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Uncomplicated Skin and Skin Structure Infections in Children: Diagnosis and Current Treatment Options in the United States

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Uncomplicated skin and skin structure infections (SSSIs), such as simple abscesses, furuncles and carbuncles, cellulitis, erysipelas, and impetigo, provide some of the most common reasons for visits to pediatric outpatient clinics.[1] They can also pose considerable diagnostic and therapeutic challenges, largely due to the ongoing evolution of bacterial antibiotic resistance. In this article, we review several of the most common skin infections in children and discuss current treatments, both oral and topical, based on the latest evidence and our clinical experience.

Common Skin Infections

In addition to being frequently encountered by general pediatric clinics, skin infections are common in other patient groups, including children who are hospitalized, who have an underlying condition (eg, diabetes), who are immunosuppressed (eg, when undergoing chemotherapy), and who are exposed to conditions affecting normal skin flora (eg, increased humidity and temperature) or skin integrity (eg, burns or wounds).[2,3] Skin and skin structure infections can also occur following an antimicrobial drug treatment that allows pathogenic bacteria to multiply on the skin.[4,5]

Uncomplicated SSSIs can occur in the various layers of the skin (Figure 1) and in underlying tissue, and they are classified as primary infections, such as impetigo, or as secondary infections of existing lesions, which include atopic dermatitis, allergic contact dermatitis, and psoriasis. Infections occurring in lacerations, sutured wounds, and abrasions are also classified as secondary infections. The features of the most common uncomplicated SSSIs are described below (Table 1).

Impetigo is a highly contagious, superficial, pyogenic skin infection that presents as either a bullous or a nonbullous form. Nonbullous impetigo accounts for more than 70% of cases and is characterized by small vesicles or pustules that rupture and develop a yellow-brown crust.[6] The bullous form is common among newborns but may affect any age-group. Bullous impetigo presents as flaccid bullae (blisters), which rupture easily and leave erythematous lesions. The areas most commonly affected by impetigo are moist, intertriginous regions, such as the neck folds, nose, groin, and axillae.[6] Impetigo can occur either as a primary infection or as a secondary infection to another condition that disrupts the skin barrier, such as impetiginized atopic dermatitis.

Atopic dermatitis is a common chronic inflammatory skin disease, which has become increasingly prevalent in recent years.[7] The primary lesions in atopic dermatitis are associated with a high prevalence

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Table 1. Features of Common Bacterial Skin and Skin Structure Infections in Children[a]

Condition	Description	Most Commonly Affected Sites	Most Common Pathogen
Impetigo (nonbullous, bullous)	Large vesicles, honey-crusted sores, or both	Face, limbs (nonbullous form); moist, intertriginous regions (bullous form)	*Staphylococcus aureus* (mainly), *Streptococcus pyogenes*
Erysipelas	Bright red, painful infection of superficial skin, with sharply demarcated raised borders	Face, arms, legs	*Streptococcus pyogenes*
Cellulitis	Painful, erythematous infection of deep skin, with poorly demarcated borders	Face and lower extremities, areas of lymphedema; can also be periorbital or perianal	*Streptococcus. pyogenes, Staphylococcus aureus, Streptococcus pneumoniae*
Folliculitis	Papular or pustular inflammation of the hair follicles	Scalp, buttocks, and extremities	*Staphylococcus aureus*
Furunculosis	Painful, firm, or fluctuant abscess originating from a hair follicle	Neck, face, buttocks, axillae, groin	*Staphylococcus aureus*
Carbuncle	A network of furuncles connected by sinus tracts	Neck, face, buttocks, axillae, groin	*Staphylococcus aureus*
Acute paronychia	Inflammation of the nail fold surrounding the nail plate, associated with pus formation	Lateral and proximal nail folds	*Staphylococcus aureus*
Wound infections	Incisional, superficial (skin and subcutaneous tissue), including abrasions	Generalized	*Staphylococcus aureus, Streptococcus pyogenes*
Cutaneous abscess	Red nodule surrounded by a pustule and bordered by a rim of erythematous swelling	Generalized	*Staphylococcus aureus*
Periporitis	Pustular lesions appearing as a result of secondary infection of sweat glands	Buttocks, upper trunk, and scalp	*Staphylococcus aureus*
Perianal cellulitis	Flat cellulitic rash, sometimes friable and may bleed, always hyperemic, commonly pruritic, occasionally painful. Can occur in infants, mimicking yeast/diaper dermatitis, toddlers and preschoolers. often discovered when rash is unresponsive to antifungals or diaper creams (although rapid antigen test positive for streptococcus, skin culture must be done to be clia compliant)	Around anus, may extend up perineum and to vagina, mimicking vaginitis	*Streptococcus pyogenes*

a. Adapted from Hedrick[6] and Scher et al.[30]

of secondary skin infections,[8] which may play a role in the worsening of the condition.[9]

Folliculitis is a bacterial skin infection that originates within the hair follicles.[10] It most commonly affects the follicles of the scalp, buttocks, and extremities. Lesions occur either in groups or as discrete lesions and develop into 1- to 5-mm yellow-grey papules or pustules with surrounding erythema.[11]

Furunculosis is a more aggressive form of folliculitis, which is characterized by lesions of small, round, discrete pustules with an erythematous base.[12] These furuncles begin around the hair follicles and extend outward, with a tendency to suppurate.[13] They can be triggered by friction, scratching, pressure, or hyperhidrosis and commonly affect the groin, nasal cavity, scalp, and external auditory canal.[14-16]

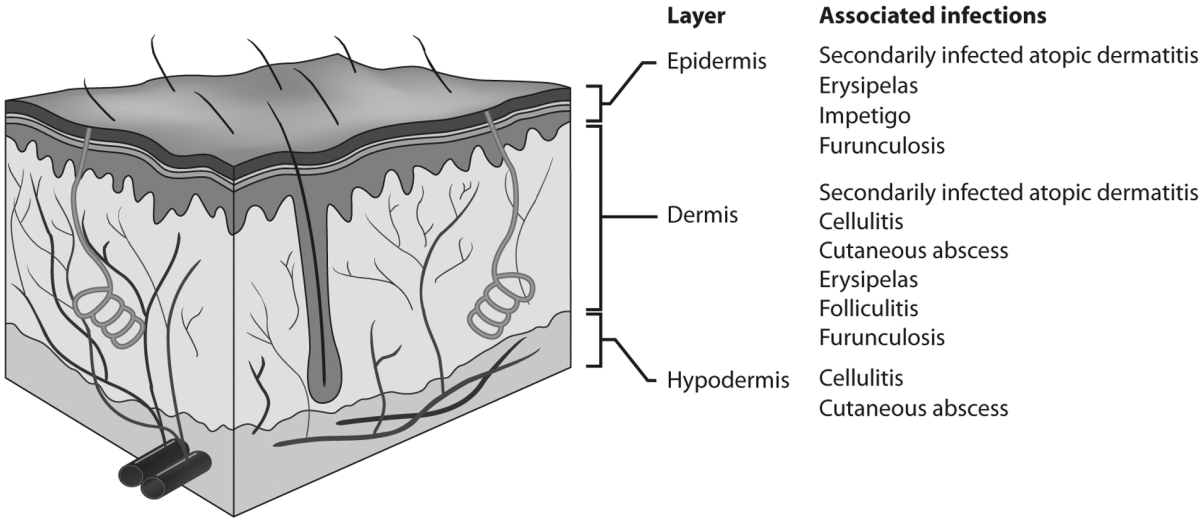

Figure 1. A schematic of skin structure showing which layers each type of infection penetrates. Lesions of impetigo are superficial, whereas more invasive cutaneous infections, such as cellulitis, furuncles, and abscesses, affect the deeper layers and may involve more than one layer.

Furunculosis is relatively uncommon in early childhood, but its incidence is increased in adolescents, particularly those living in crowded conditions with poor hygiene.[6]

Cutaneous abscesses most commonly occur following minor skin trauma and present as collections of pus within the dermis and deeper skin tissues.[6] The lesion begins as an inflamed erythematous papule that develops into a vesicle and then into a pustule; it is usually encapsulated, which differentiates it from other superficial bacterial skin infections, such as cellulitis.[13]

Acute paronychia presents as an inflamed, tender proximal or lateral nail fold and may extend beneath the nail and may suppurate.[6] Predisposing factors for the development of this infection include nail biting and chronic thumb or finger sucking,[4] or the presence of an ingrown toenail.

Bacteria Involved in Uncomplicated Skin and Skin Structure Infections

Bacteria found on the skin surface are classified as normal or resident flora, which are always present but do not usually cause infection, and transient flora, which lead to infection when the epidermis is damaged.[15] The composition of normal skin flora varies depending on their location, with the face, neck, and hands often having a higher bacterial density than other areas of the body that are less exposed to the environment.[16] Additional factors that influence an individual's microflora include gender, race or ethnicity, hospitalization, personal hygiene, use of medications, and exposure to ultraviolet light. Young children carry a more varied skin flora and have a higher number of organisms than do older children and adults.[17]

Uncomplicated SSSIs are most frequently caused by the transient bacteria *Staphylococcus aureus* or *S. pyogenes*, and some lesions may involve 2 or more infecting species (polymicrobial infections). Normal skin flora, such as *Corynebacterium, Acinetobacter*, and *Propionibacterium* species, which usually protect children from pathogens, can under certain circumstances become pathogenic themselves. Occasionally, coagulase-negative staphylococci, group B streptococci, *Escherichia coli*, and *Pseudomonas aeruginosa* are also involved in uncomplicated SSSIs.[6]

Staphylococcus aureus, a gram-positive, coagulase-positive micrococcus, is the most common member of the genus *Staphylococcus* isolated from skin infections. Hospitals in the National Nosocomial Infections Surveillance System show that the incidence of *S. aureus* infections has been increasing steadily since 1980,[18] and community-associated (CA) infections with *S. aureus* are also common.[18,19]

Staphylococcus aureus can cause folliculitis, furuncles and carbuncles, impetigo, wound infections, mastitis, staphylococcal scalded skin syndrome, and

toxic shock syndrome (Table 1). Septicemia, deep organ involvement, or septic arthritis occasionally leading to osteomyelitis can occur following local cutaneous infection. Although *S. aureus* can occasionally cause infection in intact skin, disruption of the skin surface, for instance by sutures, is associated with an increased risk of infection. The bacterium is commonly carried in the nasal passage, especially in young people between 7 and 19 years of age, in whom a prevalence of 42% has been reported compared with 32% in the general population.[20] In neonates, *S. aureus* is also commonly found around the eyes and on the skin, umbilicus, perineum, wound sites, circumcision wounds, and umbilical stumps.[21] People who carry *S. aureus* on their skin are particularly vulnerable to infection if the normally protective skin is broken.

Children with preexisting inflammatory dermatoses, such as atopic dermatitis, contact dermatitis, or psoriasis, are more susceptible to *S. aureus* colonization than healthy children.[6] Atopic dermatitis, in particular, is closely associated with *S. aureus*, and colonization by the organism may be both a cause and a consequence of atopic dermatitis.[22] Clinical signs of *S. aureus* superinfection of the already lesioned skin are oozing and yellowish crust with follicular excoriations. Increased growth of *S. aureus* in these patients may be due to the failure of the immune defense system of atopic skin to restrict bacterial growth. Interestingly, the expression of endogenous antimicrobial peptides (eg, β-defensins, cathelicidins) may also be reduced in atopic dermatitis compared with psoriasis.[23]

Methicillin-resistant *S. aureus* (MRSA) is the most common cause of nosocomial infections. The incidence of MRSA infections has greatly increased in the past 5 years due to the worldwide emergence of CA strains of MRSA in healthy children who do not have traditional health care–associated risk factors (such as having an already compromised immune system or having undergone invasive procedures).[24] Regional prevalence of CA-MRSA varies, and children appear to be one of the patient group at increased risk of developing CA-MRSA infection.[25] A recent study in an urban Baltimore hospital found that among 181 pediatric *S. aureus* cutaneous infections, 81 (45%) were caused by MRSA, and most of these (84%) were caused by CA-MRSA.[26] Rates of pediatric CA-MRSA infections, including abscesses and cellulitis, in a Houston hospital have recently increased to 78% among hospitalized patients.[27] In the United States, 2 MRSA strains—USA300 and USA400—are the predominant cause of these CA infections. When the genome sequence of USA300 was compared with that of the other staphylococcal strains, it was found to have mobile genetic elements that encode for additional virulence determinants, which could enhance bacterial fitness and pathogenicity.[24]

The second leading cause of SSSI is *S. pyogenes*, a β-hemolytic streptococcus. Approximately 10% of the general population have colonization of *S. pyogenes* in the throat, and up to 10% have colonization in the anterior snares; however, carriage on the skin is low due to the bactericidal effect of skin lipids.[15] Carriage increases after an infection and may also be influenced by the long-term use of antibiotics.[15] Although streptococci are less aggressive than staphylococci with respect to secondary infection of damaged skin, they are present in some cases of impetigo[28] and can occasionally cause furuncles. Furthermore, *S. pyogenes* infection is rarely associated with erysipelas, acute glomerulonephritis, and necrotizing fasciitis, a serious condition that requires surgical intervention.[15]

Treatment Options

The goals of treatment for all uncomplicated SSSIs are to promptly eradicate the pathogen, to resolve the infection, and to ensure a low recurrence rate. The physician must first determine whether the condition is deep or superficial. If the lesions are superficial, assessment of any complicating factors should be made. In cases of failure with first-line therapy, ideally, a swab sample or tissue specimen should be obtained to identify the pathogen and to determine its antimicrobial susceptibilities,[29] although in reality, cost and time often prevent this. Still, cultures do provide useful information in some settings, such as when pus is present (eg, bullous impetigo) or when the likelihood of MRSA or other drug-resistant pathogens is increased.[30] Cultures are also beneficial when a practitioner has empirically used an agent, for example, trimethoprim–sulfamethoxazole (TMP-SMX), which is ineffective against *S. pyogenes* infection with its potentially serious sequelae. If *S. pyogenes* is confirmed by culture, treatment can be changed to a more appropriate antimicrobial.

It is important to establish effective disease management as quickly as possible, even if the pathogen has not been identified. This may take the form of either nonpharmacologic interventions (eg, incision and drainage for the treatment of abscesses) or empiric antibiotic therapy based on available clinical information. Topical and oral antibiotic therapies form the mainstay of treatment options for managing uncomplicated SSSIs. Factors to consider when selecting an antibacterial agent empirically include identifying (or making an assumption about) the likely pathogen; the absorption, elimination, and tissue penetration of the drug, reflecting its ability to reach therapeutic levels in the skin[6]; and safety (eg, any risks due to systemic exposure, as in the case of oral treatments).

Oral Antimicrobial Therapy

Multiple, deep, and/or extensive lesions require systemic antibacterial therapy. Formerly, erythromycin and penicillin were the standard treatments,[31] but because of the emergence of resistant organisms, they are no longer routinely used. Subsequently, the recommended first-line treatments of choice were the penicillinase-resistant penicillins, and these were improved by combining the penicillin with a β-lactamase inhibitor. One treatment that is commonly used is amoxicillin and clavulanic acid (Augmentin); this combination results in an antibiotic with restored efficacy against β-lactamase–producing amoxicillin-resistant bacteria.

An alternative antibiotic should be used for patients who are hypersensitive to penicillin.[32] Cephalexin (Keflex), a first-generation and relatively inexpensive cephalosporin, is routinely used in areas of low (<5%) CA-MRSA prevalence. The new extended-spectrum, third-generation cephalosporins, such as cefdinir (Omnicef), offer efficacy against most gram-positive and gram-negative pathogens, and recent evidence-based guidelines suggest that these can be safely prescribed even for penicillin-allergic patients.[33,34] Third-generation cephalosporins and β-lactam or β-lactamase inhibitor antibacterial agents may often be required to provide broad-spectrum coverage for polymicrobial infections.

If the prevalence of CA-MRSA in the community is high (>10%), β-lactam agents should be avoided; instead, a lincosamide such as clindamycin can be useful. Oral clindamycin penetrates skin and skin structures, thereby facilitating antimicrobial activity; however, it is associated with diarrhea and pseudomembranous colitis.[35,36] Due to these safety concerns, clindamycin is often reserved for patients who are allergic to penicillin or for whom other antibiotics are unsuitable.[37] Although there are a few published reports on TMP-SMX in the treatment of MRSA infections, many experts use this drug effectively in the outpatient treatment of SSSIs.[38] However, as TMP-SMX is not effective against *S. pyogenes*, clindamycin should be the empiric choice if this pathogen is a possibility, pending susceptibility results. Of the other available oral agents, fluoroquinolones are not used in pediatric patients due to their potential association with arthropathies[30] and low staphylococcal activity.

Topical Antimicrobial Therapy

Topical antibiotics offer a convenient and effective alternative to systemic agents. They are appropriate for treating small areas of superficial, uncomplicated infection, including primary infections such as impetigo and secondarily infected dermatoses. Topical antibiotics are also useful as adjunctive therapy for larger areas with infected dermatoses to reduce the amount of contagion present and to improve the speed of resolution. The optimal topical antimicrobial agent has been described as having a broad spectrum of activity, persistent antibacterial effects, no toxicity, and a low incidence of allergy.[39]

The major clinical rationale for using a topical antibiotic is the delivery of high drug concentrations directly to the site of infection with minimal systemic absorption, thereby reducing the risk of systemic adverse effects.[40] Topical treatments are also easy to use for treating children, making them particularly useful for common childhood skin infections such as impetigo.

Topical mupirocin is indicated for the treatment of skin infections caused by gram-positive organisms, and it may also help reduce *S. aureus* nasal carriage. However, resistance to mupirocin is increasing. It varies by geographic area; a recent estimate for mupirocin-resistant *S. aureus* skin and soft tissue infections in the United States is 5.2%.[41] The development of such resistance has been linked with extended or intermittent mupirocin use.[41,42]

Other topical antibiotics include neomycin, polymyxins, and erythromycin. Neomycin is not widely used alone as it is ineffective against streptococci and is often combined with bacitracin, which inhibits staphylococci, streptococci, and gram-positive bacilli. However, neomycin is associated with several drawbacks, including the potential for delayed hypersensitivity (eg, allergic contact dermatitis is a common adverse reaction that occurs in 1% to 6% of the general population),[43] immunoglobulin E–mediated and anaphylactic reactions, and the potential for resistance.[40] Polymyxins are largely inactive against most gram-positive bacteria; however, they can be used in combination with other topical antimicrobial agents, such as zinc, bacitracin, and neomycin.

Antibiotic Resistance

As a result of emerging methicillin resistance in strains of *S. aureus* and resistance to macrolides in strains of *S. pyogenes*, the empiric antimicrobials used for the treatment of SSSIs must possess activity against these particular strains.[1,2] Antibiotic resistance is often associated with prolonged use of antibiotic therapy and is an ongoing problem.[44] As antibiotic-resistant phenotypes in staphylococci continue to evolve, the ability to treat skin infections effectively using cephalosporins, amoxicillin and clavulanic acid, or, in particular, macrolides is decreasing. Gram-positive–resistant pathogens are of particular concern, as resistance is increasing in organisms that were previously susceptible to most available antibiotics in the 1990s. Such high resistance rates necessitate the development of new agents for empiric treatment of uncomplicated skin infections.

The increasing prevalence of SSSIs caused by CA-MRSA is an emerging problem in children and throughout the general population; however, any decision to change empiric antibacterial therapy to optimize treatment success must be based on knowledge of local antibacterial resistance patterns. Recent isolates of MRSA have been shown to be capable of inducing antibiotic resistance to mupirocin, erythromycin, clindamycin, tetracycline, sulfonamides, chloramphenicol, cephalosporins, and quinolones in previously drug-susceptible staphylococci.[15] As MRSA is always a likelihood, at present, physicians should ensure that significant or unresponsive lesions are cultured to determine antibiotic susceptibilities, and an appropriate oral agent should be used as initial therapy. Most CA-MRSA strains are susceptible to doxycycline or minocycline, but these pharmaceutical treatments should be avoided in children younger than 8 years. Clindamycin usually has a high antistaphylococcal activity, but there is a potential for emergence of resistance in high-inoculum infections caused by strains inducibly resistant to erythromycin.[45] New antibacterial agents with activity against MRSA, such as linezolid, are increasingly being used in children.[46] However, linezolid is not thought suitable to use for routine treatment of mild-to-moderate SSSIs due to its high cost. It is usually reserved for patients who have severe infections requiring hospitalization or for those who have not responded to multiple treatments.

Adherence to Treatment Regimens

Although patient adherence to antibiotic treatment is essential to limit antibiotic resistance, adherence rates are generally very poor. A recent meta-analysis reported that over one-third of patients do not adhere fully to antibiotic therapy.[47] Adherence is inversely related to the duration of therapy, frequency of dosing, and the incidence of adverse effects, and adherence decreases sharply as any one of these factors increases.[48] The method and ease of administration of antibiotic therapy may also affect adherence; for example, in one study, nearly twice as many patients expressed a preference for topical treatment compared with oral treatment.[49] Furthermore, issues such as the palatability and tolerability of oral formulations are of key importance in pediatric patients. Medication adherence is a complex issue involving the child, family members, and other caregivers;[50] therefore, it is recommended that the importance of treatment adherence be stressed to all involved and appropriate educational initiatives carried out to ensure optimal use of therapy.

Specific variables influencing adherence for families filling antibiotic prescriptions and children taking these products are important considerations for the selection of an appropriate antimicrobial therapy.[51] The standard therapies used for uncomplicated SSSIs all have limitations that may negatively affect treatment adherence. In the case of oral agents, these include the frequent gastrointestinal intolerance associated with erythromycin; the

unpalatable taste of dicloxacillin, clindamycin, and TMP-SMX; and the risk of *Clostridium difficile* toxin–associated diarrhea with clindamycin, which is rare.[31] Topical agents encourage adherence due to factors such as ease of use, but they may also have their disadvantages as most topical therapies require a multiple-daily dosing over a period of time (eg, mupirocin must be administered 3 times a day for 7-10 days).[52] Improving adherence in children requires reduced dosing frequency and a shorter duration of treatment.[51] Up to a twice-daily dosing is the most comfortable regimen for school-aged children because parents can supervise administration of therapy.[50]

New and Emerging Therapies

Increasing rates of antibiotic resistance and inconvenient dosing regimens are major issues associated with current antibiotic therapies, which necessitate the development of new drugs for the treatment of uncomplicated SSSIs. New oral agents, such as linezolid and moxifloxacin, are approved for the treatment of SSSIs[15,46] but are not currently favored for treating pediatric patients. In addition, the rapid development of resistance to linezolid is already being reported, emphasizing the importance of the need for ongoing development of effective antimicrobial agents.[53] The pleuromutilin class of antibiotics offers a novel mode of action and exhibits no target-specific cross-resistance to established classes of antibacterial agents.[54] Retapamulin is the first topical pleuromutilin developed for human use. It has excellent antibacterial activity in vitro against gram-positive organisms, including isolates resistant to currently available agents, although it showed reduced clinical efficacy against a clone of MRSA found in the US.[55] Retapamulin was highly effective for the treatment of impetigo, secondarily infected traumatic lesions, and dermatoses in phase 3 trials.[55,56] Its twice-daily dosing combined with a relatively short treatment period of 5 days mean that it could prove beneficial for improving compliance among the pediatric population.

Summary

Uncomplicated SSSIs are common in children and require efficient treatment with antibiotics targeted toward the predominant causative organisms *S. aureus* and S. *pyogenes*. Treatment needs to be individualized, taking into account the location and extent of lesions, the age and general health of the patient, and the antibiotic susceptibilities of the organism. New antimicrobial therapy options available to the pediatrician are limited so far, and older antibiotic classes are at risk of limited effectiveness because of the development of drug resistance. Finally, the appropriate use of current antibacterial agents and the promotion and facilitation of high rates of adherence with treatment regimens will help maintain treatment effectiveness and delay the onset of drug resistance.

Sources of Support

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