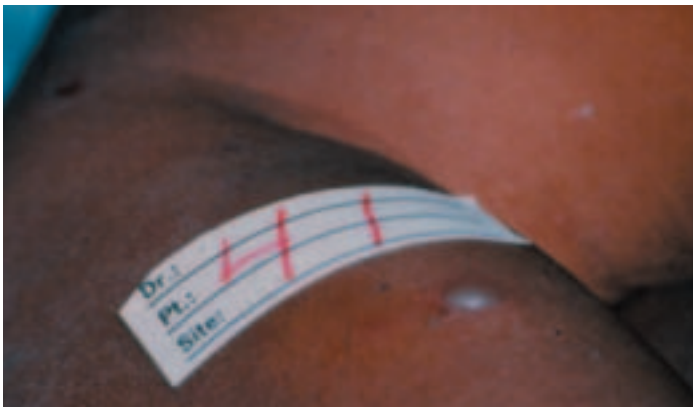


Table 1. Percentage of Antibiotic Resistance of *Staphylococcus Aureus* Isolated from Skin in the Pediatric Population at University of Miami—Jacksonville Memorial Hospital.

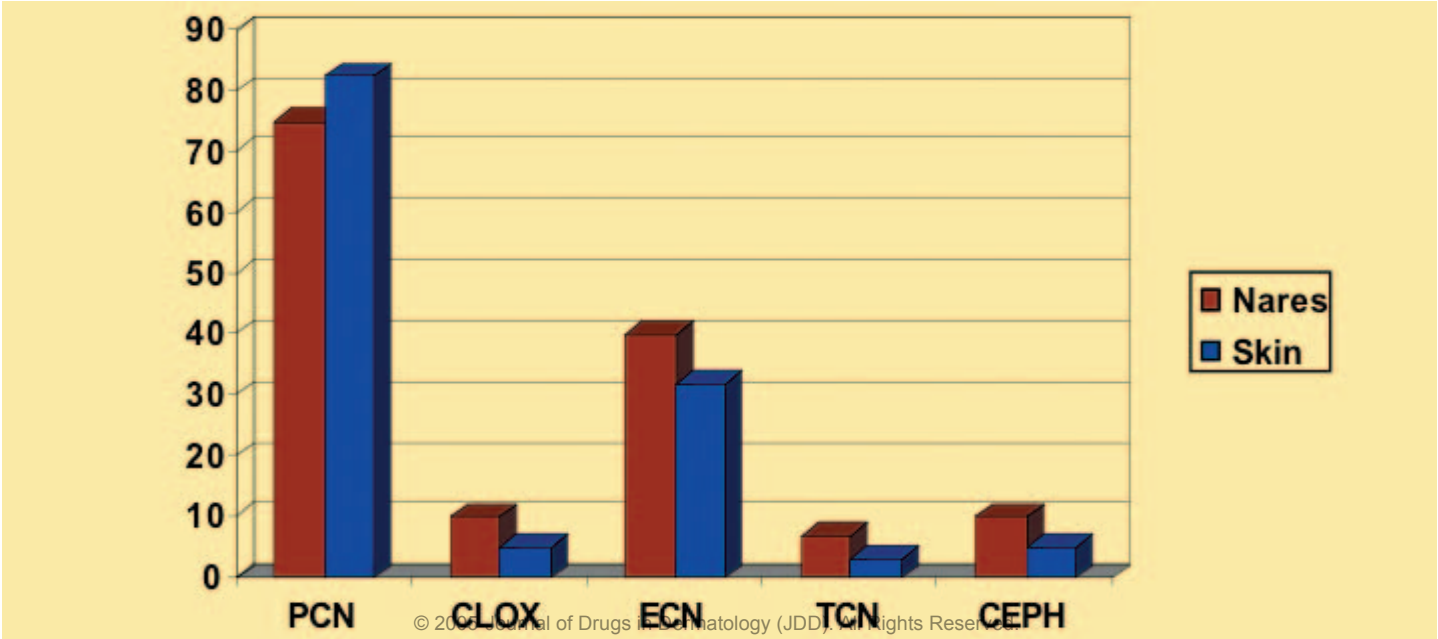
Antibiotic	1980[9]	1986-1987[14]	1990-1991[12]
Penicillin	98.7	95	94
Cloxacillin	1.3	0	21.4
Erythromycin	10.2	25	42.1

Table 2. *Staphylococcus Aureus* in 2005 (non-MRSA sensitivity).

Penicillin	8%
Erythromycin	60%
Tetracycline	96%
Cefazolin	100%
Oxacillin	100%

MRSA = methicillin-resistant *S. aureus*.

Figure 5. *Staphylococcus Aureus* Antibiotic Resistance to Penicillin (PCN), Cloxacillin (CLOX), Erythromycin (ECN), Tetracycline (TCN), and Cephalosporins (CEPH).



Conclusion

After a half century of streptococcus predominance, *S. aureus* has been the predominant organism in pediatric skin infections since the early 1980s, but this trend may change. Antibiotic susceptibilities may also change, but for now, cephalosporin and/or topical mupirocin are ideal choices for treatment. Despite reported reluctance by physicians to prescribe cephalosporins for penicillin-allergic patients due to concern about cross-sensitivity, there is substantial evidence supporting the recommendation by the American Academy of Pediatrics to do just that.[17] To be vigilant against changing predominance and to uncover possible geographic differences, regular spot checking of patient populations is recommended.

Dr. Schachner is affiliated with the Speakers Bureau of Abbott Laboratories.

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PERIOPERATIVE USE OF ANTIBIOTICS: PREVENTING AND TREATING PERIOPERATIVE INFECTIONS

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Abstract
Prevention of postoperative wound infection in dermatologic surgery and appropriate use of antibiotics to prevent endocarditis and joint-replacement infections are controversial issues. Dermatologists often may misunderstand the use of antibiotics to prevent endocarditis, surgical site infections, and prosthesis infections. In order to prevent endocarditis associated with surgical procedures, the American Heart Association (AHA) has developed clinical practice guidelines that apply to surgical patients with prosthetic cardiac valves, previous bacterial endocarditis, mitral valve prolapse with valvular regurgitation, or thickened leaflets. For these patients, the AHA recommends that antistaphylococcal antibiotics (eg, cephalosporins) be given before surgery only when the procedure involves significant risk of bacteremia (eg, incision into infected tissues). Routine dermatologic surgery of intact skin with sterile technique usually does not require prophylaxis. Antibiotic prophylaxis may also be justified in surgical patients who are at moderate to high risk for wound site infection. Patients should be given prophylactic antibiotics shortly before surgery or as soon as the risk is recognized. In patients allergic to penicillin, cross reactions are unlikely for most second- and third-generation agents (cefdinir, cefuroxime, cefixime, ceftibuten), because these agents lack a side chain similar to penicillin. By identifying the risk of infection, being aware of the risks of antibiotic therapy, and weighing the risks and benefits of each option, dermatologists can devise individualized treatments, thus optimizing outcomes of their patients.

Introduction

In surgery, antibiotic prophylaxis refers to the use of antimicrobial agents in surgical patients without an established infection.[1]

Whether or not antibiotic prophylaxis is appropriate in dermatologic procedures depends partly on the type of wound, which may fall into 1 of 4 categories: clean (class I), clean-contaminated (class II), contaminated (class III), and infected (class IV).[2] Clean wounds (eg, from excision of skin cancers or noninflamed cysts) are noncontaminated and excisions are performed using sterile techniques. Since the infection rate of clean wounds is less than 5%, antibiotic prophylaxis is generally not necessary, the exception being extended surgical procedures (eg, extensive Mohs' surgical procedures). The second type, clean-contaminated wounds, comprises dermatologic surgical procedures in contaminated areas (mouth, respiratory tract, axillae). These have a 10% infection rate. Antibiotic prophylaxis should be considered, depending on the surgical site, length, and nature of the procedure, overall health of the patient, and level of contamination.[3] The third type, contaminated wounds, has visibly inflamed tissue (eg, infected cysts) or are associated with trauma or major breaches of sterile surgical technique. Their infection rate ranges from 20% to 30%. The fourth type, infected wounds (eg, traumatic wounds), is heavily laden with necrotic tissue, foreign bodies, or pus. These wounds have a 30% to 40% rate of infection. Antibiotic prophylaxis is recommended for both contaminated and infected wounds.[2]

In dermatologic surgery, whether to prescribe antibiotics to prevent postoperative infection at the wound site and at distant sites (eg, endocarditis) is a controversial issue. Studies show that dermatologists misunderstand and overuse antibiotics to prevent endocarditis, surgical site infections, and prosthesis infections.[4-7]

The purpose of this paper is to summarize the current issues associated with antibiotic prophylaxis in cutaneous surgery.

Preventing Endocarditis

Bacterial endocarditis has considerable morbidity and mortality. Patients at high risk for endocarditis are those with prosthetic heart valves, previous endocarditis, complex cyanotic congenital heart disease, or surgically constructed systemic pulmonary shunts.[4] Patients with a history of serious heart conditions or cardiac surgery are at the highest risk for endocarditis, but the level of seriousness should also be taken into account. Patients at moderate risk are those with uncorrected patent ductus arteriosus, ventricular septal defect, primum atrial septal defect, coarctation of the aorta, or bicuspid aortic valve; acquired valvular dysfunction (rheumatic); or hypertrophic cardiomyopathy.

To prevent endocarditis in surgical procedures, the American Heart Association (AHA) has developed clinical practice guidelines[9] that apply especially to surgical patients with prosthetic cardiac valves, previous bacterial endocarditis, mitral valve prolapse with valvular regurgitation, or thickened leaflets. For these patients, the AHA recommends that antistaphylococcal antibiotics (eg, cephalosporins) be given before surgery only when the procedure involves joints, bone, nonoral soft tissue, or clinically infected wounds. The AHA does not, however, recommend prophylaxis when incisions or biopsy specimens are taken from noninfected, surgically scrubbed skin.[9]

In surgical patients whose mitral valves have normal motion and minimal Doppler-shown leaks, the risk for infection is minimal and requires no antibiotic prophylaxis. The same is true in patients with mitral valve prolapse in which leaking, murmurs, or Doppler-shown regurgitation is absent. Risk increases (1) when normal valves undergo prolapse with leaking, clicks and murmurs, and Doppler-shown insufficiency; (2) in the presence of myxomatous degeneration of the mitral valves, with or without prolapse or insufficiency; and (3) in men over age 45 years with prolapse, even in the absence of resting regurgitation. Antibiotic prophylaxis is justified in these high-risk patients.

Procedures that produce a temporary bacteremia carry an increased risk of infection. Such procedures involve mucosal surfaces and include dental, respiratory tract, gastrointestinal tract, and genitourinary procedures. Whether the surgically manipulated skin is infected is a primary consideration in antibiotic prophylaxis. If skin is clinically infected, the incidence of bacteremia with endocarditis-causing pathogens exceeds 35%.[10-12] Antibiotic prophylaxis is therefore required. In clinically uninfected skin, the incidence of infection may be minimal,[3] negating the need for antibiotic prophylaxis unless the patient is classified as high risk by the AHA. In one study,[12] bacteremia was induced in only 7% of patients undergoing skin surgery in the sebaceous-rich areas of the head and neck.

Orthopedic Prosthetic Devices

The American Academy of Orthopedic Surgeons offers comparable guidelines for antibiotic pretreatment for dental patients with total joint replacements.[9,13] Dermatologic surgeons should use guidelines similar to those for prevention of endocarditis when determining which surgical candidates need appropriate prophylactic antibiotics.

For dermatologic surgical patients with orthopedic prosthetic devices, there are no published guidelines for antibiotic prophylaxis. High risk is associated with previous prosthetic joint infections, passing of less than 2 years since joint replacement when cutaneous surgery is contemplated, malnourishment, diabetes, hemophilia, inflammatory arthropathies, and immunosuppression. Antibiotic prophylaxis is not required when skin is clean and intact and more than 2 years have lapsed since prosthesis was implanted.

Infection of prosthetic devices as a result of transient bacteremia stemming from surgical procedures is rare,[14] however. Most cases of prosthesis infection are due to infection during implantation or from suppurative infection at different anatomical locations.[14] *Staphylococcus aureus* and *Staphylococcus epidermidis* are the most frequent causative agents of prosthesis infection.

Currently, if there is mucosal involvement or an otherwise clean-contaminated class II wound due to surgery, the risk of infection is slightly elevated and prophylaxis should be considered. Any surgical wound that is clearly contaminated (class III or IV) or infected, or the patient underwent the joint surgery less than 6 months prior to cutaneous surgery, prophylaxis is necessary. These people are at the highest risk for infection.

Prophylaxis for Wound Infection

Antibiotics for prophylaxis against pathogens at various sites are shown in Table 1. Although anatomic location is a critical factor in antibiotic selection to prevent endocarditis, prosthesis, and surgical site infection,[14] the choice of antibiotic should be based on the pathogen most likely to cause infection. *S. aureus* and *S. pyogenes* are the primary pathogens in nonoral skin sites. Cephalosporins and dicloxacillin eradicate both organisms safely and cost effectively. For *Streptococcus viridans* and peptostreptococci, AHA guidelines suggest the use of amoxicillin.[3,14] Extended-spectrum cephalosporins such as cefdinir offer excellent coverage for Gram-positive infections as above but have additional coverage for common Gram-negative skin pathogens.

In patients allergic to penicillin, cross-reactions may occur with early-generation cephalosporins. Cross-reactions are unlikely, however, for most second- and third-generation agents (cefdinir, cefuroxime, cefixime, ceftibuten) because they lack a side chain similar to penicillin. Alternatives include lincosamides (clindamycin, 300 mg BID) followed by macrolides (clarithromycin and azithromycin 250 mg BID). For the groin or perineum, metronidazole (500 mg BID) may be added to levofloxacin.

Figure 1 shows a patient with postoperative infection of glabrous skin.

Risk Factors for Infection

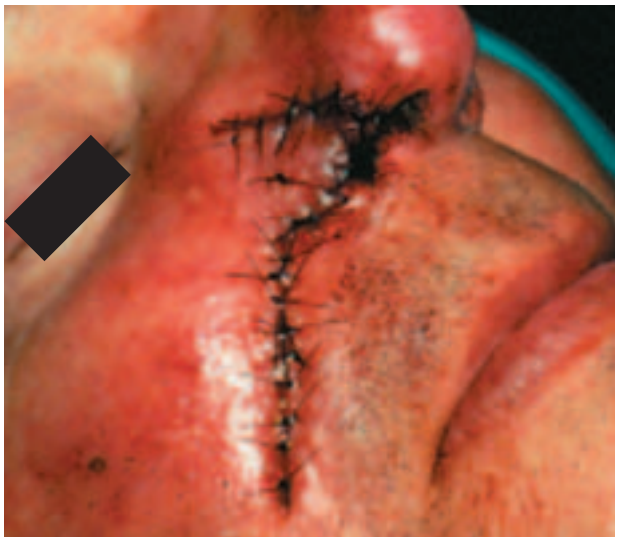
Risk factors for the development of infections at the surgical site are similar to the risk factors for bacterial endocarditis and orthopedic prosthesis infection. Diabetes mellitus is associated with impaired leucocyte mobilization and microangiopathy, and poor glucose control is associated with suboptimal wound healing. Malnutrition and chronic renal insufficiency

Table 1. Antibiotics for Prophylaxis According to Pathogen and Site.

Site	Pathogens	Antibiotic
Skin	*Staphylococcus aureus* *Streptococcus pyogenes*	Cephalosporin or dicloxacillin 500 mg BID
Oral/Nasal	*Streptococcus viridans* Peptostreptococcus	Amoxicillin 500 mg BID
Perineum	*Staphylococcus aureus* Enterococcus *Escherichia coli*	Amoxicillin/ clavulanate 500 mg BID
Ear	*Pseudomonas aeruginosa*	Levofloxacin 500 mg QD

are associated with impaired immune response, poor wound healing, and increased risk of postoperative infection. Smoking and obesity increase the risk for both superficial and deep-wound infections.[14] Other risk factors for infection include chronic use of steroids, advancing age, chronic illness, shaving less than 24 hours before surgery, length of the procedure, and concomitant infections. The infection rate doubles for each hour of the surgical procedure. Thus patients undergoing lengthy dermatologic surgical procedures such as multiple-stage Mohs surgical procedures may be candidates for surgical prophylaxis with broad-spectrum antibiotics.

Figure 1. Patient with Postoperative Infection of Glabrous Skin. This Patient Should be Treated with either Cephalosporin or Dicloxacillin.



Conclusion

Antibiotic prophylaxis is justified in surgical patients who are at moderate to high risk for endocarditis, prosthesis infection, or wound site infection or in patients undergoing lengthy procedures. Since most dermatologic surgical procedures are performed on skin not surgically scrubbed, AHA guidelines have limited application in dermatologic surgery. By identifying the risk of infection, being aware of the choices of antibiotic therapy, and weighing the risks and benefits of each option, dermatologists can devise individualized treatments, thus optimizing outcomes of their patients.

Dr. Nestor is a member of the Speakers Bureau of Abbott Laboratories.

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