Staphylococcal Infections in the Era of MRSA

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Drs Jackson and Newland have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives

1. Describe how the approach to the patient who has a staphylococcal infection varies by age, immune status, and clinical presentation.
2. Recognize that the management of staphylococcal infection in the pediatric patient relies on prompt diagnosis and localization of focus.
3. Utilize susceptibility data to plan antimicrobial therapy for staphylococcal infection.
4. Delineate the pharmacokinetic and pharmacodynamic data that guide therapy for specific infections.
5. Understand that vancomycin continues to be the cornerstone of therapy for methicillin-resistant *Staphylococcus aureus* infection in children.

Introduction

Long recognized as a ubiquitous environmental organism, *Staphylococcus aureus* is a well-known cause of both local and invasive infection. Distinguished in the laboratory by the production of coagulase and having a distinctive Gram stain appearance of grapelike clusters, *S aureus* colonizes the nares and skin in 30% to 50% of children and adults. Higher rates are noted for healthcare personnel and for those having skin disorders or burns or in individuals who use needles frequently (diabetes, hemodialysis). The percentage of children colonized with methicillin-resistant *S aureus* (MRSA) remains relatively low and has been estimated to be between 1% and 10%, despite the fact that most experienced practitioners find that they have drained more skin abscesses in the last 5 years than cumulatively in their entire careers.

Common infections involve skin (*S aureus* is the primary cause of both bullous and crusted impetigo), soft tissue, or lymph nodes; but if the organism seeds the bloodstream, dissemination to joints, bones, kidney, liver, muscles, lung, and heart valves may occur, causing substantial morbidity and potential mortality. Although there are instances when an underlying immunodeficiency should be considered in patients who have repeated staphylococcal infection, an immunodeficiency evaluation is not recommended routinely because most infections, including those caused by MRSA, occur in previously healthy individuals. In the event that a child with recurrent skin infections is noted to have an additional risk factor for immunodeficiency (eg, prior invasive bacterial infection), a diagnostic evaluation should focus on diseases associated with neutrophil defects. The intrinsic capacity of *S aureus* to bind to tissue and foreign bodies via surface-based adhesive matrix molecule receptors allows low inoculum bacteremia to produce infections related to catheters and prosthetic devices and clearly makes such infections more difficult to eradicate.

In the preantibiotic area, deaths from invasive staphylococcal infection were virtually inevitable. The availability of penicillin in the early 1940s, which proved to be an effective

Abbreviations

CSF:	cerebrospinal fluid
GAS:	group A *Streptococcus*
IDSA/PIDS:	Infectious Diseases Society of America/Pediatric Infectious Diseases Society
IPF:	intrapleural fibrinolysis
MRI:	magnetic resonance imaging
MRSA:	methicillin-resistant *Staphylococcus aureus*
MSSA:	methicillin-sensitive *Staphylococcus aureus*
TMP-SMX:	Trimethoprim-sulfamethoxazole
TSS:	toxic shock syndrome
TSST-1:	toxic shock syndrome toxin-1
VATS:	video-assisted thorascopic debridement

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drug for *S aureus* infection, changed the outlook for such patients; but, not surprisingly, less than 10 years later, 65% to 80% of strains were noted to be resistant. It is rare to identify a penicillin-susceptible *S aureus* strain today because nearly all isolates now produce penicillinase.

The introduction of methicillin, one of the first semisynthetic penicillinase-resistant penicillins, was heralded as a welcome addition to the clinicians' treatment armamentarium once strains became penicillin resistant, but reports of methicillin resistance swiftly followed its approval in 1959. MRSA resistance emerged initially from the hospital setting, becoming an important cause of healthcare-acquired infections over the next 4 decades. Clonal spread of MRSA with different dominant phage types was first reported in the 1960s, and outbreaks of disease, such as staphylococcal scalded skin syndrome due to phage type 3-containing *S aureus*, were well documented in hospital nurseries and surgical and intensive care units.

The early reports of invasive community-associated MRSA infection in 1999 focused attention on MRSA isolates that were from a single clonal strain and caused the deaths of four otherwise healthy children (12 mo to 13 y) from Minnesota and North Dakota. The community-associated strains were found later to produce a unique SCC*mec*, type IV cassette (a large mobile genetic element used for subtyping MRSA), which is smaller than that associated with healthcare-associated MRSA. Susceptibility data confirmed that such strains were uniformly susceptible to clindamycin and trimethoprim-sulfamethoxazole (TMP-SMX). The unique antibiogram (in vitro sensitivity) of community-associated MRSA distinguished such strains and was explained easily because the SCC*mec* cassette from hospital-associated strains is larger and usually carries genes associated with clindamycin and TMP-SMX resistance. Both hospital-associated and community-associated strains have more resistance genes than the classic methicillin-susceptible *S aureus*.

Since then, so-called community-associated MRSA has become a common gram-positive infection causing both local and invasive infections in the pediatric population. This new, distinct community-associated MRSA clone has been called USA 300, based on the Centers for Disease Control and Prevention (CPC) nomenclature. The unique resistance pattern and the organism's capacity to produce severe local infections as well as invasive infections are notable. The exact mechanism of enhanced virulence is not completely clear; but initial in vitro and clinical studies have pointed to extracellular proteins, including Panton Valentine leucocidin, phenol soluble modulin peptides, or other products produced by these isolates.

This article will describe the diverse presentations of local and invasive staphylococcal infection in children and define management and prevention strategies. Focused discussion of skin and soft tissue infection, lymph node infection, pneumonia, septic arthritis, and osteomyelitis will be presented along with management recommendations highlighting the evidence supporting these recommendations. Lastly, less common manifestations of *S aureus* infections, including cardiac and central nervous system infection, will be discussed.

It is crucial to note that occult bacteremia caused by *S aureus* does not occur, and any time a blood culture grows this organism (methicillin-sensitive *S aureus* [MSSA] or MRSA) a search for a focus of infection (skin, soft tissue, lymph node, or concealed sites, including bone, joint, lung, liver, kidney, heart) should commence. Although MRSA infections clearly have increased, data from our institution demonstrate that MSSA remains an important cause of invasive infection in more than 50% of such cases. Currently available agents that will be discussed include vancomycin, daptomycin, linezolid, clindamycin, doxycycline, and TMP-SMX (Table 1). Newer agents will be described, including ceftibiprole, tigecycline, televancin, and quinupristin-dalfpristin but will not be discussed in detail because utilization in the pediatric population is limited.

Simple Skin and Soft Tissue Infections

Most experienced clinicians have mastered the art of abscess drainage in the last 5 years because MRSA-associated skin abscesses have emerged as a common childhood malady. It is estimated that 90% of all community-associated MRSA infections are skin and soft tissue in origin. That being said, practitioners should be able to classify specific skin and soft tissue processes skillfully, including cases in which necrotizing infection is present and should understand when pathogens other than *S aureus* should be considered, targeting cases when simple incision and drainage and oral antibiotics are insufficient.

Recommendations for management of children who acquire pustules, furuncles, carbuncles, and simple skin abscesses have been published by the American Academy of Pediatrics (Fig. 1). The algorithm highlights the importance of recognizing the variable types of skin and soft tissue infections and advocates grading the severity of the infection clinically and taking into account the patient's age and other risk factors for more serious infection before implementation of the clinical plan (Table 1).

Table 1. Drugs Appropriate for Treatment of Pediatric Staphylococcal Infection

Drug	Dose, mg/kg per day (max daily dose)	Total Daily Dose Divided	Route	Comments
TMP/SMX	8–12	Every 12 h	Oral	No coverage GAS
Doxycycline	4 (200 mg/d)	Every 12 h	Oral	>8 y
Clindamycin	40 (4.8 g) 30 (1.8 g)	Every 6 h Every 8 h	IV Oral	Poor palatability
Daptomycin	6–10	Once daily	IV	Consult infectious diseases; not appropriate for pneumonia
Vancomycin	60	Every 6 h	IV	Consult infectious diseases; after first dose, adjust based on renal function
Linezolid	30: <12 y 20: :12 y (1,200 mg/d)	Every 8 h Every 12 h	IV/Oral	Consult infectious diseases; same dose for oral transition; myelosuppressive, expensive
Oxacillin	200 (12 g)	Every 6 h	IV	MSSA only
Cefazolin	100 (12 g)	Every 8 h	IV	MSSA only
Cephalexin	50 (4 g)	Every 8 h	Oral	MSSA only; oral transition: 100 mg/kg/d for skeletal infection

GAS = group A *Streptococcus*, IV = intravenous, MSSA = methicillin-sensitive *Staphylococcus aureus*

In the previously healthy child who does not appear ill and has a pustule, furuncle, or a small abscess (<5 cm) drainage alone is curative and should be performed along with a request for culture. In cases of neonatal pustulosis, drainage with culture and topical treatment with mupirocin could be considered if the infant is full term, has local pustules and is well. In general, newborns with large areas of pustule involvement, or any systemic signs, any child afflicted with an immunocompromising condition, or any previously healthy child who appears toxic or has extensive limb involvement should have further evaluation and hospitalization for management.

In the previously healthy child, selecting the patient who requires drainage plus empirical antibiotic treatment requires factoring in additional, specific host and clinical features. In the following four circumstances, antibiotic treatment should be provided for the child with a simple skin or soft tissue infection: 1) the child has high fever or other systemic symptoms; 2) the abscess is larger than 5 cm, or is located in a critical location or in a difficult to drain area; 3) there are multiple abscesses or a carbuncle (a localized bacterial skin infection larger than a boil that usually has several openings through which pus can drain); or 4) signs and symptoms persist following incision and drainage.

Although nearly 70% of staphylococcal skin infections currently are related to MRSA, the availability of culture and susceptibility information is important because rates of resistance to certain antibiotics, including clindamycin, appear to be increasing nationally. Further, not every skin and soft tissue infection is staphylococcal in origin.

Cellulitis, which is diagnosed when the practitioner identifies a well-defined area of tender, erythematous swelling of the skin and soft tissue, is by nature an infection for which drainage is not feasible and antibiotic treatment is essential (Fig. 2). Although cellulitis may be staphylococcal in etiology, especially when it involves a traumatic lesion (insect bite, injury), erysipelas is a diagnosis that should be considered when the margins of the cellulitis are distinctly raised, the lesion is extremely painful (commonly named "St. Anthony's fire" in the past), or the consistency of the involved area has an orange peel appearance ("peau d'orange"). In such instances, group A *Streptococcus* (GAS) is the usual pathogen and penicillin is the drug of choice. In the past, erysipelas occurred primarily on the face, but more recently, and particularly in children, such infections are most common on the extremities, and individuals who have preexisting lymphedema appear to be at particularly high risk (Fig. 3).

There are basically three choices of empiric antibiotics for treating potentially MRSA-infected skin or soft tissue infection in a child who is well enough to be treated as an outpatient: clindamycin, doxycycline (in children older than 8 y of age), and TMP-SMX. If both staphylococcal and streptococcal coverage is deemed appropriate, clindamycin alone generally is the drug of choice. Neither doxycycline nor TMP-SMX is appropriate for treatment

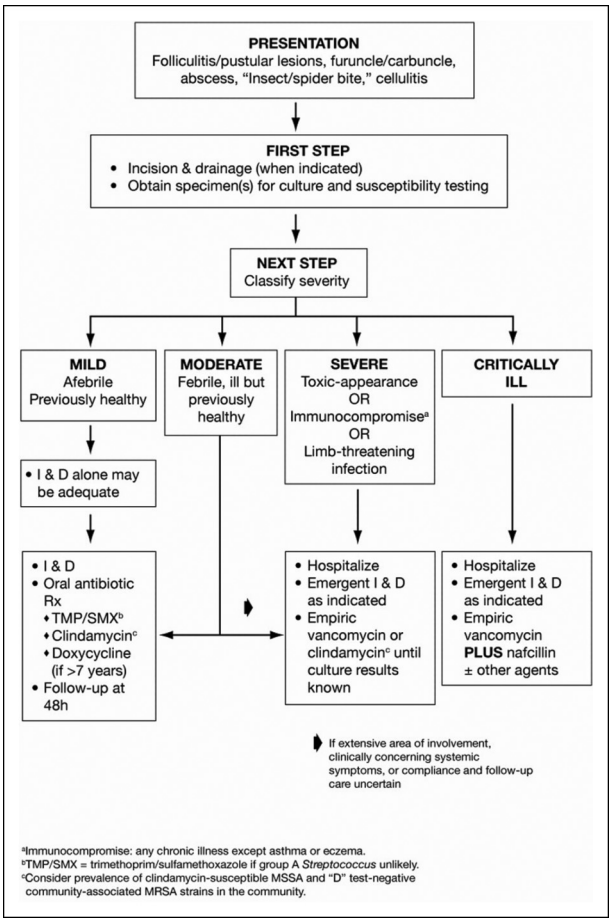

Figure 1. Large CA-MRSA disease burden mandates prompt diagnosis, appropriate management. Adapted from Baker, JC. *AAP News*. 2007; 28;1. I&D=incision and draining; MSSA=methicillin-sensitive *Staphylococcus aureus*; MRSA=methicillin-resistant *Staphylococcus aureus*.

of a skin or soft tissue infection if there is a high likelihood that GAS is a pathogen. In this scenario, cephalexin or penicillin should be added to TMP-SMX. Cephalexin remains a good empiric choice for MSSA and GAS infections or in situations when combined infection with these two pathogens is suspected.

Pneumonia and Empyema

Community-acquired pneumonia is common, and pneumococcus remains the most common bacterial pathogen outside of the neonatal period. However, *S aureus* is an important cause of pneumonia and is more likely to cause an illness that involves multisystem dysfunction. Pneumatoceles have been reported to be associated with complicated and uncomplicated *S aureus* pneumonia. Three

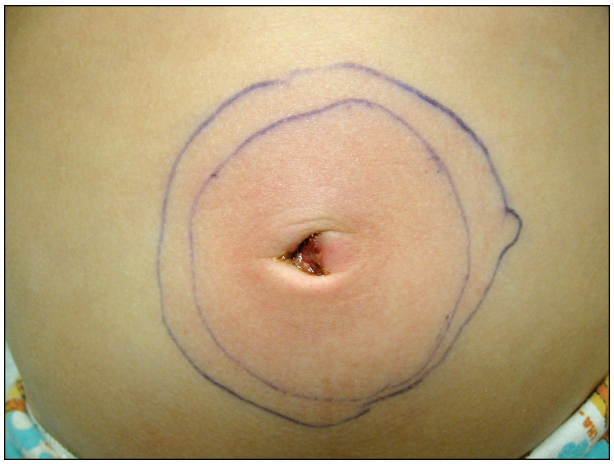

Figure 2. Typical skin manifestation of MRSA infection.

types of complicated *S aureus* pneumonia can be observed: necrotizing pneumonia, pneumonia with empyema, and pneumonia with lung abscess. Pulmonary involvement from septic emboli also may occur in disseminated staphylococcal disease or when there is endocarditis. The clinical presentation in children with staphylococcal pneumonia is typical of any bacterial pneumonia, including high spiking fevers and signs of respiratory distress (hypoxemia, tachypnea, retractions, nasal flaring, chest pain, splinting, etc). The hallmark of staphylococcal pneumonia in young infants, however, may be the rapidity with which the disease progresses.

When the child with pneumonia is toxic appearing, has significant respiratory distress, or has a sizeable pleural effusion, a complicated process, including empyema, should be considered. With the emergence of MRSA, an increase in necrotizing pneumonias with empyema

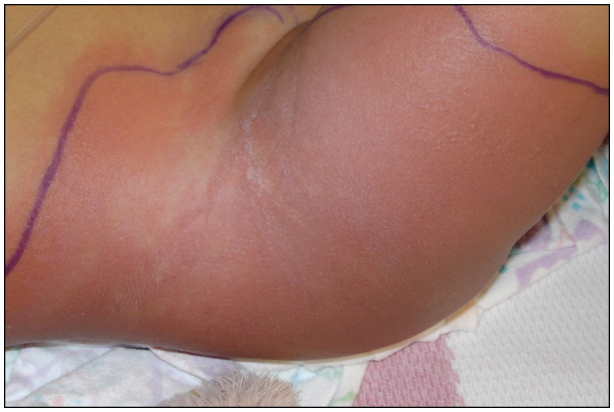

Figure 3. Erysipelas on the extremity of a child (group A streptococcal infection).

has been observed in certain geographic regions. Empyema, defined as an accumulation of pus in the pleural space, can be identified by chest ultrasonography (preferred method based on Infectious Diseases Society of America/Pediatric Infectious Diseases Society [IDSA/PIDS] Guidelines) or computed tomographic scan; imaging will demonstrate loculated fluid, which is the typical feature of complicated pleural space infection. Pleural fluid should be analyzed for features of empyema, which include pH <7.1, lactic acid dehydrogenase concentration >1, 000, and bacteria on gram-stained smear or culture.

Finally, *S aureus* can manifest as an intraparenchymal lung abscess. Although the majority of lung abscesses are observed in patients with underlying conditions and likely are due to aspiration of anaerobic bacteria, normal healthy children can have lung abscesses that result from a *S aureus* infection. These infections cause cavitary lesions within the lung parenchyma, and often air-fluid levels are present on plain radiograph. The clinical presentation of children who have lung abscesses is daily fevers with or without respiratory symptoms. The largest review of this entity observed a majority of patients presenting predominantly with fever and cough; so imaging is the major method of identification and differentiation from other forms of lung infection.

Septic emboli with secondary pulmonary involvement are a potential complication in patients with staphylococcal musculoskeletal infections, particularly multifocal infections. The pathogenesis of these emboli is vascular thrombosis, usually adjacent to the soft tissue/muscle/bone focus, with embolization to the lungs. Suspicion is higher when an area of cellulitis or myositis fails to respond as expected or the patient with a soft tissue or bone infection develops respiratory distress. On chest radiograph, small, round multifocal densities within the lungs represent foci of embolization.

Empiric coverage for children suspected of having staphylococcal pulmonary disease should be vancomycin (15 mg/kg per dose every 6 h) or clindamycin (10 mg/kg per dose every 6 h). Vancomycin should be initiated in the critically ill child who has hemodynamic instability and severe respiratory distress or failure. Clindamycin is an appropriate choice; however, the clinician needs to know the overall resistance rate of all their aureus isolates to clindamycin before its use. The recent IDSA guidelines suggest that if the overall resistance rate of *S aureus* to clindamycin is greater than 10%, the drug should not be used for empiric therapy.

In addition to antibiotic therapy, prompt drainage of the pleural space is essential when pleural fluid is detected and empyema has been confirmed. Depending on local expertise, either video-assisted thorascopic debridement (VATS) or chest tube with intrapleural fibrinolysis (IPF) should be performed if an empyema is confirmed. Two randomized, controlled trials comparing VATS versus IPF have demonstrated equal effectiveness in terms of length of fever and duration of hospitalization and demonstrated an IPF failure rate of 16%.

No high quality, controlled data exist on the appropriate length of therapy for empyema and lung abscess, although most clinicians treat for 3 weeks. Chest tubes associated with VATS or IPF usually can be removed 3 to 4 days after insertion. Transition to oral therapy could be considered when clinical, microbiologic, and laboratory improvement have been confirmed. Therefore, when a patient has become afebrile, no longer requires oxygen, has cleared the organism from the bloodstream (in the 10% of cases where bacteremia has been confirmed), and is tolerating an oral diet without vomiting, an oral antibiotic can be utilized based on susceptibilities. A decrease in the C-reactive protein concentration also can aid in assessing improvement. In children infected with MRSA that is clindamycin resistant, linezolid is an appropriate oral agent, using standard dosing recommendations (Table 1).

Septic Arthritis and Osteomyelitis

Skeletal infections represent the most common invasive infection in children caused by *S aureus* in general, and MRSA specifically. Hematogenous seeding is the mechanism for bone and joint infection in nearly all children. The rate of infection, where both bone and joint are involved, traditionally has been highest in infants and young children owing to the unique vascular supply in younger ages.

Antalgic gait is the most common clinical presentation in the ambulatory child in view of the typical pattern of bone and joint involvement. In the younger infant, irritability and limb disuse may be present. However, it may not be possible to identify the affected joint or bone on initial examination.

Osteomyelitis is diagnosed in 6 of 1,000 admissions to a children's hospital, with 50% of the cases occurring in those younger than 5 years of age. A single long bone (femur, tibia, or fibula) is most commonly involved (over 50% of cases), followed by humerus and then pelvis. Typically, the hallmark of osteomyelitis is limp with point tenderness over the metaphysis of the affected bone, usually in the setting of fever. Septic arthritis has been noted most often in infants and toddlers and affects the knee and hip most often. Pain and swelling of a joint is

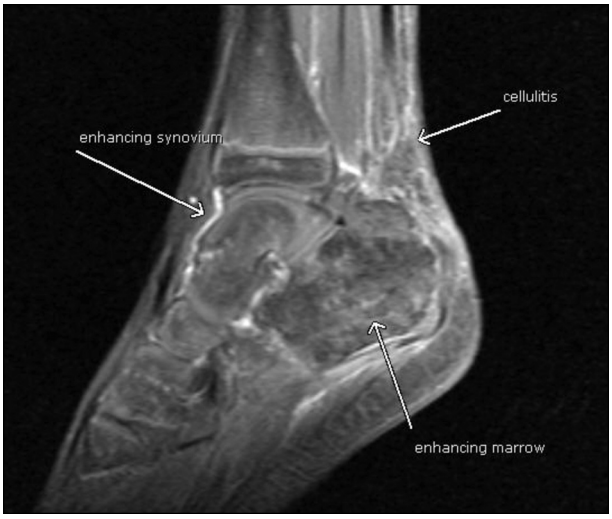

Figure 4. Magnetic resonance imaging changes of osteomyelitis. Methicillin-resistant *Staphylococcus aureus* bacteremia and superinfection associated with varicella in an underimmunized teenager.

most common, although infants may manifest with pain on movement of the hip during diaper change.

When acute skeletal infection is suspected, laboratory studies may be helpful in confirming the diagnosis. Erythrocyte sedimentation rate (elevated in 80% to 90% of cases), C-reactive protein (elevated in 98% of cases), and blood culture should be obtained in all patients; however, only 50% of blood cultures will identify the specific pathogen. Plain radiographs should be obtained but usually are not diagnostic in cases of osteomyelitis because the tell-tale periosteal bone reaction can take 2 weeks or so to develop. Magnetic resonance imaging (MRI) is sensitive and specific for skeletal infection and may direct the surgical drainage (Fig. 4). Joint fluid analysis and culture should be obtained in all cases of septic arthritis. Polymerase chain reaction for *S aureus* and *Kingella kingae* (an important pathogen in infants) is recommended on debrided tissue and synovial fluid. Incubating synovial fluid in a blood culture bottle in addition to plating it on standard culture media may enhance the identification of a pathogen.

Infections involving hips and shoulders should be surgically drained. In the setting of osteomyelitis, culture of bone can be essential but is not performed routinely; if bone is debrided in cases of osteomyelitis, culture and histopathologic examination should be performed. Debridement of necrotic bone is essential, however, for good outcome. Recently available polymerase chain reaction (PCR) assays on joint fluid for *S aureus* and *kingae* may be useful in the diagnosis of septic arthritis in regions where <50% of routine joint fluid cultures reveal a pathogen.

Disseminated MRSA infection with musculoskeletal involvement has been reported increasingly. Such infections can be limb and life-threatening and require prompt recognition and aggressive drainage and debridement in addition to prolonged antibiotic therapy. The typical patient is school-aged and presents with fever and an antalgic gait and appears toxic on examination. MRI can be essential in defining bone, joint, or muscle involvement and also may guide surgical drainage.

In some cases, deep venous septic thrombosis occurs and involves the vessels adjacent to involved bone, similar to thrombosis noted adjacent to pyomyositis sites. Pulmonary embolic phenomena similarly may complicate septic thrombophlebitis in these cases and often are evident on routine chest radiograph as diffuse nodular lesions. The common iliac, saphenous, popliteal, and femoral veins are involved most frequently, and Doppler ultrasonography or computed tomography scan are most useful for diagnosis. The typical involvement of, and association with, pelvic vasculature is so distinctive that some refer to this condition as "pelvic syndrome."

If the child is hemodynamically stable and the pathogen has been identified as MSSA, cefazolin, oxacillin, or nafcillin can supply appropriate initial coverage. Vancomycin traditionally has been the recommended antibiotic treatment of skeletal infection in children when disease appears to be life or limb threatening. Concerns have been raised, however, regarding relatively poor penetration of vancomycin into bone, and animal model data in some cases suggest efficacy is relatively poor. Treatment failure unquestionably is greater in cases where abscesses are drained inadequately or necrotic bone is not debrided.

In light of the above data, some experts empirically add rifampin (10 mg/kg every 12 h with oral route preferred) to vancomycin because rifampin has excellent intracellular activity and penetrates bone well. Limited data suggest, at least in the animal model, that outcomes are improved in such cases. However, in vitro studies have demonstrated antagonism between vancomycin and rifampin.

In the setting of MRSA skeletal infection, alternatives to vancomycin include daptomycin, linezolid, and clindamycin. Clindamycin is considered an appropriate drug, provided that there is no evidence of intravascular infection, and that the isolate is susceptible, because this agent has excellent penetration into leukocytes, bone, and joints. Following aggressive debridement and clindamy-

cin treatment, usually for 3 to 7 days intravenously (IV), therapy can be switched to oral clindamycin and treatment continued for 4 to 6 weeks. A shorter course of therapy (3 wk) could be considered for the child who has uncomplicated septic arthritis caused by MRSA.

Although only a few small case series exist to support efficacy, linezolid does achieve good concentrations in bone, and dosing for treating osteomyelitis is similar to that used in MRSA pneumonia or soft tissue infection. IV linezolid may not be necessary because IV and oral linezolid are equivalent for all practical purposes. Due to the high risk of bone marrow suppression after 2 or more weeks of therapy, all patients require close follow-up, and complete blood counts should be performed weekly.

Daptomycin (6 to 10 mg/kg IV once daily) generally is reserved for cases in which MRSA skeletal infection has been refractory to standard therapy, keeping in mind that, as it is inactivated by surfactant, daptomycin is currently not recommended for treatment of pneumonia. This drug, however, has been used effectively in treating right-sided endocarditis and it has been suggested that daptomycin can be used in the setting of septic pulmonary emboli, which is commonly seen when there is disseminated staphylococcal infection with musculoskeletal involvement. Theoretically, embolic phenomena represents vascular rather than alveolar disease and, as such, daptomycin should be effective.

Still, we suggest that there are several limitations in the consideration of daptomycin for treatment in the pediatric patient and that this drug should, for now, be utilized only with the input of the infectious disease specialist. Efficacy data are still just evolving. Nearly all isolates have minimum inhibitory concentration values ≤1 mcg/mL, but no specific breakpoint for resistance has been assigned. Muscle pain and weakness with elevated creatinine phosphokinase (CPK) concentrations are the most commonly reported adverse events, and CPK should be monitored weekly if such therapy is considered.

Sepsis and Toxic Shock Syndrome

Staphylococcus aureus, both MRSA and MSSA, can cause severe, life-threatening disease manifesting as either a severe sepsis syndrome or toxic shock syndrome (TSS). Severe sepsis syndrome is likely the result of many different virulence factors, including multiple toxins and other factors, while the pathogenesis of TSS is based on the production of toxic shock syndrome toxin-1 (TSST-1).

Most recently, an increase in the incidence of severe sepsis syndrome has been reported in children infected with MRSA. A study from Texas Children's Hospital observed an increase from one case of MRSA sepsis in the period 1999 to 2001 to 12 cases occurring from 2002 to 2004. The classic clinical presentation is a teenager with multifocal bone or joint infections, pulmonary findings (embolic disease, pneumatoceles, complicated parapneumonic effusions), hypotension, or coagulopathy. Additionally, patients who have had antecedent influenza have been observed to suffer from severe *S aureus* sepsis with substantial mortality. Before the advent of varicella vaccine, both GAS and *S aureus* were noted to be associated with severe invasive disease as a complication of wild type varicella infection. This complication continues to be seen in the vaccine era in the under immunized population. Although children who contract sepsis-like syndrome resemble those having TSS, they did not fulfill all of the established diagnostic criteria and more often may have positive blood cultures.

Similar in clinical presentation to the severe sepsis syndrome, TSS has been well described for both MSSA and MRSA infections. TSS first was described in 1978, and the first epidemic was reported in 1979 to 1980 related to the use of high absorbency tampons. Subsequently, surgical associated cases have been described as well as cases without an identifiable infectious focus; the pathogenesis of these cases has been postulated to be due to infection of hematomas or other similar pools of blood-containing secretions.

TSS is by definition a toxin-mediated illness related to *S aureus* strains that produce TSST-1. The common denominators among patients appear to be lack of antibodies to the TSST-1 toxin produced by the bacteria, coupled with compromise in mucosal or skin integrity, as well as the presence of a foreign body (tampon, surgical implants). Importantly, TSS can be observed in children who have invasive staphylococcal disease, including pneumonia and skeletal infection, most often without a positive blood culture. In *S aureus* TSS, blood cultures are positive in <5% of patients. The clinical case definition for staphylococcal TSS is well described.

The empiric antibiotics of choice in children presenting with potential *S aureus* sepsis or TSS are vancomycin (15 mg/kg per dose every 6 h), oxacillin (50 mg/kg per dose every 6 h), and clindamycin (10 mg/kg per dose every 6 h). Due to recent reports of increasing MIC values of MRSA against vancomycin (vancomycin creep), all empiric dosing, especially in children who have sepsis or TSS, should be 15 mg/kg every 6 hours. The addition of oxacillin (or nafcillin) allows for a more rapid rate of killing than vancomycin (in the event that the pathogen is MSSA). Other beta-lactam antibiotics that have MSSA

coverage include cefazolin (first generation cephalosporin having good staphylococcal but limited gram-negative and inadequate CNS coverage) and cefepime (a fourth generation cephalosporin with good MSSA coverage, broader gram-negative and CNS coverage). One of these agents can be added to the regimen in place of oxacillin or nafcillin. Clindamycin abrogates the production of the toxin by the bacteria as well as having antibacterial effects in susceptible organisms and is recommended specifically for inclusion in the empiric coverage for the patient suspected of having TSS. The length of therapy is dependent on the clinical manifestations associated with the sepsislike illness or TSS. For example, patients afflicted with sepsis and osteomyelitis will need to be treated for at least 4 weeks. In cases of tampon-associated TSS, the recommended length of therapy is 10 to 14 days.

Less Common Sites of Infection

Endocarditis is rare in children although cases caused by *S aureus,* including MRSA have been reported. That being said, echocardiographic assessment to exclude endovascular disease is recommended in the child who has congenital heart disease, in those having multiple repeated positive blood cultures (>3 d), and in those children whose clinical manifestations are suggestive of endocarditis. Transthoracic echocardiography generally is acceptable unless the child is older than 10 years of age or has a thick chest wall. Although vancomycin generally is regarded as an essential drug in the empiric therapy for endocarditis, it is essential to recognize that vancomycin kills staphylococci slowly in comparison to beta lactams and beta lactam (nafcillin or oxacillin) therapy is preferred in cases of MSSA endocarditis.

Empirical therapy for the child with endocarditis should include vancomycin plus nafcillin or oxacillin (200 mg/kg per day divided into four doses). Once susceptibilities are known, a single agent can be utilized. The addition of an aminoglycoside is not recommended because these drugs do not add to efficacy but are associated with toxicity and resistance. Daptomycin is an alternative to vancomycin in the adult population, and higher dosing (10 mg/kg per day) is advised. Daptomycin would be considered in the child who has refractory disease. In general, linezolid, tigecycline, TMP-SMX, quinupristin-dalfopristin, and clindamycin are NOT considered for first-line therapy of endocarditis.

Central nervous system infection caused by *S aureus* is not common, but when it occurs, infection often is difficult to treat because it can be difficult to achieve desired drug concentrations in cerebrospinal fluid (CSF) with many of the typically used antistaphylococcal antibiotics. Penetration across uninflamed meninges is 1% of serum concentrations, although higher concentrations are achievable in neurosurgical infections or in cases where the meninges are inflamed (up to 10%). For this reason, many experts add rifampin to vancomycin because penetration is excellent and bactericidal concentrations can be expected in CSF. Most commonly, central nervous system infection with MRSA is associated with a ventricular shunt or other neurosurgical foreign body. In all cases, clinical success depends on removal of the infected foreign body. Linezolid's penetration into CSF in children is variable and overall limited efficacy data are available. To date, there are no good data on daptomycin concentrations in the CSF, although animal model data suggest that concentrations of 3 to 4 mcg/mL can be achieved with dosing of 15 mg/kg once daily.

Recurrent Skin Infections

The approach to treatment of the child who has current skin abscess (usually caused by MRSA) is not well researched. Based on recommendations from the IDSA/PIDS guideline for management of MRSA infection, the first step is enhanced hygiene and environmental cleaning. Concurrent with these basic steps is treatment for anyone in the family who has active disease. We have found that coexisting infection in the parent is common but often not revealed by the family except by explicit questioning; further, parents who have been identified as having recurrent skin infections often have not received effective therapy (drainage or MRSA-targeted antibiotic treatment). Nasal mupirocin and skin decolonization (chlorhexidine or bleach baths) also are recommended. At this time, routine nasal culturing of the child or family members is not recommended, and treatment with antibiotic-based decolonization regimens (usually rifampin plus an additional agent) should be reserved for patients with recalcitrant infection, utilizing infectious disease consultation, or those who have a planned surgical procedure where a foreign body is being implanted.

Other and Future Pediatric Drugs

Tigecycline, a derivative of tetracycline in the glycylcycline drug group, and quinupristin-dalfopristin, a streptogramin antibiotic, are not Food and Drug Administration (FDA)-approved for children, nor are they first-line drugs in the child who has MRSA infection, mainly because of their associated toxicities. Approximately 40% of patients experience nausea and vomiting with tigecycline, and myopathy and nearly uniform infusion

reactions (chills, myalgias) occur with quinupristin-dalfopristin.

Televancin, a new ipoglycopeptide, has bactericidal activity against MRSA and is FDA-approved in adults who have complicated skin and soft tissue infection. There are no published data on children as yet, but this drug holds promise.

Ceftibiprole, a fifth-generation beta lactam having MRSA activity, is still in pharmacokinetic trials in children in 2010, and has yet to obtain FDA approval for treatment in adults.

Principles of Treatment

The treatment of staphylococcal infections is based on the presentation, location, and severity of illness. Basic principles in treating children include draining abscesses (except pulmonary), utilizing culture and susceptibility data, knowing the local antimicrobial susceptibility patterns of *S aureus*, and understanding the pharmacokinetic and pharmacodynamic properties of antistaphylococcal agents in various clinical conditions.

Drainage

Draining of abscesses has been demonstrated to be an effective method in the treatment of many infections. Importantly, antibiotics fail to penetrate abscesses adequately and uniformly, and the milieu in an abscess can be analogous to biofilm, with organisms not being metabolically active, so antibiotic targets are not available. Furthermore, drainage of abscesses without the addition of antibiotics may be sufficient in the treatment of certain infections. In skin and soft tissue infections, both a retrospective and a pediatric randomized, controlled trial showed that drainage alone of abscesses less than 5 cm in size was as effective as drainage plus antibiotics.

Drainage should not be limited to skin and soft tissue infections. This strategy also should be employed in the treatment of pyomyositis or subperiosteal abscesses because drainage will help eliminate a large burden of disease that will aid in a better treatment response. In cases in which tissue necrosis has occurred, debridement of the necrotic area is essential because tissue without blood supply will persist as a nidus of infection, in part due to failure of penetration of most antibiotics. For children with staphylococcal infection in whom persistent fever is noted, a search for a sequestered focus is essential (based on strong evidence and consensus).

Susceptibility Patterns

Treatment of staphylococcal infection invariably is driven by susceptibility information, and because the epidemiology and antimicrobial resistance of such infections has changed over the last 10 years, local or patient-specific data are essential in ensuring good outcome. With MRSA comprising from 20% to 70% of *S aureus* isolates across the country, local data are essential to guide the clinician in the most appropriate empiric antibiotic choice. It is important to note that >90% of MRSA infections are uncomplicated skin or soft tissue infection. Also, in the setting of invasive disease, MSSA remains an important pathogen.

Clinicians need to be aware of *S aureus* antibiotic resistance rates in their geographic locales. With the increase in MRSA in the past 15 years, many clinicians began to use clindamycin as their empiric antibiotic of choice. However, MSSA still causes serious infections. So choosing empiric antibiotics requires consideration of local resistance rates for both MRSA and MSSA. MRSA resistance to clindamycin may be as little as 5% or as high as 30%, and clindamycin resistance rates in MSSA may be as high as 25% in some areas. Additionally, with increased use of clindamycin, it is likely that this rate is only going to increase. Recent guidelines suggest that if local data demonstrate a >10% rate of MRSA or MSSA resistance to clindamycin, adding a second drug or altering the choice of empiric therapy should be considered, particularly in more than minimally ill children. In uncomplicated skin infections that require treatment, TMP-SMX is a reasonable alternative if GAS is not suspected as the main or copathogen (based on some research studies and consensus).

Clinical Considerations

The initial empiric antibiotic choice in patients with a suspected *S aureus* infection is dependent also on the clinical presentation. In children who appear septic, are hemodynamically unstable, or have impending respiratory failure, vancomycin is the empiric antibiotic of choice. *S aureus* fully resistant to vancomycin has not yet been reported in pediatrics. Addition of oxacillin or nafcillin (more rapidly bactericidal to MSSA) to the vancomycin regime is recommended because the combination decreases the length of bacteremia in MSSA infections. Finally, when evidence of toxin is present the addition of clindamycin provides an antibiotic that down-regulates the production of the toxin by the *S aureus* bacteria. Children who are not severely ill can be treated initially with clindamycin unless endocarditis or a central nervous system infection is suspected, or if clindamycin resistance rates locally are greater than 10% (based on some research studies and consensus).

Summary

- Management of MRSA infection in the pediatric patient continues to rely on prompt diagnosis and localization of focus, and utilization of susceptibility data.
- Drainage or debridement of abscess or necrotic material as well as knowledge of pharmacokinetic and pharmacodynamic data should guide appropriate therapy for specific infections.
- Although vancomycin continues to be the cornerstone of therapy for MRSA infection in children, the increasing identification of strains having a vancomycin MIC at or beyond 1 mcg/mL may serve to change the scope of treatment for such infections in the future.

Suggested Reading

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PIR Quiz

Quiz also available online at: http://pedsinreview.aappublications.org.

NOTE: Beginning in January 2012, learners will be able to take *Pediatrics in Review* quizzes and claim credit online *only*. No paper answer form will be printed in the journal.

5. An otherwise healthy 4-year-old boy presents with his second community-acquired MRSA skin infection in the past year. The first involved scattered folliculitis on his right forearm; he cleared promptly with oral trimethoprim-sulfa. His current problem is a 3-cm abscess on the right leg that you have just incised and drained. Given the history, you should

   A. Assume his host defense system is intact.
   B. Evaluate for immune globulin deficiency.
   C. Explore T cell function.
   D. Obtain complement studies.
   E. Suspect a disorder of chemotaxis.

6. A previously well 5-year-old girl has a 4-cm fluctuant abscess on her left buttock. She is afebrile. The remainder of her examination is normal. The best choice of initial therapy is incision and drainage accompanied by

   A. Local wound care alone.
   B. Oral cephalexin.
   C. Oral clindamycin.
   D. Oral doxycycline.
   E. Oral trimethoprim-sulfa.

7. A previously well 5-year-old girl has a 4-cm fluctuant abscess on her left buttock. Erythema and tenderness extends 4 cm beyond the area of fluctuation. She has a temperature of 38°C and appears mildly ill. The remainder of her examination is normal. The best choice of initial therapy is incision and drainage accompanied by

   A. Local wound care alone.
   B. Oral cephalexin.
   C. Oral doxycycline.
   D. Oral trimethoprim-sulfa (some might recommend clindamycin in this patient).
   E. Parenteral vancomycin.

8. You practice in a community where 50% of staphylococcal infection is caused by MRSA and your local antibiogram shows 8% clindamycin resistance. Today a previously healthy 7-year-old boy presents to your office with fever and a right-sided limp for the past 3 days. On examination, there is point tenderness over the metaphysic of his right distal tibia. An MRI demonstrates characteristic changes of osteomyelitis and suggests the presence of necrotic bone. While awaiting a surgical procedure as well as blood culture and susceptibility results, the best choice of initial therapy is intravenous

   A. Cefazolin.
   B. Clindamycin.
   C. Daptomycin.
   D. Linezolid.
   E. Nafcillin.

9. A previously healthy 10-year-old ill-appearing girl presents to the emergency department with a 4-day history of fever and a boil on her left shoulder. She is hypotensive and has a diffuse erythrodermatous rash. IV cefepime was given in the emergency department; additional antimicrobial coverage in this child should include

   A. Daptomycin and cefazolin.
   B. Linezolid and gentamicin.
   C. Nafcillin and ceftriaxone.
   D. Vancomycin and TMP-SMX.
   E. Vancomycin and clindamycin.

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