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# Acute Bacterial Skin Infections in Pediatric Medicine

## Current Issues in Presentation and Treatment

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Physicians to Children & Adolescents

## Contents



## Abstract

Bacterial skin and skin structure infections commonly encountered in children include impetigo, folliculitis, furunculosis, carbuncles, wound infections, abscesses, cellulitis, erysipelas, scarlet fever, acute paronychia, and staphylococcal scalded skin syndrome. If diagnosed early and treated appropriately, these infections are almost always curable, but some have the potential to cause serious complications such as septicemia, nephritis, carditis and arthritis if diagnosis is delayed and/or treatment is inadequate. During the initial evaluation, it is important to determine whether the infection is superficial or deep, and whether it is localized or spreading. Prompt treatment is essential if the infection appears to be spreading, as the sequelae can be life threatening. Once the proper diagnosis is made, the next important step is selecting the most appropriate therapy. In children presenting with mild or moderately severe bacterial skin and skin structure infections and not requiring inpatient management or urgent operative débridement, prompt provision of oral antimicrobial therapy avoids the risk of worsening infection or hospitalization. Empiric antimicrobial therapy should be directed at the most likely pathogens, (e.g. *Staphylococcus aureu*s or *Streptococcus pyogenes*), although some infections (e.g. subcutaneous abscesses and cellulitis following animal or human bites) may have a polymicrobial origin. In choosing the appropriate

antimicrobial therapy, one must take into account the resistance profile of the target pathogen, the agent's antibacterial profile and intrinsic activity against the target pathogen, and its pharmacokinetic properties (including absorption, elimination, and extent of tissue penetration). Other factors to consider include tolerability of the drug, convenience of the dosing regimen, and acceptability and palatability of the oral formulation administered. Any treatment plan for bacterial skin and skin structure infections should aim to minimize the emergence of resistant organisms so that the risk of their dissemination to others in the community is reduced. Oral antimicrobial agents currently available that may be considered include: beta-lactamase–stable penicillins (e.g. cloxacillin, dicloxacillin, and amoxicillin-clavulanate potassium), the macrolides (e.g. erythromycin, clarithromycin, and azithromycin), and the cephalosporins. Cephalosporins are now the most commonly used class, particularly because of increasing resistance among strains of *S. pyogenes* to erythromycin (and by implication, the other macrolides). The second- and third-generation cephalosporins have many advantages, with their extended spectra of antimicrobial activity, favorable pharmacokinetic and tolerability profiles, and convenient dosage schedules. The third-generation agent, cefdinir, has good activity against a broad range of likely pathogens, including staphylococci, a twice-daily administration schedule, a favorable efficacy and tolerability profile, is well accepted by young children when administered as an oral suspension, and may be an attractive alternative in the pediatric setting.

## Introduction

Bacterial skin infections are commonly encountered in children.[1-4] In one survey, 24% of pediatric clinic consultations in the US, involved dermatologic complaints, of which bacterial skin infections comprised the highest percentage (17.5%).[5] When diagnosed early and treated appropriately, bacterial infections of the skin and skin structure are usually curable. If diagnosis is delayed or treatment is inadequate, some infections have the potential for serious sequelae such as nephritis, carditis, arthritis, and septicemia. Selection of the appropriate therapy is the most important step in the management of skin infections, and requires an understanding of the *in vitro* antibacterial activity, pharmacokinetic properties, tolerability of the agent selected, as well as potential resistance of microorganisms.[2] Bacterial skin infections in children vary from generally localized conditions, such as impetigo and folliculitis, to systemic conditions, such as staphylococcal scalded skin syndrome (SSSS). This article provides an overview of the clinical features and etiology of some of the more common acute skin and skin structure infections encountered in the pediatric age group, and outlines important considerations in their treatment. In doing so, it focuses on mild or moderately severe infections, seen in outpatient settings that commonly warrant oral antimcrobial therapy. More severe infections such as necrotizing fasciitis and synergistic necrotizing cellulitis, which constitute dermatologic emergencies, are outside the scope of this review.

## 1. Overview of Common Bacterial Skin and Skin Structure Infections: Clinical Features and Etiology

The most common bacterial skin and skin structure infections likely to be encountered in children include impetigo, folliculitis, furunculosis, carbuncles, wound infections, abscesses, cellulitis, erysipelas, scarlet fever, acute paronychia, and staphylococcal scalded skin syndrome (table I). Most of these infections are caused by *S. aureus* and group A β-hemolytic streptococci, notably *S. pyogenes*.[2,3] Of these, *S. aureus* is the most commonly encountered pathogen, but in some settings *S. pyogenes* is the principal pathogen and in others, both organisms may be isolated. Other organisms, such as *S. epidermidis,* group B streptococci, *Escherichia coli, Pseudomonas aeruginosa* and other Gram-negative bacteria, are only occasionally involved. Anaerobic organisms may be present in some infections, such as cutaneous abscesses, but in general, their role in uncomplicated skin and skin structure infections is not well defined, particularly because clinical success rates for infections from which they have been isolated appear unrelated to the antimicrobial activity of the chosen antibiotic against anaerobic bacteria.[2]

In children without predisposing risk factors, skin and soft tissue infections caused by methicillin-resistant staphylococcus aureus (MRSA) are becoming more commonplace.[6-11] MRSA is no longer only hospital acquired and has been seen with increasing frequency in the community setting. The isolates from these patients are less frequently multiply resistant to non-beta-lactam antibiotics especially clindamycin, than nosocomially-acquired MRSA isolates. Regardless of its susceptibility to methicillin, cellulitis and abscesses have been the predominant clinical manifestation of infection among all children with community-acquired infections due to *S. aureus*.

Bacterial skin infections occur when the normal flora is altered by the influence of factors such as ambient skin temperature, humidity, poor hygiene, crowded living conditions, pre-existing inflammatory dermatoses, and previous antimicrobial drug treatment, permitting pathogenic bacteria to adhere to and multiply on the skin.[3,4] Children with certain conditions such as diabetes mellitus, compromised immune systems, renal failure requiring hemodialysis, atopic dermatitis, and psoriasis are more susceptible to *S. aureus* colonization. In children with atopic dermatitis, for ex-

**Table I.** Features of common bacterial skin and skin structure infections in children

| Condition | Most frequent pathogens | Most commonly affected sites | Predisposing factors | Complications[a] |
|---|---|---|---|---|
| Impetigo (non-bullous, bullous) | *Staphylococcus aureus* (mainly), *Streptococcus pyogenes* | Face, limbs (non-bullous form) Moist, intertriginous regions (bullous form) | Overcrowding, poor hygiene, moist climatic conditions, minor skin abrasions, insect bites | Cellulitis (non-bullous form), septicemia, osteomyelitis, septic arthritis, lymphangitis, lymphadenitis, guttate psoriasis, staphylococcal scalded skin syndrome, acute post-streptococcal glomerulonephritis |
| Furuncles and carbuncles[b] | *S. aureus* | Neck, face, buttocks, axillae, groin | Overcrowding, poor hygiene, hyperhidrosis, obesity, seborrhea, diabetes, anemia, malnutrition, immunodeficiency | Septicemia, cavernous sinus thrombophlebitis (rare), local scarring |
| Cellulitis | *S. pyogenes* Less commonly: *S. aureus, Pasturella multocida, Aeromonas hydrophila* | Lower extremities, areas of lymphedema | Cutaneous abnormalities (e.g. skin trauma, ulceration, dermatitis, fungal infections) | Severe necrotizing subcutaneous infection (rare); lymphatic damage/obstruction (recurrent cellulitis) |
| Erysipelas | *S. pyogenes* | Face, arms, legs | Interdigital fungal infections | Chronic lymphedema (recurrent erysipelas) |
| Scarlet fever | *S. pyogenes* (erythrogenic toxin-producing strains) | Trunk, extremities, pharyngotonsillar area | Previous exposure to causative organism | Allergic glomerulonephritis, rheumatic fever, toxic myocarditis, suppurative arthritis, osteomyelitis, meningitis |
| Acute paronychia | *S. aureus* (mainly), *Pseudomonas* sp., *Proteus* sp. | Lateral and proximal nail folds | Dermatitis, trauma, nail biting, chronic thumb/finger sucking | Nail distortion, necrosis of tendons |
| Staphylococcal scalded skin syndrome (Ritter-Lyell syndrome) | *S. aureus* (toxin-producing phage group II) | Generalized (widespread detachment of superficial epidermis) | Prior pharyngitis, conjunctivitis or rhinorrhea | Sepsis, dehydration, fluid/electrolyte imbalance, pneumonia, cellulitis |

a If not treated promptly or adequately.

b Carbuncles usually affect an older age group.

ample, *S. aureus* can be isolated from skin lesions in approximately 90% of cases.[1,2,4]

Bacterial skin infections can usually be recognized by common presenting symptoms such as erythema/warmth, pain/tenderness, swelling, induration, crusting, and drainage. In diagnosing the condition, it is important to determine if the infection has the potential to become a serious or life threatening condition. The clinician must determine whether the condition is superficial or deep; localized or spreading; and whether it has purple discoloration, skin necrosis, or blistering. If the infection appears to be spreading, prompt treatment is essential, as the sequelae can be life threatening. Cellulitis, in particular, requires prompt intervention (see section 1.5).[1]

### 1.1 Impetigo

Impetigo is a highly contagious, superficial, pyogenic skin infection that presents as either a non-bullous or bullous form, and is commonly found in preschool and school-age children. The non-bullous form is the more common presentation, accounting for about 70% of cases.[3,4] Predisposing factors include overcrowding, poor hygiene, moist climatic conditions, minor skin abrasions, insect bites, pre-existing viral, fungal or parasitic infections, and pruritic conditions accompanied by scratching. The non-bullous form is predominantly caused by *S. aureus*, but *S. pyogenes* is involved in a number of cases and there are no discerning features that will allow the two causative organisms to be distinguished.[12] Non-bullous impetigo is characterized by small vesicles or pustules, usually on the face and limbs, which rupture and develop a yellowish-brown colored crusting. In most cases, the lesions are asymptomatic but they can be mildly pruritic. Autoinoculation with spread to surrounding areas is common. In severe cases, constitutional symptoms such as fever, malaise, and regional lymphadenopathy may occur. Spontaneous cure usually occurs in 2–3 weeks, but a prolonged course may be seen in patients with atopic dermatitis or parasitic infestations.[3,4]

The bullous form of impetigo is usually caused by toxin-producing, coagulase-positive strains of *S. aureus,* and generally presents as flaccid bullae that rupture easily, leaving moist erythematous lesions. The areas commonly affected are moist, intertriginous regions such as the neck folds and axillae.[3,4] The diagnosis of impetigo is usually made clinically and is confirmed by culture of lesional material, which is best taken from the base after removal of the crust, or from intact bullae. Differential diagnoses include herpes simplex type 1 (HSV-1) and varicella-zoster infections. Potential complications of impetigo include cellulitis (mostly in the non-bullous form), septicemia, osteomyelitis, septic arthritis, lymphangitis, lymphadenitis, guttate psoriasis, staphylococcal scalded skin syndrome, and acute post-streptococcal glomerulonephritis. The incidence of the latter complication varies between 2–5% but may be higher if nephrogenic strains of streptococci are involved.[3,4]

### 1.2 Furuncles and Carbuncles

Furuncles (boils) present as acute, tender perifollicular papules and papulonodules and are most often seen on the neck, breasts, face, buttocks, axillae, and groin. The initial nodule progresses to a pustule that discharges a core of necrotic tissue and sanguineous pus. The lesions can be single or multiple, with a tendency to occur in crops. Furunculosis is relatively uncommon in early childhood but the incidence increases in adolescents, particularly those living in crowded conditions with poor hygiene. Other predisposing factors include hyperhidrosis, obesity, diabetes, seborrhea, anemia, malnutrition, and immunodeficiency. Furuncles generally result from *S. aureus* infection, which can be cultured from pus obtained from the lesions. Spontaneous healing may occur following drainage but scarring can result. The lesions may recur in some patients, and in such cases, the infecting strains of *S. aureus* will often be found in the nares, axillae, or groin.[3,4,13] Carbuncles are large, confluent furuncles with multiple drainage points. They develop more slowly than furuncles and result in deep suppuration, often with extensive local sloughing, and may be accompanied by fever and prostration. Carbuncles are seen most frequently on the nape of the neck. They generally occur in an older age group than furuncles.

### 1.3 Folliculitis

Folliculitis is a superficial pustule or inflammatory nodule that surrounds a hair follicle. The lesions are small, dome-shaped pustules with an erythematous base, and may accompany or follow other pyodermas. The sites commonly affected are the scalp, extremities, perioral and paranasal regions, and areas of skin that are occluded or prone to moisture and friction, such as the axillae and medial thighs. Predisposing factors include a humid environment, poor hygiene, maceration, and drainage from wounds and abscesses. Folliculitis may become chronic where the hair follicles are numerous or deep in the skin. A Gram stain and culture of pus usually identify the causative organism.[3,4,13] The most common causative organism is *S. aureus*. 'Hot tub' folliculitis, usually caused by *P. aeruginosa*, occurs hours to days after immersion in poorly chlorinated pools, whirlpools or hot tubs.

### 1.4 Cutaneous Abscesses

Cutaneous abscesses commonly follow minor skin trauma and present as a localized collection of pus causing soft tissue swelling surrounded by erythema. Variable accompanying features include local cellulitis, lymphangitis, regional lymphadenopathy, fever and leukocytosis. Lesions occurring on the head, neck, trunk, extremities, and axillae are most often caused by *S. aureus,* but anaerobic organisms such as *Peptococcus* sp. and *Propionibacterium* sp. may also be involved. Abscesses occurring in the perineal region are commonly caused by anaerobes (e.g. *Peptococcus* sp., *Peptostreptococcus* sp., *Lactobacillus* sp., *Bacteroide*s sp., and *Fusobacterium* sp.) or by a combination of anaerobes and aerobes (particularly α-hemolytic and non-hemolytic streptococci).[13]

### 1.5 Cellulitis

Cellulitis is characterized by disseminating, acute inflammation within solid tissue, hyperemia, white blood cell infiltration, and edema but without cellular necrosis or suppuration. It is most commonly seen in the lower extremities, and may be preceded by skin trauma, ulceration, dermatitis, or fungal infection, but often no predisposing condition or site of entry is apparent. In small children, cellulitis may present as a perianal infection.[14] The major symptoms are local erythema and tenderness, frequently with lymphangitis and regional lymphadenopathy. Petechiae are common, and vesicles and bullae may develop and rupture, occasionally with necrosis of the affected skin. Systemic manifestations such as fever, chills, headache, tachycardia, hypotension, and delirium may precede the cutaneous findings, although many patients show no signs of illness.[3,13] Unlike erysipelas (see section 1.6), which is more superficial, cellulitis is a deeper infection and involves the dermis and cutaneous tissue.[4] *S. pyogenes* is the most common cause of cellulitis. Enzymes produced by this organism break down cellular components that would otherwise contain and localize the inflammation. Less common causes include groups B, C, D and G β-hemolytic streptococci and *S. aureus*, or a combination of these organisms. These organisms produce cellulitides that are usually associated with an open wound or abscess, and are less extensive than those caused by streptococci. Cellulitis occurring after animal and human bites may be caused by *Pasteurella multocida* and *Eikenella corodens*, respectively, whereas infection resulting from immersion in stagnant water may be caused by

*Aeromonas hydrophila*. Facial (buccal) cellulitis in children, which is primarily caused by *Haemophilus influenzae* type b (Hib), is now rarely encountered since the advent of Hib vaccines.[15] This condition can also be caused by *Streptococcus pneumoniae,* although cases are rare. Unless pus has formed or an open wound is present, the causative organism of cellulitis may be difficult to isolate, even on aspiration or skin biopsy. However, blood cultures may occasionally be positive.[3,13] It is likely that in regions where the pneumococcal conjugate vaccine is administered, pneumococcal cellulitis will be less prevalent in the future.

### 1.6 Erysipelas

Erysipelas is a superficial cellulitis characterized by painful, sharply demarcated, erythematous, slightly elevated, indurated lesions usually occurring on the face but also on the arms and legs. Patches of peripheral redness and regional lymphadenopathy may occasionally be present, and with recurrent infection, chronic lymphedema may be noted. Systemic manifestations such as fever, chills, headache, and myalgia are often present.[3,13] As with cellulitis, the most common causative organism is *S. pyogenes;* groups C or G β-hemolytic streptococci are rarely involved. Again, the causative organism is difficult to isolate from lesions but may occasionally be cultured from the blood.

### 1.7 Scarlet Fever

Scarlet fever is not the major health problem it used to be, but is still seen in pediatric practice. It is characterized by a *S. pyogenes* infection followed by a fine, papular, erythematous rash. Initially, the scarletiniform eruptions appear on the axillae, groin, and neck, and then become more generalized on the trunk and extremities within 24 hours. Usually scarlet fever is a result of "strept throat" but may be caused by a primary *S. pyogenes* infection of the skin, soft tissue, surgical wound (surgical scarlet fever), or uterus (puerperal scarlet fever).

Scarlet fever is caused by erythrogenic toxins (SPE-B and SPE-C) produced by *S. pyogenes*. These toxins are believed to cause a delayed-type hypersensitivity reaction. The diagnosis is made on clinical grounds but can be confirmed by the isolation of group A streptococci from the site of the infection. Potential complications of scarlet fever include allergic glomerulonephritis, rheumatic fever, toxic myocarditis, suppurative arthritis, osteomyelitis, and meningitis.[4]

### 1.8 Acute Paronychia

Unlike chronic paronychia, which is most often caused by *Candida albicans*, acute paronychia is usually bacterial in origin. It presents with erythema, edema, and tenderness of the proximal and lateral nail fold or may extend beneath the nail and suppurate. Necrosis of tendons may result with extension of the infection along tendon sheaths, but this is rare. The most common causative organism is *S. aureus,* although other organisms, such as *Pseudomonas* sp., *Proteus* sp. and anaerobic bacteria, may also be present. Predisposing factors for the development of acute paronychia include dermatitis, trauma, nail biting and chronic thumb or finger sucking.[3,13]

### 1.9 Staphylococcal Scalded Skin Syndrome (Ritter-Lyell Syndrome)

This condition occurs predominantly in children <6 years of age. SSSS is a toxin-mediated epidermolytic disease characterized by erythema and widespread detachment of the superficial epidermis. Initially, it presents as localized crusted lesions, most often at the umbilical stump or in the diaper region, accompanied by systemic signs (e.g. fever, chills, and malaise). Within 24 hours, tender scarlet areas arise and become generalized, and large, flaccid bullae appear which rupture rapidly, leaving erythematous, moist, eroded areas, notably in flexural areas. When rubbed, the epidermis peels off easily, often in large sheets. Widespread desquamation of the skin occurs within 36–72 hours. Loss of the protective skin can lead to sepsis and fluid and electrolyte imbalance.[4,13] The organism causing SSSS is a toxin-producing *S. aureus*, usually a phage group II strain. The toxin elaborated by this organism is known as exfoliatin, as it splits off the upper part of the epidermis just beneath the granular cell layer. As in scarlet fever, the toxin enters the circulation and affects the skin systemically. The inciting infection is usually in the eye or nasopharynx.[13] In children presenting with the typical clinical features, it is important to differentiate SSSS from toxic epidermal necrolysis (TEN), caused by drug hypersensitivity. The diagnosis can be confirmed by skin biopsy and examination of frozen tissue sections or exfoliative cytology. Cultures should be obtained from the skin and nasopharynx to identify the causative organism.

## 2. Antimicrobial Treatment

Once the diagnosis has been established, it is important to determine if the infection requires inpatient management and/or urgent operative débridement. Assuming that the infection is localized and not severe, important considerations in treating the condition include: (1) acquisition of specimens, if possible, for culture and sensitivity, (2) incision and drainage of the lesion, where indicated (e.g. for subcutaneous abscesses or furuncles), (3) prompt initiation of treatment, (4) directing empiric antimicrobial therapy to the most likely pathogen (taking into account local resistance patterns), (5) management of any comorbid conditions such as atopic dermatitis or parasitic infestations, and (6) as warranted,

institution of measures to limit transmission of the pathogen, including education of patients and their families on the need to maintain good hygiene. The goals of treatment are to achieve prompt eradication of the pathogen with consequent early resolution of the infection and a low recurrence rate. In addition, the treatment plan for bacterial skin and skin structure infections should aim to minimize the emergence of resistant organisms. Appropriate measures in this regard include not treating patients with trivial infections or those who are carriers. An appropriate antimicrobial agent should be used that will maximize the odds of eradicating the pathogen. Treatment should continue for an appropriate length of time (usually 10 days). In the event of treatment failure, such as the absence of a satisfactory clinical response after approximately 7 days of therapy, an antimicrobial agent with activity against the identified pathogen should be substituted. Finally, strict handwashing with an antiseptic soap or the use of disposable gloves should be standard practice.

### 2.1 General Considerations in Selection of Antimicrobial Therapy

For most skin and skin structure infections, empiric antibacterial therapy should be directed against the most likely pathogen, *S. aureus* and *S. pyogenes*. Exceptions to this include: (1) infections known to be due to another organism, e.g. 'hot tub' folliculitis which is commonly caused by *P. aeruginosa,* and (2) those known to have a polymicrobial etiology (e.g. subcutaneous abscesses and cellulitis following animal or human bites).[2] Factors to consider when selecting an antimicrobial agent are presented in table II. The resistance profile of the target organism is a key factor because therapeutic failure may result if an inappropriate agent is chosen. Data available from sources outside of the US indicate that the majority of skin isolates of *S. aureus* are now resistant to penicillin, and they are becoming increasingly resistant to erythromycin.[16,17] In addition, clinically significant resistance of *S. pyogenes* to erythromycin has emerged in the last two decades.[18,19] The emergence of antimicrobial resistance is a relatively recent phenomenon that has, in part, been a consequence of the excessive use of antimicrobial drugs during the 1980s and their inappropriate prescribing, such as for viral infections. To promote the judicious use of antimicrobial agents and thus reduce antimicrobial resistance, a variety of campaigns and interventions have been introduced, including the dissemination of treatment guidelines that have the potential to improve prescribing practices, although their impact on clinical practice has been variable.[20] Another important consideration in the selection of antimicrobial therapy is cost-effectiveness. Although the third-generation cephalosporins, for example, have relatively high acquisition costs, particularly in comparison with the penicillins, the indirect costs of therapy also need to be taken into account. From a societal perspective, the direct costs of therapy may be outweighed by other costs, such as the need for laboratory tests, additional treatment for complications of the infection or adverse drug effects (e.g. diarrhea and hypersensitivity reactions), and the costs of lost productivity through days off work (by parents) and school attributable to inadequate resolution of the infection through an inappropriate choice of medication.[21] Although detailed cost-effectiveness studies have yet to be conducted, it is conceivable that the overall efficacy and tolerability of the third-generation cephalosporins may provide economic benefits in the management of bacterial skin infections in children.

### 2.2 Oral Antimicrobial Therapy: Advantages and Limitations of Available Agents

Among the various antimicrobial agents available for treatment of bacterial infections of the skin and skin structure in children are penicillins, macrolides, cephalosporins, and lincosamides. Currently available oral formulations of agents from these classes and their usual pediatric dosages in bacterial skin and skin structure infections are shown in table III. Other classes of antimicro-

**Table II.** Factors in selecting an appropriate antimicrobial agent for treatment of bacterial skin and skin structure infections in children

- Intrinsic activity against the most likely pathogens, particularly *Staphylococcus aureus* and *Streptococcus pyogenes,* but also other aerobic and anaerobic bacteria (depending on the diagnosis)
- Consideration of the antibiotic resistance profile of the target organism (e.g. widespread resistance to penicillin among strains of *S. aureus,* and increasing resistance to erythromycin among strains of *S. pyogenes*)
- Propensity to select for emergence of resistant micro-organisms
- Pharmacokinetic properties:
  —absorption (bioavailability and influence of food on absorption)
  —elimination (in relation to frequency of administration)
  —tissue penetration (ability to achieve and maintain therapeutic concentrations at the site of infection)
- Dosing convenience (once-daily or twice-daily schedules vs three times daily or four times daily schedules)
- Tolerability (particular potential to cause gastrointestinal intolerance)
- Acceptability and palatability of the oral formulation (important in encouraging medication compliance)
- Cost, direct and indirect (including consideration of the decreased productivity that may arise from parents being at home with their child if the initial treatment does not provide rapid resolution of the condition, and costs of managing any adverse drug effects)

bials, such as the fluoroquinolones and tetracyclines, are not appropriate choices for use in children, due to concerns over the possible development of drug-induced arthropathy in the case of the fluoroquinolones, and staining of permanent teeth in children under 8 years of age in the case of the tetracyclines. Although the agents shown in table III have all demonstrated efficacy in clinical trials in children with bacterial skin or skin structure infections, it needs to be borne in mind that such trials will occasionally exclude patients with bacterial isolates resistant to the drug being studied, which makes interpretation of their results and comparisons with data from other trials difficult.

#### 2.2.1 Penicillins

Although *S. pyogenes* remains sensitive to oral penicillin V (phenoxymethylpenicillin), resistance among *S. aureus* strains is widespread and in some areas, almost 100% of isolates produce inactivating beta-lactamases.[17,22] Consequently, penicillin V and the broader-spectrum semisynthetic analogs ampicillin and amoxicillin, which are also inactivated by beta-lactamases, are no longer appropriate choices for the treatment of uncomplicated bacterial skin infections. However, beta-lactamase–stable penicillins such as cloxacillin, dicloxacillin, and the combination of amoxicillin and the beta-lactamase inhibitor clavulanate potassium, exhibit good antistaphylococcal activity and good tissue penetration, and remain appropriate choices in settings where *S. aureus* or *S. pyogenes* are involved (e.g. impetigo, furunculosis, folliculitis, and mild cellulitis). In view of the extended spectrum of activity of amoxicillin against both Gram-positive and Gram-negative bacteria, the amoxicillin-clavulanate potassium combination can also be used if a polymicrobial infection is suspected (e.g. subcutaneous abscesses and cellulitis following animal or human bites).[1,2] However, the use of amoxicillin-clavulanate potassium is compromised by the occurrence of amoxicillin-induced rash and diarrhea, which occur in <4% and 10% of children, respectively.

#### 2.2.2 Macrolides

##### Erythromycin

Erythromycin, the first of the macrolide antimicrobials to be discovered, has been in therapeutic use since the 1950s, and its efficacy for the treatment of pediatric skin and skin structure infections has been well described. However, several drawbacks limit the use of erythromycin for this indication, including the occurrence of frequent gastrointestinal intolerance, a short elimination half-life requiring four-times-daily administration, and increasing resistance among strains of *S. aureus* and *S. pyogenes* during the last two decades. The occurrence of erythromycin resistance appears to correlate with the frequency of usage of the drug in the community and can be either of the macrolide, lincosamide, streptogramin B (MLS) type or the Mef or pump type. The MLS type is conferred by methylation of a specific bacterial ribosomal RNA residue and results in decreased antibiotic binding to the target 50s subunit of the bacterial ribosome and a decreased ability to block bacterial protein synthesis[2,23,24]. The MEF retains susceptibility to clindamycin.

##### Clarithromycin and Azithromycin

The newer macrolides, clarithromycin and azithromycin, exhibit improved pharmacokinetic properties, enhanced activity against Gram-negative organisms (notably *H. influenzae*), and fewer gastrointestinal adverse effects in comparison with erythromycin. Both clarithromycin and azithromycin are more acid-stable than erythromycin and have higher bioavailabilities following oral administration. They also achieve higher tissue concentrations and have longer elimination half-lives (table IV), which permit once-daily administration in the case of azithromycin and twice-daily administration in the case of clarithromycin.[23-25] The antibacterial activities of clarithromycin and azithromycin against *S. pyogenes* and methicillin-susceptible *S. aureus* are similar and 2- to 4-fold lower, respectively, than that of erythromycin. Like erythromycin, both are generally inactive against methicillin-resistant *S. aureus*. The occurrence of resistance to erythromycin implies that cross-resistance to clarithromycin and azithromycin will occur.[23-25]

Clinical trials of clarithromycin and azithromycin in children with skin and skin structure infections have demonstrated the efficacy of both agents, although azithromycin has yet to be approved for this indication in children <12 years of age in the US. In a randomized, investigator-blinded comparative study of 231 children with mild-to-moderate bacterial skin or skin structure infections, clarithromycin 7.5 mg/kg twice daily was compared with the first-generation cephalosporin cefadroxil 15 mg/kg twice daily. High clinical cure rates of 96% and 98%, respectively, were achieved with both agents.[26] Similarly, a randomized, open-label study of azithromycin 10 mg/kg once daily for 3 days and second-generation cephalosporin, cefaclor 20 mg/kg daily in 3 divided doses for 10 days in 200 children with mild-to-moderate infections found that the two treatments were equally effective, 94% of patients receiving azithromycin were cured or improved as were 95% of those receiving cefaclor.[27] In both of these studies, the macrolide agents were as well tolerated as their cephalosporin comparators. In conclusion, while clarithromycin has approval by the Federal Drug Administration (FDA) for the treatment of skin infections in children and adults, and azithromycin has approval in adults, the increasing rates of infection with macrolide-resistant strains of *S. pyogenes* and *S. aureus* limit the usefulness of these agents.[19]

#### 2.2.3 Cephalosporins

Prior to the 1990s, the cephalosporins were generally regarded as second-line agents in the treatment of bacterial skin and skin structure infections. Since 1990, however, a number of newer

**Table III.** Oral antimicrobial agents approved for use in children for skin and skin structure infections in the US

| Drug/Group | Pediatric dosage forms | Usual dosage (mg/kg/day)[a] | Dosing interval |
|---|---|---|---|
| **Cephalosporins** | | | |
| *First-generation agents* | | | |
| Cefadroxil | Suspension, 125 mg/5mL, 250 mg/5mL, 500 mg/5mL | 30 | q12h |
| Cephalexin | Suspension, 125 mg/5mL, 250 mg/5mL<br>Capsule, 250 mg<br>Tablet, 250 mg | 25–50 | q6h or q12h |
| Cephradine | Suspension, 125 mg/5mL, 250 mg/5mL<br>Capsule, 250 mg | 25–50 | q6h or q12h |
| *Second-generation agents* | | | |
| Cefaclor | Suspension, 125 mg/5mL, 187 mg/5mL, 250 mg/5 mL, 375 mg/5mL<br>Capsule, 250 mg | 20–40 | q8h |
| Cefprozil | Suspension, 125 mg/5mL, 250 mg/5mL<br>Tablet, 250 mg | 20 | q24h |
| Cefuroxime axetil | Suspension, 125 mg/5mL, 250 mg/5mL<br>Tablet, 125 mg, 250 mg | 30 | q12h |
| Loracarbef[b] | Suspension, 100 mg/5mL, 200 mg/5mL<br>Capsule, 200 mg | 15 | q12h |
| *Third-generation agents* | | | |
| Cefdinir | Suspension, 125 mg/5mL<br>Capsule, 300 mg | 14 | q12h |
| **Macrolides** | | | |
| Clarithromycin | Suspension, 125 mg/5mL, 250 mg/5mL<br>Tablet, 25 0mg | 15 | q12h |
| Erythromycin | Suspension, 125 mg/5mL[c], 200 mg/5mL[d], 250 mg/5mL[c], 400 mg/5mL[d]<br>Drops, 100 mg/2.5mL[d]<br>Chewable tablet, 200 mg[d]<br>Tablet, 250 mg[e], 333 mg[f] | 20–50 | q6h |
| **Penicillins** | | | |
| Amoxicillin | Suspension, 125 mg/5mL, 200 mg/5mL, 250 mg/5mL, 400 mg/5mL<br>Drops, 50 mg/mL<br>Chewable tablet, 125 mg, 200 mg, 250 mg | 20–40 | q8h |
| Amoxicillin-clavulanate potassium (co-amoxiclav) | Suspension, 125/31.25 mg/5mL, 200/28.5 mg/5mL, 250/62.5 mg/5mL, 400/57 mg/5mL<br>Chewable tablet, 125/31.25mg, 200/28.5 mg, 250/62.5 mg, 400/57mg | 20–40 (as amoxicillin) | q8h |
| Ampicillin | Suspension, 125 mg/5mL, 250 mg/5mL<br>Capsule, 250mg | <20kg: 50 >20kg: 250 mg[g] | q6h |
| Cloxacillin | Solution, 125 mg/5mL<br>Capsule, 250 mg | <20kg: 50 >20 kg: 250 mg[g] | q6h |
| Dicloxacillin | Suspension, 62.5 mg/5mL<br>Capsule, 250 mg | 12.5 | q6h |
| Penicillin V (phenoxymethylpenicillin) | Solution, 125 mg/5mL, 250 mg/5mL<br>Tablet, 250 mg | 25–50 | q6h |
| **Lincosamides** | | | |
| Clindamycin | Solution, 75 mg/5mL<br>Capsule, 75 mg | 8–16 | q6h or q8h |

a Total daily dosage administered in divided doses, unless stated otherwise.

b Carbacephem compound.

c Erythromycin estolate.

d Erythromycin ethyl succinate.

e Erythromycin base or stearate.

f Erythromycin base.

g Individual unit dose.

**Table IV.** Pharmacokinetic parameters of the available macrolide antimicrobial agents following single oral doses of 500 mg (after Zuckerman with permission[24])

| Drug | Pharmacokinetic parameters (mean values) | | | | |
|---|---|---|---|---|---|
| | F (%) | $C_{max}$ (μg/mL) | $t_{max}$ (h) | AUC (μg/mL•h) | $t_{½}$ (h) |
| Erythromycin | 25 | 0.3–2.0 | 4 | 14.2 | 1.4–2.0 |
| Clarithromycin | 55 | 2.1–2.4 | 2 | 12–18.9 | 4.3–4.9 |
| Azithromycin | 37 | 0.4 | 2 | 3.4 | 40 |

**AUC** = area under the plasma concentration-time curve; $\mathbf{C_{max}}$ = peak plasma concentration; **F** = bioavailability; $\mathbf{t_{½}}$ = elimination half-life; $\mathbf{t_{max}}$ = time to peak plasma concentration.

compounds have become available with improved activity against the primary pathogens. They have favorable pharmacokinetic characteristics that provide effective concentrations above minimum inhibitory levels in tissues, and less frequent (once- or twice-daily) administration schedules. These advances, together with the good tolerability profiles of this entire class of antimicrobials, have led to oral cephalosporins becoming the most commonly used antimicrobials for outpatient treatment of bacterial skin and skin structure infections in the US.[1,2] Although hypersensitivity reactions to cephalosporins occur occasionally, the risk of such reactions in individuals with a history of non-anaphylactic penicillin hypersensitivity appears to be very low (probably <2%) and they are generally safe to administer in such patients.[28,29]

### First-generation Cephalosporins

The first-generation cephalosporins have good activity against *S. pyogenes* and methicillin-susceptible strains of *S. aureus* and are clinically effective in bacterial skin and skin structure infections in children. However, with the exception of cefadroxil, they have elimination half-lives of less than 1 hour (table V) and usually need to be administered three or four times daily. Cefadroxil carries an advantage over other first-generation agents by having a longer elimination half-life and higher concentrations in skin blister fluid relative to serum for at least 6 hours after an oral dosage, which permits once- or twice-daily administration. Another advantage of cefadroxil is that its absorption is unaffected by food, milk, or infant formula.[2]

Clinical trials of cefadroxil in children with uncomplicated bacterial skin and skin structure infections have provided evidence of its efficacy when administered either once or twice daily. In comparative studies in which a twice-daily regimen was used, cefadroxil 15 mg/kg every 12 hours proved equally effective in achieving a clinical cure in bacterial skin infections as clarithromycin[26] but it was less effective than cefuroxime axetil.[30] With a once-daily regimen, cefadroxil 30 mg/kg every 24 hours was significantly more effective than cephalexin 15 mg/kg every 12 hours in achieving a good clinical response in a randomized multicenter study of 462 children and adolescents (94% vs 86% of patients, respectively, p = 0.024).[31]

### Second-generation Cephalosporins

In comparison with first-generation cephalosporins, the second-generation agents provide expanded activity against many strains of Gram-negative bacteria, including *H. influenzae* type b and enteric bacteria. Among the available second-generation cephalosporins, cefprozil, cefuroxime axetil, and loracarbef have the advantage of having longer elimination half-lives that permit

**Table V.** Pharmacokinetic parameters of the oral cephalosporins used in bacterial skin and skin structure in children (where available, values cited are from studies in children)

| Agent | F (%) | $t_{½}$ (h)[a] | CL (L/h)[a] | Vd (L/kg) | Protein binding (%) |
|---|---|---|---|---|---|
| *First-generation agents* | | | | | |
| Cefadroxil[b] | ≈ 90 | 1.3–1.6 | 12 | 0.4 | 20 |
| Cephalexin[b] | 90 | 0.8–1.0 | 15 | 0.3 | 10–15 |
| Cephradine[b] | >90 | 0.8 | 17 | 0.25 | 8–17 |
| *Second-generation agents* | | | | | |
| Cefaclor[b] | 90 | 0.6–0.9 | 30 | 0.5 | 25 |
| Cefprozil[b] | ≈ 95 | 1.3 | 12.6 | 0.23 | 36 |
| Cefuroxime axetil[c] | | 1.4–1.9 | 8 | 0.25 | 50 |
| Loracarbef[b,d] | ≈ 90 | 1.1 | 15 | 0.34 | 25 |
| *Third-generation agents* | | | | | |
| Cefdinir[b] | 20–25 | 1.3–1.6 | 49–65 | 0.67 | 61–73 |
| Cefpodoxime proxetil[b,e] | ≈ 50 | 2.1–2.7 | 26–29 | 1.0 | 21–29 |

a In patients with normal renal function.

b Values shown are in children.

c Values shown are for cefuroxime (formed following de-esterification of the administered prodrug by non-specific esterases in the intestinal mucosa).

d Carbacephem compound.

e Values shown are for cefpodoxime (formed following de-esterification of the administered prodrug by non-specific esterases in the intestinal mucosa).

**F** = bioavailability; **CL** = apparent total body clearance; $\mathbf{t_{½}}$ = elimination half-life; **Vd** = apparent volume of distribution.

once-daily (cefprozil) or twice-daily (cefuroxime axetil and loracarbef) administration (table V), and greater stability against β-lactamases than cefaclor.[2,32-34] In a review of comparative clinical trials with cefprozil in pediatric and adult patients with bacterial skin or skin structure infections, once-daily cefprozil therapy provided equivalent clinical efficacy to cefaclor (three times daily), erythromycin (four times daily), and amoxicillin-clavulanate potassium (three times daily).[35,36] In a study confined to children, cefprozil 20 mg/kg every 24 hours and cefaclor 20 mg/kg/day in 3 divided doses achieved similar clinical and bacteriologic response rates of 97% and 96%, respectively.[36] Similarly, a study of loracarbef 7.5 mg/kg every 12 hours and cefaclor 20 mg/kg/day in 3 divided doses in children reported equivalent clinical response plus bacteriologic eradication rates with these agents of 97.3% and 92.3%, respectively.[37] In a comparison of twice-daily therapy with cefuroxime axetil 15 mg/kg every 12 hours and cefadroxil 15 mg/kg every 12 hours, similar bacteriological eradication rates were achieved with the two agents (97.1% vs 94.3%, respectively), in 287 children with bacterial skin or skin structure infections. However, the clinical response rate was slightly higher in those who received cefuroxime axetil (97.8% vs 90.3%, respectively, $p < 0.05$).[30]

Third-generation Cephalosporins

The newer, third-generation agents cefdinir and cefpodoxime proxetil have an extended spectrum of activity against Gram-positive and Gram-negative aerobes, including most Gram-negative enteric organisms. Although cefdinir has demonstrated *in vitro* bactericidal activity (minimum inhibitory concentration [MIC] $\leq$ 1 μg/mL) against most strains of Gram-negative aerobes, the drug's efficacy in treating infections due to these pathogens remains to be established in adequate and well-controlled clinical trials. While cefpodoxime proxetil shows only moderate activity against the Gram-positive aerobe *S. aureus,* [38]cefdinir has good activity against this organism (though not against methicillin- or oxacillin-resistant strains) and is stable to numerous β-lactamases.[39-45] Brief (up to 2 hours) post-antibiotic effects, (i.e. continuation of inhibitory activity after its removal), have been reported with cefdinir for *S. aureus* and *S. pyogenes*.[46] Both third-generation agents have elimination half-lives that permit twice-daily administration (table V), and penetrate well into skin blister fluid.[38,39,44,45,47] They are also well tolerated by children, with adverse event profiles similar to other cephalosporins.[38,39,44,45] Clinical trials have demonstrated the efficacy of both cefdinir and cefpodoxime proxetil in children with skin or skin structure infections. In a randomized investigator-blinded study that compared cefdinir 7 mg/kg every 12 hours and cephalexin 10 mg/kg every 6 hours in 394 children with skin infections such as impetigo, infected dermatitis, wound infections, cellulitis, and acute paronychia, clinical cure rates were slightly greater, but not significant, with cefdinir, 98.3% vs 93.8% with cephalexin, $p = 0.056$, and bacteriological eradication rates were similar (99.4% and 97.4%, respectively).[48] Both drugs were well tolerated, although diarrhea was slightly more common with cefdinir. Underlining its good efficacy and tolerability profile, a comparison of the palatability of the oral suspension formulation of cefdinir with oral suspensions of amoxicillin-clavulanate potassium, cefprozil, and azithromycin in children aged 4–8 years found that acceptance of the cefdinir formulation was statistically significant compared with that of the other three agents.[49,50] There have been no reported comparative studies of cefpodoxime proxetil with other antimicrobial agents in children with bacterial skin or skin structure infections. Thus, the FDA has not approved cefpodoxime proxetil for the treatment of skin infections in children <12 years of age. In an open-label study that enrolled 110 children with impetigo, furunculosis or acute paronychia, cefpodoxime proxetil 2.2–5 mg/kg every 12 hours or every 8 hours achieved a high global cure rate of 95.1% and bacteriological eradication in 98.9% of patients.[51]

#### 2.2.4 Lincosamides (Clindamycin)

Although clindamycin has been used over the past two decades to treat bacterial skin and skin structure infections, particularly recurrent or recalcitrant infections such as furunculosis caused by *S. aureus,*[52,53] the relative risk (versus that of other antimicrobial agents) of *Clostridium difficile*-associated pseudomembranous colitis with this agent and its three- or four-times-daily dosage schedule has limited its use in the pediatric setting. However, because of its good activity against both anaerobic bacteria and Gram-positive organisms, clindamycin remains of value in serious skin and skin structure infections caused by mixed aerobic and anaerobic pathogens (e.g. abscesses and necrotizing subcutaneous infections), as well as recurrent staphylococcal infections such as furunculosis or carbunculosis.[2] Additionally, clindamycin is effective against many community-acquired MRSA strains, an increasingly important problem in the US. Susceptibility testing, including the Kirby-Bauer disk test must be done before use in such infections.

#### 2.2.5 Mupirocin

The use of topical agents to treat superficial skin infections can limit exposure to systemic agents and deliver high drug concentrations to the site of infection. Mupirocin, formerly called pseudomonic acid A, is a chemically unique topical antibiotic produced by the submerged fermentation of *Pseudomonas fluorescens*. Mupirocin inhibits bacterial protein synthesis by reversibly and specifically binding to isoleucyl transfer, RNA synthetase.[54,55] At low concentrations, mupirocin is bacteriostatic against *S. aureus*. At high concentrations, mupirocin is bactericidal. Mupirocin is highly active against staphylococci and streptococci, the major pathogens found in skin infections.[56]

Mupirocin has been shown to be as effective as oral antibiotics in a number of clinical trials.[18,57-60]

## 3. Conclusions

For children with acute bacterial skin or skin structure infections who require systemic antimicrobial therapy, early institution of an appropriate oral agent with good *in vitro* activity against the likely pathogen(s) and good bioavailability, especially at the site of infection, is essential. Empiric antimicrobial therapy for bacterial skin and skin structure infections should be instituted with an agent that has excellent antimicrobial activity against the likely pathogen(s). In addition to the agent's spectrum of activity and pharmacokinetic characteristics, factors to consider when selecting appropriate antimicrobial therapy include the convenience of the dosage schedule, tolerability, palatability, and local antibiotic resistance patterns among the likely causative pathogens. Selection of an inappropriate agent in locations where there is widespread antimicrobial resistance (e.g. penicillin resistance among staphylococci resulting from beta-lactamase production or macrolide resistance among streptococci) may lead to treatment failure. Although clinical trials have not provided clear evidence of the superiority of third-generation cephalosporins over other antimicrobial agents, the extended spectra of activity of the third-generation cephalosporins against Gram-positive and Gram-negative aerobes (demonstrated *in vitro* for the latter pathogens and not in clinical trials) and their favorable pharmacokinetic and tolerability profiles offer distinct advantages for antimicrobial treatment of bacterial skin and skin structure infections, particularly those known or suspected to be due to beta-lactamase–producing staphylococci or erythromycin-resistant streptococci. Cefdinir has good activity against a broad range of likely pathogens (including staphylococci), twice-daily administration schedule, favorable efficacy and tolerability profile, and is well accepted by young children when administered as an oral suspension. In this regard, cefdinir would appear to be an alternative capable of maximizing the potential for successful antimicrobial treatment of bacterial skin and skin structure infections in children.

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