Diagnosing and Selecting Treatment for Office-Based SSSIs

Stan L. Block, MD

Learning Objective

- In order to improve clinical outcomes, identify the skin and skin structure infections commonly encountered in children in outpatient settings and the importance of early diagnosis and treatment.

Key Points

- Superficial skin infections have become both more protean in appearance and more aggressive.
- Methicillin-resistant *Staphylococcus aureus* (MRSA) now accounts for a significant portion, and sometimes even a majority, of skin infections in most areas.
- Management of skin infections often requires antibiotic selection specifically targeting MRSA and the use of incision and drainage for larger abscesses.

Management of impetigo, furuncles, and other superficial skin infections was once a fairly straightforward treatment algorithm. However, diagnosis and treatment is becoming increasingly complicated.

Bacterial skin infections often initially masquerade as fungal infections, spider bites, and prima facie innocuous-appearing abscesses.

In the last few years, the pathogenesis of skin infections, which are primarily caused by *S. aureus*, has changed fairly notably. Most of these infections appear to be caused by a more aggressive strain of *S. aureus* that produces Panton-Valentine leukocidin, an enzyme that reduces the bacteriocidal activity of the host's leukocytes for *S. aureus.* These strains are usually resistant to methicillin and tend to invade deeper into the subcutaneous tissues, particularly if untreated or inadequately treated. To complicate the management of skin infections further, *S. aureus* is not the sole pathogen that needs to be

considered: *Streptococcus pyogenes* has recently been isolated in as many as 25% of impetigo cases where it may occur alone or as a copathogen with *S. aureus,* and very rarely associated with acute glomerulonephritis and possibly rheumatic fever. In addition, *S. pyogenes* occasionally accounts for some cases of furunculosis, and may even evolve into invasive fasciitis and myositis.

In pediatric patients, management of uncomplicated superficial skin infections has revolved around the use of topical agents, such as mupirocin, or oral therapy with cephalosporins, macrolides, and amoxicillin/clavulanate. Deeper or more serious infections were treated with oral or parenteral clindamycin or even daily doses of ceftriaxone. For deeper or more extensive cases of impetigo and skin abscesses, practitioners must now decide whether to even attempt to initiate therapy with beta-lactam antibiotics, such as cephalexin, cefdinir, or amoxicillin/clavulanate. Because of the high levels of resistance of both *S. aureus* and *S. pyogenes* to macrolides, this class of antibiotics is no longer a preferred option for skin infections, even for patients with documented beta-lactam allergies. Monitoring local antibiotic susceptibility patterns for *S. aureus* and *S. pyogenes* is no longer merely an intellectual exercise, but has become essential for optimal management of these infections. Once the rate of MRSA in an area exceeds 20% to 30%, clinicians should probably entirely avoid the use of oral or parenteral beta-lactams as initial therapy.

Currently, in areas where MRSA is common, the two preferred choices for empiric oral treatment of skin infections in pediatric patients are trimethoprim/sulfamethoxazole and clindamycin. However, these two antibiotics have distinct limitations. In oral suspension formulations, both have major taste issues. A small but growing percentage of MRSA strains have demonstrated clindamycin-inducible resistance. Clindamycin must be administered three times daily and has been associated, rarely, with antibiotic-induced pseudomembranous colitis. Trimethoprim/sulfamethoxazole penetrates tissues marginally for more serious infections, is not approved by the US Food and Drug Administration for skin infections, has been associated, rarely, with Stevens-Johnson syndrome, and is ineffective for *S. pyogenes* infections.

Close follow-up of any skin abscess is now mandatory. Most children who are infected with abscesses larger than 2 cm or that worsen, should undergo incision and drainage of the lesion. Thus, practitioners must learn the procedure for incision and drainage. Culture and susceptibility patterns should be obtained for all aspirated or drained abscesses. Children who fail therapy with the above antibiotics require treatment with rarely used and more expensive antibiotics, such as linezolid, vancomycin, and others.

Suggested Readings

Stevens DL, Bisno AL, Chambers HF, et al. IDSA guidelines: practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis.* 2005;41:1373-1406.

Diagnosing and Selecting Treatment for Hospital-Based SSSIs

Candice E. Johnson, MD, PhD

Learning Objective

- Assess and determine when to hospitalize a child with an invasive skin infection in order to properly treat these infections.

Key Points

- Skin and skin structure infections (uSSSIs) range in severity from mild cases of impetigo that can generally be handled in office-based settings to more severe types of infections that require hospitalization and intravenous antibiotics.
- The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) is rising, contributing to the severity and difficulty of management of these uSSSIs.
- Aspiration, incision, and drainage should be performed for as many lesions as possible, usually in conjunction with antibiotic therapy. Antibiotic therapy should be re-evaluated within 1 to 2 days and changed if the patient's condition is not improved.

uSSSIs are common diseases treated by physicians in both office settings and emergency departments (EDs). This presentation discusses the spectrum of uSSSIs up to those of such severity that an infectious disease specialist should be consulted.

Unfortunately, the increase in prevalence of MRSA over the past 8 years has increased both the clinical severity and the diagnostic uncertainty in treating uSSSIs. The rates of MRSA in all skin infections seen in selected EDs across the United States in 2004 ranged from 15% to 74% in adults,[1] but group A streptococci also cause uSSSIs in children.

There is no single oral drug that covers both pathogens except clindamycin, and in some locales, such as South Texas, resistance to clindamycin is increasing.[2]

Impetigo and impetiginized atopic dermatitis are the mildest and most common skin infections seen in general practice. A topical agent covering both staphylococci and streptococci is useful for impetigo. In the past, 2% mupirocin has been successful in treating impetigo, but resistance rates in a recent global surveillance study were 10% among *S. aureus* isolates and 35% among coagulase-negative staphylococci from uSSSIs,[3] suggesting the need for new alternatives. Retapamulin, a new topical pleuromutilin, is in clinical trials for uSSSIs. In the same global surveillance study, retapamulin was more active in vitro than 14 comparative agents and retained activity against *S. aureus* and streptococci resistant to many other available antibiotics.[3]

Next in severity in the spectrum of uSSSIs are streptococcal ulcers called ecthyma, and then cellulitis and erysipelas, the latter of which is a rapidly spreading cellulitis due to group A *S. pyogenes.* The value of needle aspiration of the point of maximum induration cannot be stressed enough, especially in areas experiencing clindamycin-resistant MRSA, where the necessary treatment is intravenous vancomycin.[4] In the absence of a positive culture from the blood or the aspirate, it is impossible to select an oral agent after clinical improvement occurs.

The most serious uSSSI is necrotizing fasciitis, which was an increasingly common complication of varicella infections until the varicella vaccine was introduced. It is still important to diagnose rapidly, since the necrosis of the deeper tissues may cause gangrene within hours. The presence of violet discoloration and bulla over the cellulitic area suggest that a surgeon should rapidly perform a tissue biopsy and that both a beta-lactam and clindamycin be initiated.[5]

MRSA is particularly prone to cause focal abscesses, often with necrotic centers resembling spider bites.[6] Local drainage, with or without packing, is often enough to cure the infection even when an antibiotic is given that fails to cover the MRSA strain.[7] At a minimum, a needle aspirate to determine etiology and sensitivities is needed. Lesions >5 cm in diameter are those most likely to need hospitalization for IV antibiotics, and vancomycin is most commonly used, often in conjunction with clindamycin, to stop toxin production.[7]

Although localized impetigo is a common, mild form of uSSSI in children that can be treated with topical therapy, other forms of uSSSIs can be quite invasive and severe. MRSA is increasingly in prevalence, further adding to the complexity of diagnosis and treatment. As a precaution, all children with uSSSIs should be isolated from the waiting room as if they have MRSA. Diagnosis and treatment for skin lesions should include aspiration or incision and drainage whenever possible, usually in conjunction with antibiotic therapy. Antibiotics should be re-evaluated in 1 to 2 days and changed if necessary.

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Factors Contributing to Resistance: Update in the Management of Challenging uSSSIs

Gary V. Doern, PhD

Learning Objective

- Using knowledge of the process by which selective pressure and gene action result in the development of antibiotic resistance and cross-resistance, construct treatment strategies that minimize the risk of resistance in pediatric patients with uSSSIs.

Key Points

- Because of the mechanism of methicillin resistance with *Staphylococcus aureus*, such strains must be considered as being resistant to all currently licensed beta-lactam antimicrobial agents.
- Hospital-acquired methicillin-resistant *S. aureus* are typically multiply drug resistant.
- Community-acquired methicillin-resistant *S. aureus* are less likely to be multiply drug resistant but are also more virulent.

Methicillin was introduced as an agent for the management of infections caused by penicillin-resistant *Staphylococcus aureus* in 1958. It was the first of the semisynthetic "antistaphylococcal penicillins". Subsequently, two additional agents in this family, oxacillin and nafcillin, were introduced. By 1961, clinical isolates of *S. aureus* resistant to these agents were recognized. Such strains are referred to as MRSA (methicillin-resistant *S. aureus*). The mechanism of resistance is production of an altered penicillin binding protein, PBP 2a, as a result of the *mec*A gene product. All beta-lactam antimicrobials have poor binding affinity for PBP 2a and as a result, *mec*A-positive

strains of *S. aureus* are not only resistant to antistaphylococcal penicillins but are also resistant to all other beta-lactam antimicrobials.

MRSA has typically been most often recognized as a pathogen in hospitals and long-term care facilities (LTCFs) in the United States (ie, hospital-acquired MRSA, or HA-MRSA). Currently, MRSA rates in these settings have reached levels of 65% to 75%. Unfortunately, HA-MRSA are typically resistant to several antimicrobial classes in addition to the beta-lactams. These include the macrolides, clindamycin, the aminoglycosides, trimethoprim-sulfamethoxazole, and the fluoroquinolones. During the decade of the 1990s, MRSA also emerged as a significant pathogen in the community in the United States. Community-acquired MRSA (CA-MRSA) are less often found to be multiply drug resistant in comparison to HA-MRSA; however, CA-MRSA are also typically noted to be more virulent and thus, more often associated with rapidly progressive, life-threatening infections. The most common sites of infection due to CA-MRSA are skin and skin structures; however, bronchopulmonary infections are also noted frequently. The question arises, in view of the high rates of MRSA today in hospitals and LTCFs and the emergence of MRSA as a significant and common pathogen in the community, how do we now optimize the management of infections due to *S. aureus* in these settings? This question serves as the focus of this presentation.

Suggested Readings

Anderegg TR, Sader HS, Fritsche TR, Ross JE, Jones RN. Trends in linezolid susceptibility patterns: report from the 2002-2003 worldwide Zyvox Annual Appraisal of Potency and Spectrum (ZAAPS) Program. *Int J Antimicrob Agents*. 2005;26:13-21.

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Fridkin SK, Hageman JC, Morrison M, et al. Methicillin-resistant Staphylococcus aureus disease in three communities. *N Engl J Med*. 2005;352:1436-1444.

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Epidemiology of Family and Community Infections

John E. McGowan, Jr, MD

Learning Objective

- Apply knowledge of prevalence, risk factors, and typical history of pediatric uSSSIs to help prevent and identify uSSSIs in at-risk children.

Key Points

- *Staphylococcus aureus* is responsible for almost three quarters of all uncomplicated skin and skin structure infections (uSSSIs). Streptococci account for most of the remaining superficial SSSIs.
- Strains of *S. aureus* recovered from family and community cases of SSSIs increasingly are resistant to the beta-lactam drugs historically effective against this pathogen. In addition, more community-associated strains of group A streptococci have been resistant to macrolide antimicrobials.
- Methicillin-resistant *S. aureus* (MRSA) has an increasing presence in children's hospitals around the United States.
- Resistant organisms are associated with certain closed population groups of importance for pediatricians, such as school sports teams and daycare centers.
- Family outbreaks of MRSA infections have been reported. As a result, prevention of secondary cases must be part of attending to patients with SSSIs due to MRSA.

The etiology of uSSSIs in family and community settings has changed over the past few years to include more organisms that are resistant to commonly used antimicrobial agents. This is exemplified by impetigo, which is of particular interest to the pediatrician because its peak incidence of occurrence is in children younger than 5 years of age (although older children may also be affected). Impetigo consists of purulent lesions that, when cultured, usually contain group A streptococci or *S. aureus*. Beta-lactam antibiotics have been used effectively for many years to treat such cases. However, in recent years, strains of *S. aureus* recovered from uSSSIs increasingly have shown resistance to beta-

lactam antimicrobials, and more strains of group A streptococci have been resistant to the macrolide class.

During the past decade, the prevalence and severity of *S. aureus* strains resistant to methicillin and similar beta-lactam antimicrobials have increased dramatically in both healthcare-associated and community settings worldwide. Increasing prevalence of MRSA has been reported in children's hospitals around the United States. In some centers, MRSA is more prevalent as a pathogen in children than are strains susceptible to beta-lactam drugs. In some reports, invasive cases of community-acquired MRSA infections were associated with higher prevalence rates of uSSSIs and severe complications. Resistant organisms may be spread within certain closed population groups of importance for pediatricians, such as school sports teams and daycare centers. Family outbreaks of MRSA infections have been reported, so prevention of secondary cases must be part of attending to patients with uSSSIs due to these organisms.

A particularly disturbing recent development is the report that MRSA strains typical of community infection have become a source of healthcare-associated infections. So-called "community" strains of MRSA are now sources of outbreaks among healthy newborns, in hospital nurseries and maternity units alike. The future impact of such strains, which may contain more virulence factors than strains encountered earlier, is yet to be determined.

Suggested Readings

Ladhani S, Garbash M. Staphylococcal skin infections in children: rational drug therapy recommendations. *Paediatr Drugs.* 2005;7:77-102.

Zaoutis TE, Toltzis P, Chu J, et al. Clinical and molecular epidemiology of community-acquired methicillin-resistant *Staphylococcus aureus* infections among children with risk factors for health care-associated infection: 2001-2003. *Pediatr Infect Dis J.* 2006;25:343-348.

MOA: Differentiating New Drug Class from Currently Available Treatments

Michael E. Pichichero, MD

Learning Objective

- Compare and contrast the mechanism of action and spectrum of activity of currently available therapies for uSSSIs and the new antibiotic class, the pleuromutilins, to determine how each can best be used to improve patient outcomes.

Key Points

- *Staphylococcus aureus* and *Streptococcus pyogenes* are the two most common bacterial causes of uSSSI.
- Although the many antibiotics used to treat uSSSIs have distinct mechanisms of action, their efficacy is being compromised by the rapid emergence of resistance in *S. aureus.*
- New agents with a low potential for the development of resistance in *S. aureus* are needed.

Uncomplicated skin and skin structure infections (uSSSIs), including impetigo, cellulites, and other pyodermas, are frequent in children, and are one of the most common reasons for visits to pediatric offices and outpatient clinics. *Staphylococcus aureus* and *Streptococcus pyogenes* are the most common bacterial causes of skin infection, and a variety of antibiotics are effective against these organisms.[1] There are five general mechanisms of antibacterial activity: action on the bacterial cell wall; inhibition of nucleic acid synthesis; interference with protein synthesis; action on the cell membrane; and interference with the enzyme system. Confronted with these attacks, bacteria have developed ways to escape destruction by producing enzymes that inactivate the antibiotic, preventing the antibiotic from reaching its target site(s), or by changing the target site entirely.[2] The continuing emergence of drug-resistant bacteria has led to an increased

need for new antibiotics and new targets. Cephalosporins, currently the most widely used oral antibiotics for uSSSIs, have good activity against *S. pyogenes* and methicillin-susceptible *S. aureus.*[3] But they tend to have very low activity against methicillin-resistant S. *aureus*, which are increasingly implicated in uSSSIs.[4] Retapamulin, the first of a new pleuromutilin class of antibacterials, has demonstrated a low potential for the development of resistance in *S. aureus* in vitro.[5]

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Treatment options vary from simple topical therapy to much more extensive oral or intravenous antibiotic therapy. Guidelines from the Infectious Diseases Society of America (IDSA) provide a standard for treatment selection.

For treatment of impetigo in patients with a limited number of lesions, the IDSA guidelines recommend a topical agent. According to the guidelines, the best currently available topical agent is mupirocin, which offers efficacy equivalent to oral antibiotics, although there is some concern about resistance. Retapamulin represents an emerging topical agent that was not available at the time the guidelines were released. It has activity against *S. aureus* and streptococci, with a low potential for resistance. Retapamulin is being studied in clinical trials of impetigo, as well as secondarily infected dermatitis and traumatic lesions. For cases of impetigo with more extensive lesions or for those that did not respond to topical therapy, the IDSA guidelines recommend oral treatment with dicloxacillin, cephalexin, erythromycin, clindamycin, or amoxicillin/clavulanate, but note that penicillinase-resistant penicillins and first-generation cephalosporins are the preferred options.

For other uSSSIs caused by methicillin-sensitive *S. aureus*, the IDSA guidelines recommend nafcillin or oxacillin, cefazolin, clindamycin, dicloxacillin, cephalexin, doxycycline or minocycline, or trimethoprim/sulfamethoxazole. The guidelines also recommend that MRSA infections be treated with vancomycin, linezolid, clindamycin, daptomycin, doxycycline or minocycline, or trimethoprim/sulfamethoxazole. Since publication of the IDSA guidelines, tigecycline, an intravenous (IV) antibiotic, has received US Food and Drug Administration (FDA) approval for treatment of complicated SSSIs, such as infected burns, deep soft-tissue infections, and infected ulcers, including those caused by MRSA. In phase III studies, it proved comparable to vancomycin/aztreonam in terms of safety and efficacy. Another IV alternative to vancomycin, dalbavancin, is currently pending FDA approval for complicated SSSIs.

Minor uSSSIs can be treated empirically, but the patient should be re-evaluated in 24 to 48 hours to confirm a clinical response. Patients with more severe infection or progressive infection during empiric therapy should have treatment targeted according to Gram stain, culture, and sensitivity analysis.

Suggested Readings

Ellis-Grosse EJ, Babinchak T, Dartois N, et al. The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. *Clin Infect Dis*. 2005;41(suppl 5):S341-S353.

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Importance of Local Topical Wound Care

Lawrence Charles Parish, MD

Learning Objective

- Demonstrate appropriate local care of topical wounds, including proper skin care and implementation of topical antibiotics when appropriate, in order to promote rapid and effective wound healing.

Key Points

- Accurate clinical diagnosis of bacterial skin infections is required, with laboratory confirmation where possible.
- Localized lesions without systemic symptoms can generally be treated with topical therapy, while more extensive infection requires systemic antimicrobial therapy.
- Cleaning, compresses, and incision and drainage of abscesses are appropriate ancillary therapy, but overscrubbing and the inappropriate use of antifungals are to be avoided.

Bacterial skin infections may be either primary or secondary. Primary infections occur in normal skin, and are usually caused by *Staphylococcus aureus,* Group A beta-hemolytic streptococci (*Streptococcus pyogenes*), and *Corynebacterium*, while secondary infections, such as infected surgical wounds, originate in diseased skin. In making a diagnosis of bacterial skin infection, the clinician should consider whether there is an underlying disease and whether various topical remedies have altered the presentation. Appropriate ancillary therapy, such as compresses, is recommended, and the first step in treating pyogenic uncomplicated skin and soft tissue infections should be incision and drainage of abscesses. Antibiotic treatment depends on the severity of the infection. Topical antibiotics are a therapeutic option for impetigo, superficial folliculitis, furunculosis, and minor abrasions. More serious and widespread infections, including carbuncles, ecthyma, cellulitis and erysipelas, require systemic therapy. Even when a culture is performed,

initial therapy is empiric. Mupirocin and retapamulin are useful topical agents; systemic therapy may consist of a cephalosporin, semi-synthetic penicillin, tetracycline, trimethoprim/sulfamethoxazole, erythromycin, or clindamycin. Fourteen case studies are presented.

Selected Readings

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