Staphylococcus aureus

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Practice Gap

Staphylococcus aureus can cause numerous disease processes, and management varies with pathology and severity. It is important for the general pediatrician to identify factors that increase a patient's risk of developing *S aureus* infection to ensure appropriate treatment.

Objectives After completing this article, readers should be able to:

1. Understand the epidemiology of common *Staphylococcus aureus* diseases.
2. Recognize risk factors that increase patient susceptibility to *S aureus* infections.
3. Understand the difference in clinical presentations and pathogenesis between *S aureus* infection and toxin-mediated illness.
4. Understand the importance of bacterial cultures, antibiotic susceptibilities, and local community prevalence of methicillin and clindamycin resistance.
5. Identify which antibiotics are appropriate for empirical treatment of methicillin-sensitive and methicillin-resistant *S aureus.*
6. Understand the level of evidential support regarding decolonization practices and when such practices are recommended.

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ABBREVIATIONS

BLRBL	β-lactamase–resistant β-lactam
CA-MRSA	community-acquired methicillin-resistant *Staphylococcus aureus*
CNS	central nervous system
IE	infective endocarditis
IV	intravenous
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-sensitive *Staphylococcus aureus*
PBP	penicillin-binding protein
SSSS	staphylococcal scalded skin syndrome
SSSI	skin and skin structure infection
TMP-SMX	trimethoprim-sulfamethoxazole
TSS	toxic shock syndrome
VISA	vancomycin-intermediate *Staphylococcus aureus*
VRSA	vancomycin-resistant *Staphylococcus aureus*

Abstract

Staphylococcus aureus is a bacterium that can cause a variety of illnesses through suppurative or nonsuppurative (toxin-mediated) means. *S aureus* is a common cause of skin and skin structure infections as well as osteoarticular infections in the pediatric population. *S aureus* is also identified in cases of septicemia, infective endocarditis, pneumonia, ocular infections, and central nervous system infections. To design appropriate empirical therapy, pediatricians should be knowledgeable about the resistance patterns of *S aureus* in their communities, including methicillin and clindamycin resistance. This article reviews the microbiology, colonization and transmission, and antibiotic resistance of and clinical diseases caused by *S aureus.*

CASES

1) *A 7-month-old boy, previously healthy, is seen in the emergency department with a 1-day history of rash, which had the initial appearance of a sunburn. Involved areas are now peeling. His parents describe him as being very fussy and having decreased number and volume of wet diapers. On physical examination he is afebrile, with a temperature of 99.5°F (37.5°C), heart rate of 164 beats/min, respiratory rate of 32 breaths/min, blood pressure of 72/46 mm Hg, and pulse oxygen saturation of 99% on room air. He has numerous bullae over his body and a positive Nikolsky sign.*

   Staphylococcal scalded skin syndrome (SSSS).

2) *A 12-year-old boy hospitalized for inflammatory bowel disease management has a central venous line for total parenteral nutrition. He suddenly develops a new fever (102.0°F [38.9°C]), is shivering, and complains of being "cold." Physical examination reveals a toxic-appearing boy who is febrile to 103.1°F (39.5°C) and has a heart rate of 126 beats/min, respiratory rate of 24 breath/min, blood pressure of 90/40 mm Hg, and pulse oxygen saturation of 98% on room air. The central line insertion site is without erythema or drainage. His examination reveals a new cardiac systolic murmur, tachycardia, and poor perfusion. Blood cultures are obtained from his central line as well as a peripheral venipuncture, and he is given intravenous (IV) antibiotics due to his toxic clinical appearance. Within 24 hours, blood cultures grow* S aureus. *The central line is removed and his antibiotics are appropriately tailored once antibiotic susceptibilities are available on the bacteria. However, he continues to have positive blood cultures for 5 days after removal of the central line and appropriate antibiotic therapy. Due to his new cardiac murmur and the persistence of positive blood cultures, an echocardiogram is performed and a large thrombus is detected on his tricuspid valve.*

   Bacteremia and infective endocarditis (IE) with a central line.

3) *A 3-year-old toddler, previously healthy with normal growth and development, is seen for an urgent visit for a chief concern of limping for 2 days. He is usually a very active child and plays and runs around the house in the morning with his siblings. This morning he woke up and refused to walk or play. In the clinic, he is febrile to 101.5°F (38.6°C), heart rate of 130 beats/min, respiratory rate of 38 breaths/min, blood pressure of 80/56 mm Hg, and pulse oxygen saturation of 97%. On physical examination, the child is keeping his right leg abducted, flexed, and externally rotated. He refuses to move it from this position and does not allow you to move it passively. Imaging is obtained and shows an effusion of the hip. He is diagnosed as having septic arthritis and is taken to surgery.*

   Osteoarticular infection

BACTERIAL VIRULENCE FACTORS

To understand the basic hardiness and virulence of this bacterium, a review of the structure, extracellular products, and genetic elements is paramount. (1)

S aureus is a gram-positive bacterium that appears in clusters on Gram-stain. (1) It is catalase positive and, unlike other staphylococcal species, coagulase positive. (1) There are several methods to identify *S aureus*, eg, polymerase chain reaction and peptide nucleic acid fluorescence in situ hybridization, although the best known and most used is the bacterial culture. (2)

S aureus has a variety of virulence factors that, singly and in combination, can result in severe infection. Catalase, produced by *S aureus*, is an enzyme that allows intracellular survival of this bacterium by breaking down hydrogen peroxide, a host defense mechanism. (3) Surface proteins of *S aureus* include coagulase (the catalyst that generates fibrin from fibrinogen) and clumping factors (which cause clotting). (1) Toxins and extracellular substances include hemolysins (which destroy erythrocytes), leukocidins (which cause skin necrosis), and exfoliative toxin and enterotoxins B and C (which propagate the systemic inflammatory response). (1) Panton-Valentine leukocidin is a toxin that can do all the above. (4) These virulence factors allow *S aureus* to cause the variety of clinical syndromes for which this bacterium is known, including the development of abscesses.

S aureus can acquire new genetic elements. (1) Local environmental stressors, such as low pH, low oxygen, poor availability of nutrients, extremes in temperatures, and antibiotic use, may force altered genetic expression through regulatory mechanisms. (1) In total, intrinsic and acquired genetic material expands the ability of *S aureus* to affect the patient while surviving in harsh conditions.

RESISTANCE PATTERNS

S aureus has proved adept at developing antibiotic resistance. This is accomplished through acquisition of mobile genetic elements that transfer resistance and virulence from other bacterial species and staphylococcal strains. (1) External pressures (namely, overuse of antibiotics) can also force a previously susceptible isolate to become resistant.

The most well-known story of *S aureus* resistance follows the introduction of penicillin. *S aureus* developed resistance via production of β-lactamase, which prevents the antibiotic from binding to the penicillin-binding protein (PBP) on *S aureus*. This lack of binding to PBP obstructs the ability of the penicillin drug to inhibit bacterial cell wall synthesis. (1) This β-lactamase was not

native to *S aureus*, it was acquired via a plasmid-encoded penicillinase. (1)(5)

The evolution of methicillin resistance should be familiar. Semisynthetic penicillins (the prototype being methicillin) were developed by scientists to circumvent the problem of *S aureus* β-lactamase resistance. However, shortly after the introduction of these compounds, some *S aureus* strains became methicillin resistant. Methicillin resistance was acquired via the *mecA* gene encoding for PBP2a, which decreases the binding affinity of antibiotics to the target bacterium. (5)(6) It is proposed that *S aureus* acquired the *mecA* gene from other staphylococcal species. (6)

An ominous example of acquisition of resistance pertains to vancomycin, regarded by medical providers as a workhorse against gram-positive pathogens. Vancomycin-intermediate *S aureus* (VISA) was identified in the 1990s. Although the resistance mechanisms of VISA are not completely understood, the result is a minimum inhibitory concentration (MIC) of vancomycin greater than or equal to 4 μg/mL to overwhelm *S aureus* (the usual MIC is <2 μg/mL). (1) Vancomycin-resistant *S aureus* (VRSA) is defined as possessing a MIC for vancomycin that is greater than or equal to 16 μg/mL. (1) The first case of VRSA was reported in 2002. The resistance of VRSA is attributed to the *VanA* gene, which was acquired from enterococcus, an entirely different bacterial genus. (1)

The susceptibility of *S aureus* isolates to clindamycin is variable. The provider should be aware that methicillin-sensitive *S aureus* (MSSA) and methicillin-resistant *S aureus* (MRSA) isolates may be intrinsically resistant to clindamycin or resistance may be inducible. The latter is suspected if there is discordance in a laboratory result: clindamycin-susceptible but erythromycin-resistant *S aureus*. (2) In this situation, the laboratory will conduct a procedure on the bacteria known as the D test. (2) In the case of a positive D test result (inducible clindamycin resistance), an alternate drug is used. A study from found MSSA and MRSA clindamycin-resistance rates as high as 32.7% and 90.8%, respectively. (7) In 1 study using a multihospital database in the United States from 2007 through 2011, 24,644 clinically relevant *S aureus* isolates were reported. Of those that had clindamycin susceptibility testing completed, 39.1% to 40.4% were clindamycin resistant (the authors did not distinguish between MRSA and MSSA). (8)

Knowledge of community antibiotic resistance patterns to *S aureus* should guide empirical antibiotics used to treat community-acquired MRSA (CA-MRSA) and hospital-acquired MRSA. The latter is usually multidrug resistant, whereas CA-MRSA is often susceptible to clindamycin, doxycycline, and trimethoprim-sulfamethoxazole (TMP-SMX). (2) When confronted with suspected *S aureus*, providers should be aware of the proportion of CA-MRSA compared with MSSA in their community, and the resistance of the prevailing *S aureus* strains (especially against clindamycin). This information may be obtained by contacting local infectious diseases practitioners or the director of a local facility's microbiology laboratory.

COLONIZATION AND TRANSMISSION

Staphylococcus is considered a part of normal human flora termed *colonization*. A common body area of *S aureus* colonization is the anterior nares. An estimated one-third of the human population (including the pediatric population) has asymptomatic *S aureus* colonization. (2)(9)(10)(11) In 2016, among kindergarten attendees in Iran, 25% were colonized with MSSA and 6% with MRSA. (12) In a prospective study of children in St Louis with community-onset *S aureus* skin and skin structure infections (SSSIs), more than half of the patients were colonized with 1 strain, 44% with 2 strains, and 4% with 3 strains. (13) Therefore, it is not unusual for a pediatric patient to be colonized with *S aureus*, and to possibly harbor more than 1 *S aureus* isolate.

Colonization is a risk factor for infection, and infection often occurs with the same *S aureus* strain that colonized the individual. In the previously cited study from St Louis, 67% of children were colonized with the same strain of *S aureus* that caused their SSSI. (13) In a survey of outcomes of children in the 6 months after knowledge of *S aureus* colonization, SSSI developed in 23% of children colonized with MRSA, 8% of children colonized with MSSA, and 7% without evidence of previous colonization. (14)

Infections may not always result from the patient's colonizing *S aureus* strain. One prospective study determined that more than half of the *S aureus* SSSIs in children were caused by a strain with which the child was not colonized. (15) Asymptomatic colonized individuals may spread the organism to others. (11) Sources for noncolonizing strains include household contacts. However, 1 study demonstrated that less than half of the strains responsible for the infection were the same strain with which the patient or household contact was colonized. (2)(13)

SUPPURATIVE ILLNESSES

The pathologic development of the following suppurative infectious syndromes are similar regardless of causative bacterial agent. The discussion of illnesses later herein is summarized in Table 1. The provider should allow the severity of disease and the suspicion of MRSA to guide the choice of empirical antibiotics.

TABLE 1. **Infectious Syndromes Caused by *Staphylococcus aureus* in Pediatrics**

INFECTIOUS SYNDROME	INCIDENCE/ EPIDEMIOLOGY	PATHOGENESIS AND/ OR RISK FACTORS	TREATMENT	TREATMENT IF HIGH CONCERN FOR MRSA	TREATMENT DURATION
SSI - mild	Roughly a third of the population is colonized with *S aureus*	Direct inoculation	Mupirocin 2% topical ointment	No change	7 days or guided by response to treatment
SSI - furuncles	Roughly a third of the population is colonized with *S aureus*	Direct inoculation	Application of moist heat. If unresponsive or large, incision and drainage ± antibiotics	No change	7 days or guided by response to treatment
SSI - other (including if systemic signs are present)	unknown	Direct inoculation	BLRBL	Vancomycin, clindamycin, linezolid, doxycycline, TMP-SMX	7 days or guided by response to treatment
Bacteremia	1.54–1.95 per 1,000 pediatric hospitalizations	Foreign body, respiratory, osteoarticular, or SSSI hematogenous spread of infection	BLRBL + vancomycin		Minimum 14 d after first negative blood culture
Infective endocarditis	0.41–0.43 per 100,000 children (*S aureus* 24%–36%)	Heart defect, foreign body, intravenous drug use	BLRBL + vancomycin ± gentamicin ± rifampin		2–8 wk after first negative blood culture
CNS infection	5%–6% of bacterial meningitis; ~23% of VP shunt infections	Direct inoculation, foreign body, midline spinal defect	Nafcillin/oxacillin + vancomycin		2 wk for meningitis; 4–8 wk for intracranial abscess
Pneumonia	1% of CAP requiring hospitalization; 6%–32% of necrotizing pneumonia	Inhalation, hematogenous seeding	BLRBL	Vancomycin, clindamycin,[b] linezolid	7 d or guided by response to treatment
Osteoarticular infection	7.1 per 100,000 children (overall, not specific to *S aureus*)	Hematogenous, direct inoculation, contiguous spread	BLRBL	Vancomycin,[c] clindamycin,[b] linezolid	3–4 wk for septic arthritis; 4–6 wk for osteomyelitis
Ocular infections	12.1% of ophthalmologic infections are caused by MRSA	Direct inoculation, contiguous and/or hematogenous spread	BLRBL	Vancomycin, clindamycin,[b] linezolid	2 wk

BLRBL=β-lactamase–resistant β-lactam, CAP=community-acquired pneumonia, CNS=central nervous system, MRSA=methicillin-resistant Staphylococcus aureus, *MSSA=methicillin-sensitive* Staphylococcus aureus, *SSSI=skin and skin structure infection, TMP-SMX=trimethoprim-sulfamethoxazole; VP=ventriculoperitoneal.*

[a]*Mild SSSIs include impetigo, localized folliculitis, and superficial secondary bacterial infection.*

[b]*Clindamycin may be considered if a high percentage of* S aureus *isolates in the community are susceptible to clindamycin.*

[c]*Vancomycin is included in the empirical treatment if community rates of MRSA are greater than 10%.*

Skin and Skin Structure Infections

One of the more common manifestations of *S aureus* is SSSI (previously named *skin and soft tissue infection*). (16)(17) Although 1 study reported an increasing rate of hospitalizations for pediatric SSSI over a 10-year period, only 20% of these were secondary to *S aureus*, including 10% from CA-MRSA. (18) Methicillin-resistant *S aureus* SSSI seems to be more prevalent in the late spring to late summer months. (18) (19) Thus, the provider should be aware that only a minority of SSSIs requiring hospitalization are caused by *S aureus* and that SSSIs secondary to MRSA may have a seasonal propensity.

In addition to nonintact skin being a risk factor for SSSI, an additional risk is seen in patients with atopic dermatitis. Atopic dermatitis is an inflammatory disorder of the skin, which

increases the risk of developing secondary dermatologic (and other) bacterial infections from many organisms, but importantly from *S aureus*. Separate from its ability to cause infection, *S aureus* produces several toxins and proteins that impair the ability of regulatory T cells to suppress an overly active local immune reaction, thus allowing the local inflammatory response from atopic dermatitis to proceed. (20) Ways to reduce or eliminate *S aureus* bacterial burden (decolonization, described later in this review) become of greater importance in patients with inflammatory skin disorders, who may be at risk for not only infection by *S aureus* but also worsening of their underlying disease pathophysiology.

For mild skin infections such as impetigo, localized folliculitis, or superficial secondary bacterial infection, mupirocin 2% topical is appropriate treatment. (2)(21) Furuncles may respond by application of moist heat, which promotes suppuration. (21)(22) However, for larger furuncles or furuncles that do not spontaneously drain or decrease in size, incision and drainage is the treatment of choice. (21)(22)

Antibiotics may not provide additional benefits after incision and drainage. However, there are clinical scenarios in which a systemic antibiotic is indicated. (21)(23) Infection-related concerns include abscesses in multiple sites (extensive disease), abscesses that cannot be adequately drained, rapid progression of infection, associated septic phlebitis, or a lack of improvement or a recurrence after incision and drainage. (21) Patient factors that may prompt the use of systemic antibiotics include evidence of systemic illness (fever, hypotension), individuals at extremes of age, or those with comorbidities (diabetes mellitus, human immunodeficiency virus infection, immunocompromised status, and neoplastic disease). (2)(21) If possible, abscesses should be cultured before the initiation of antibiotic therapy. (21)

Appropriate treatment depends on whether the suspected or confirmed pathogen is MSSA or MRSA. Antibiotic treatment for MSSA includes a β-lactamase–resistant penicillin or, if allergic, a first-generation cephalosporin. (2)(21) If there is concern for MRSA (given community prevalence), TMP-SMX, doxycycline, clindamycin, or linezolid can be used for MRSA treatment. (2)(21) Purulent cellulitis should be treated empirically for MRSA until cultures result to guide treatment; duration is 5 to 10 days. (21) Trimethoprim-sulfamethoxazole should never be used as empirical monotherapy for cellulitis given the historically poor treatment of *Streptococcus pyogenes*. (2) Parenteral empirical MRSA treatment includes vancomycin, linezolid, or clindamycin. (21)

Bacteremia. The incidence of *S aureus* bacteremia has been reported to be 1.54 to 1.95 in 1,000 pediatric hospitalizations in the United States. (24)(25) Risk factors that increase the incidence of *S aureus* bacteremia include extremes of age (<12 months old), sex (males with slightly higher incidence), and ethnicity (higher rates in the African American population in the United States). (26)(27)

For *S aureus* bacteremia, a β-lactamase–resistant β-lactam (BLRBL) combined with vancomycin is the treatment of choice until guided by antibiotic susceptibility results. (2)(21) For uncomplicated bacteremia, the treatment duration is (minimum) 14 days after microbiological clearance. Complicated bacteremia includes metastatic spread (emboli to lungs, solid organ, or brain), IE, lack of defervescence within 72 hours of appropriate antibiotic treatment, persistently positive cultures after 2 to 4 days of appropriate treatment, presence of an implanted device(s), or recurrence within 3 months after completing therapy. (21)(26)(28) Duration of treatment may be extended for immunocompromised patients, those with catheter-related bacteremia, and those with complicated outcomes. (2) Expert consultation with an infectious diseases expert should be sought for treatment of complicated bacteremia.

Infective Endocarditis. Infective endocarditis is not as common in the pediatric population as in the adult population. In incidence studies, more than half of the cases of pediatric IE possess an underlying cardiac condition. (29)(30) The incidence of IE has not changed appreciably between the early 2000s and the 2010s, (0.41–0.43 per 100,000 children). The most common responsible organism was *S aureus*, accounting for 24% to 36% of IE. (26)(29)(30) So although IE is not common in pediatrics, the clinician should be aware that *S aureus* accounts for one-third of these infections.

For *S aureus* IE, vancomycin plus a BLRBL is the treatment of choice until guided by susceptibility results. For MSSA, a BLRBL (eg, nafcillin, oxacillin, or cefazolin) is the treatment of choice with the option of adding gentamicin for synergy for the first 3 to 5 days of treatment. (31) For MRSA, vancomycin is the treatment of choice, with or without gentamicin for the first 3 to 5 days of treatment. (31) If the patient has prosthetic material, rifampin and gentamicin should be added to the treatment regimen for the first 2 weeks. (21)(31) Consultation with an infectious diseases specialist is warranted in pediatric IE. Treatment duration is 2 to 8 weeks. (2)(21)(31) Infective endocarditis due to *S aureus* has a higher mortality rate (22%–66%) than other causes of IE. (26)

Infections of the Central Nervous System. *S aureus* is not a common cause of central nervous system (CNS) infection. (32)(33) Microbiological surveillance during 2004 to 2011 in a health-care system in England and Wales showed that *S aureus* accounted for 5% of bacterial meningitis in children younger than 14 years and 6% of bacterial meningitis in

infants younger than 3 months. (34) A retrospective analysis from Korea analyzing outcomes of children with ventriculoperitoneal shunts revealed a rate of infection of 0.075 cases per shunt-year. (35) *S aureus* was the second most commonly identified organism (apart from coagulase-negative staphylococcus), accounting for 22.9% of ventriculoperitoneal shunt infections. (35) It is exceedingly rare for a child to develop an *S aureus* brain abscess solely from contiguous spread from sinusitis, without a preexisting bony defect. (36) In a child experiencing *S aureus* meningitis without a history of CNS trauma or procedures, a midline spinal defect (occult spina bifida) should be sought.

Foreign bodies (such as a ventriculoperitoneal shunt) will serve as a nidus of infection and should be removed. Any abscess or collection of infection in or near the brain warrants a surgical evaluation. (21) Empirical treatment of *S aureus* CNS infection is vancomycin with nafcillin or oxacillin. (2) Duration of treatment varies, from 2 weeks for meningitis to 4 to 8 weeks for intracranial abscesses. (21)(36)

Pneumonia. Compared with other bacteria, *S aureus* is a less common cause of pneumonia (community and hospital acquired). Active population surveillance for community-acquired pneumonia at 3 pediatric hospitals in the United States found that *S aureus* accounted for 1% of community-acquired pneumonia requiring hospitalizations. (37) Necrotizing pneumonia (destruction of lung parenchyma with vascular changes) is an uncommon but severe complication of community-acquired pneumonia. A retrospective study in Poland noted that necrotizing pneumonia in children accounted for 3% of all hospital admissions for pneumonia from 2008 to 2013. (38) *S aureus* is 1 of the recognized causative organisms of necrotizing pneumonia and accounts for 6% to 32% of all necrotizing pneumonia. (38)(39) A large proportion of *S aureus* isolates responsible for necrotizing pneumonia possess the gene for Panton-Valentine leukocidin (previously described in this review as a virulence factor). (39) Overall, *S aureus* is an uncommon cause of pneumonia, but the clinician should be aware of the ability of some strains of *S aureus* to cause necrotizing pneumonia.

The empirical treatment of pneumonia suspected to be from *S aureus* depends on severity of presentation and prevalence of MRSA. Pneumonia from MSSA should be treated with a BLRBL. Vancomycin remains the preferred empirical antibiotic for MRSA-suspected severe pneumonia, but it has relatively poor lung tissue penetration. (21) For MRSA pneumonia, clindamycin may be an adequate choice if the provider knows that a high percentage of *S aureus* isolates in the community are susceptible to clindamycin. (21) An alternative antibiotic for MRSA pneumonia (particularly if oral therapy is desired for a MRSA isolate that is clindamycin resistant) is linezolid. (21) Suggested duration of treatment for *S aureus* pneumonia is 7 days, although complications such as necrotizing pneumonia may prolong treatment.

Osteoarticular Infection. Approximately half of all bacterial osteoarticular infections occur in children younger than 5 years. (40) A population-based prospective study conducted in France in 2008 to 2009 reported the incidence of osteoarticular infections in children to be 7.1 in 100,000 children, with *S aureus* most commonly identified as the causative organism. (4)(41) Although MSSA remains a predominant cause of osteoarticular infections, the incidence of MRSA has been increasing (accounting for 0.8% in 1997 and increasing to 15.1% in 2012). (40)(42)

Initial empirical antibiotic treatment for osteoarticular infections should be administered IV. Empirical therapy for presumed or proven MSSA involvement should be nafcillin or oxacillin, although cefazolin may be used given that dosing is convenient at every 8 hours compared with every 6 hours for the semisynthetic penicillins. The empirical treatment for osteomyelitis and septic arthritis is vancomycin when CA-MRSA rates are greater than 10%. (2)(4) Alternatives include clindamycin (if clindamycin resistance is low and there is no associated bacteremia) and linezolid. (4)(21) The minimum treatment duration is 3 to 4 weeks for septic arthritis and 4 to 6 weeks for osteomyelitis, predicated on clinical response and normalization of inflammatory markers, particularly the erythrocyte sedimentation rate (ESR). (4)(21) The decision on final therapy, including drug and mode of delivery (IV versus oral), should include discussion on whether the pathogen has been identified, whether the treatment course was complicated by poor clinical or microbiologic response (such as prolonged secondary bacteremia), compliance of patient and family with possible oral regimen, and availability of medical facilities for families to seek care for unexpected complications. Early involvement of an orthopedic surgeon is important in both diagnosis and treatment of osteoarticular infections. (4)

Ocular Infections. *S aureus* has been identified as a causative organism in ocular infections. (43)(44) Ocular infections range from mild to severe, conjunctivitis to orbital cellulitis. A retrospective review of pediatric MRSA ocular infections in a northern California health-care system showed a 12.1% increase in MRSA causing ophthalmologic infections over a 5-year period (2000–2005). (45) Of all MRSA ocular infections, 40% manifested as conjunctivitis, with preseptal cellulitis (25%), orbital cellulitis

(19%), dacryocystitis (11%), and eyebrow abscesses (3%) being reported (2% of reported MRSA ocular infections did not define the primary site). (45) Of note, organism identification is low, approximately 30% in some studies. (43)(44)

Empirical treatment for preseptal cellulitis should target *S aureus* and *S pyogenes*. (46)(47)(48) For postseptal cellulitis, antibiotic treatment should include activity against anaerobic and gram-positive organisms. (46) In a MRSA-prevalent community, vancomycin or clindamycin should be used for empirical treatment pending susceptibility results. (46) Parenteral antibiotics should be continued until the eye is clearly improving, at which point the patient can be transitioned to oral therapy to complete a 2-week duration. (46)

TOXIN-MEDIATED ILLNESS

Food Poisoning

S aureus food poisoning is due to the ingestion of preformed enterotoxins that are introduced into food by a person colonized or infected with *S aureus*. (1) There is rapid onset of illness—approximately 4 hours between ingestion and onset of symptoms. (1) Symptoms include nausea, vomiting, diarrhea, abdominal pain, and, in some patients, fever. (1)

Because this illness is due to ingestion of preformed toxin, antibiotics are unnecessary, and the patient needs supportive care only. (1)

Staphylococcal Scalded Skin Syndrome

Some strains of *S aureus* produce exfoliative toxins that are implicated in SSSS. (1) The toxins spread hematogenously and result in fever, erythema, and destruction of the proteins that are responsible for maintaining a crucial connection in the skin. (1) The toxin cleaves the desmoglein 1 glycoprotein in the stratum corneum, leading to bullae. These will rupture and result in denuded skin. Some of these patients have a positive Nikolsky sign. Staphylococcal scalded skin syndrome is a clinical diagnosis, but *S aureus* may be cultured from an affected site. (1)

Viable *S aureus* can continue to produce exfoliative toxins and propagate the disease. Antibiotics should be given for SSSS; this will not reverse the destruction of the skin but can prevent further damage. (1) The treatment of choice is an IV BLRBL or vancomycin if CA-MRSA prevalence is high. (2) (22) It may help to regard and manage patients with SSSS as if they possess severe partial-thickness burns, given possible high insensible losses due to capillary leak and damaged skin barrier.

Toxic Shock Syndrome

Toxic shock syndrome (TSS) is mediated by TSS toxin 1, or the combination of staphylococcal enterotoxin B and staphylococcal enterotoxin C toxins. The signs and symptoms include rapid onset of fever, a widespread rash resembling a sunburn (erythroderma), hypotension, and multisystem organ dysfunction. (1)(2) Risk factors for TSS include the presence of a strain able to produce the aforementioned toxin(s). The initial site of entry or infection may be unremarkable because TSS toxin 1 has the ability to dampen the local inflammatory response. (1) The mucous membranes (vagina, nasopharyngeal), wound (if present), and blood should be cultured as part of the diagnostic evaluation. (1) The main focus of treatment includes management of hypovolemic shock (given high insensible losses due to capillary leak), respiratory failure, and infection.

Intravenous antibiotics should be initiated empirically to treat *S aureus* and to inhibit protein synthesis to prevent further toxin from being produced. (1)(2) This antibiotic regimen includes an IV BLRBL and clindamycin (for disruption of protein synthesis, ie, toxin production), and often vancomycin given concern for MRSA. Once culture results are available, the antibiotics should be tailored to susceptibilities, and treatment duration is 10 to 14 days. (2) If there is a localized infection that is the inciting event, treatment should include adequate incision and drainage, and removal of a foreign body if present. (2)

ANTIMICROBIALS

The choice of antibiotic for infections suspected or confirmed to be secondary to *S aureus* depends on several factors. First is the severity of the presenting illness. Inadequate treatment may not be immediately detrimental for a patient presenting in the office with cellulitis but will have dire consequences in a patient with sepsis. Another factor is the rate of MRSA present in the community, which drives the use of vancomycin or other MRSA-active agents for empirical treatment. Bactericidal agents are always preferred over bacteriostatic antibiotics, although β-lactam allergies or the presence of MRSA may not always allow the use of bactericidal agents. Table 2 summarizes the following antibiotics.

For MSSA, nafcillin, oxacillin, and a first-generation cephalosporin (cefazolin) are first-line parenteral antibiotics. The mechanism of action of β-lactams (penicillins and cephalosporins) is inhibition of bacterial cell wall synthesis. β-Lactams bind to PBPs, which prevents a new disaccharide

TABLE 2. **Antibiotics Used for *Staphylococcus aureus* in the Pediatric Population**

ANTIBIOTIC	MECHANISM OF ACTION	ADMINISTRATION	DOSING	MAXIMUM
Nafcillin	Inhibition of bacterial cell wall synthesis by binding of PBPs	IV	200 mg/kg per day divided every 6 h	2 g/dose, 12 g/d
Oxacillin	Inhibition of bacterial cell wall synthesis by binding of PBPs	IV	200 mg/kg per day divided every 6 h	2 g/dose, 12 g/d
Cefazolin	Inhibition of bacterial cell wall synthesis by binding of PBPs	IV	75–150 mg/kg per day divided every 8 h	6 g/d
Cephalexin	Inhibition of bacterial cell wall synthesis by binding of PBPs	PO	50–100 mg/k per day divided every 6–8 h	4 g/d
Vancomycin	Inhibition of bacterial cell wall synthesis by binding of D-alanyl-D-alanine	IV	15–20 mg/kg per dose every 6 h[a]	2 g/d
Clindamycin	Inhibition of bacterial protein synthesis by binding 50S ribosome to inhibit transpeptidation	IV or PO	40 mg/kg per day divided every 6–8 h	IV: 4.8 g/d PO: 1.8 g/d
Linezolid	Inhibition of bacterial protein synthesis by binding 50S ribosome to inhibit the initiation process	IV or PO	Age <12 y: 10 mg/kg per dose every 8 h Age ≥ 12 y: 600 mg every 12 h	600 mg/dose
Doxycycline	Inhibit bacterial protein synthesis by binding 30S ribosomal subunit preventing tRNA from binding	IV or PO	2.2 mg/kg per day divided every 12 h	200 mg/d
TMP-SMX	Inhibition of bacterial DNA synthesis by blockage of metabolic pathways	IV or PO	6–12 mg TMP/kg per day divided every 12 h	160 mg TMP/dose

IV=intravenous, PBP=penicillin-binding protein, PO=oral, TMP-SMX=trimethoprim-sulfamethoxazole.
[a]*Vancomycin dosing and goal trough level depend on the age of the patient, severity of infection, and renal insufficiency.*

from joining the peptidoglycan polymer, therefore blocking the formation of the peptidoglycan layer that surrounds the bacterium. The BLRBLs are bactericidal against *S aureus* and are superior to vancomycin, which has a slow kill time against *S aureus*, making it, in effect, bacteriostatic. (21) Adverse effects of BLRBLs include bone marrow suppression and interstitial nephritis. Overall, a BLRBL should be used for MSSA infections. Oral conversion to cephalexin is possible when using these empirical agents.

For MRSA, vancomycin is usually the first consideration in patients with serious infections, including bacteremia and endovascular infections. Vancomycin is a glycopeptide that inhibits the synthesis of the bacterial cell wall. Vancomycin binds to a subunit of the peptide side chain (D-alanyl-D-alanine). Owing to its large molecular size, vancomycin occupies a sizable area and, thus, prevents further synthesis of the peptidoglycan polymer around the bacterium. For clinical use, vancomycin is often considered bacteriostatic. Although the minimum bactericidal concentration is similar to the MIC of vancomycin against *S aureus*, the rate of *S aureus* killing is slower for vancomycin compared with other antistaphylococcal antibiotics. (49) Dosing of vancomycin is based on the age of the patient, severity of infection, and known or developing renal insufficiency. Therapeutic drug monitoring is usually conducted with serum trough levels (obtained by venipuncture 1 hour before dose). For invasive and severe infections, the goal trough level for vancomycin is 15 to 20 μg/mL. (21) When the practitioner is empirically using vancomycin, de-escalation to an oral agent may be difficult if bacterial cultures were not obtained before initiation of therapy or remain sterile.

Other antibiotics used for MRSA as well as MSSA infections (usually with less severe clinical presentations) include clindamycin, linezolid, doxycycline, and TMP-SMX.

Clindamycin is an attractive option for practitioners who want to use an agent with generally effective treatment of MSSA and MRSA. The mechanism of action of clindamycin is inhibition of protein synthesis by binding the 50S ribosomal subunit preventing transpeptidation. Advantages of clindamycin include excellent tissue penetration (bone, abscess) and the high bioavailability of the oral drug. However, clindamycin is a bacteriostatic drug against *S aureus* and may not have activity against all isolates of MSSA or MRSA. These 2 reasons should be recalled if the

provider is facing a patient with poor clinical response while taking empirical clindamycin. Furthermore, clindamycin has poor penetration into cerebrospinal fluid and should not be used in primary bacteremia because it does not have this Food and Drug Administration (FDA) indication. (21) The most common adverse effect of clindamycin is diarrhea. (21)(50) The practitioner should balance the benefits and risks of using clindamycin when confronted with a suspected *S aureus* infection.

Linezolid is often used in the ambulatory setting as an oral alternative to IV vancomycin, particularly for SSSI and pneumonia. (21) The mechanism of action is inhibition of protein synthesis by binding the bacterial 50S ribosomal subunit, which prevents the assembly of the entire initiation complex. Linezolid is bacteriostatic against *S aureus*. (50) Bioavailability is almost 100%. (50) Adverse effects include reversible bone marrow suppression (thrombocytopenia, neutropenia, and/or anemia), irreversible neuropathy, gastrointestinal upset, lactic acidosis, and hyperglycemia. (21)(50) The benefit of linezolid is ease of transition between parenteral to oral administration and its effectiveness against MRSA.

Doxycycline is an excellent choice for outpatient treatment for SSSI and is active against MRSA. Doxycycline is a tetracycline that is bacteriostatic at lower concentrations and bactericidal at higher concentrations. (21)(50) The mechanism of action is inhibiting protein synthesis by binding the 30S ribosomal subunit preventing transfer RNA from binding. Adverse effects include gastrointestinal upset (nausea and vomiting) and phototoxicity. (50) It is prudent to avoid prolonged courses (>21 days) in young children given concern for discoloration of developing tooth enamel.

Outpatient treatment with TMP-SMX is an attractive option for MRSA. (21) It is bacteriostatic. The mechanism of action is a blockage of metabolic pathways that are essential for bacterial DNA synthesis and, therefore, growth. The sulfonamide component can displace bilirubin from albumin. This displacement increases the serum level of unconjugated bilirubin and elevates the risk of bilirubin-induced neurologic dysfunction. (21) Although FDA labeling cautions against use in infants younger than 2 months, it may be used safely in full-term infants as early as 2 weeks after birth as physiologic jaundice is resolving. (1) For those with renal disease there is an increased risk of hyperkalemia from use of this medication. (21) Often, TMP-SMX is used in the outpatient setting, but the practitioner should bear in mind that it has poor activity against *S pyogenes*, often in the differential diagnosis for SSSIs.

DECOLONIZATION

The goal of decolonization is the reduction of the infectious burden of a particular organism from a specific body site. In the general population, 20% have persistent colonization with *S aureus*, 60% are intermittently colonized, and 20% are never colonized. (1) Decolonization of patients with persistent or intermittent colonization may be desirable in situations involving recurrent SSSIs, atopic dermatitis, or those anticipating surgeries with implantable or prosthetic materials (such as prosthetic joints).

A decolonization program should include considering the body area of interest, the medication, the duration of the program, and the number of household members needed to treat to reduce transmission. The most common area of *S aureus* colonization is the anterior nares. (1) Many decolonization regimens use mupirocin and anerdian in the anterior nares. (51) Mupirocin is prepared as a 2% antibiotic ointment with activity against several gram-positive and gram-negative organisms. (51) Anerdian is a compound containing ethanol, iodine, and chlorhexidine. (51) Targeting the entire body surface area with washes such as chlorhexidine for a duration of 5 days, or bleach baths (ratio is one-quarter to one-half cup of bleach in a full bath) administered 2 to 3 times a week, have been used with varying effects on colonization. (2) The most effective regimen (body area, medication, duration) has not been found.

There is no evidence that decolonization has sustained effects. (51) A Cochrane review regarding decolonization found 188 articles regarding effectiveness of *S aureus* decolonization. Only 2 studies were deemed eligible for analysis, and both were inconclusive: 1) mupirocin versus placebo and 2) anerdian versus no treatment. (51)(52)(53) Another publication that reviewed 19 articles suggested a reduction in surgical site infections after decolonization. (9) These decolonization regimens varied and included mupirocin alone, or mupirocin with either chlorhexidine or triclosan. (9) Not all the studies had statistically significant reductions in surgical site infections. (9)

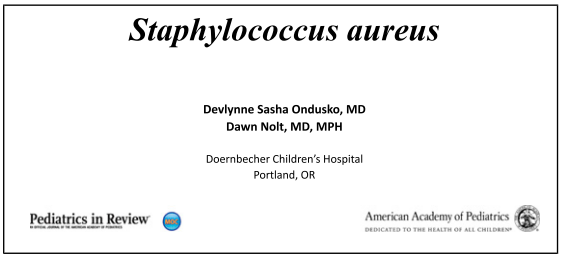
Despite the lack of evidential support, decolonization can be considered in certain circumstances, as described previously herein. For patients with atopic dermatitis or recurrent SSSI, decolonization can be considered if recurrence persists despite excellent hand hygiene and wound care. (11) Decolonization may not work, as evidenced by 1 study showing that 20% of patients displayed persistent colonization. (54) If decolonization is successful, risk of recurrence is high: up to 70% of decolonized patients experience recurrence of SSSI within 1 year. (11)

Outside of surgical site infection prevention, most decolonization regimens include household members. As noted previously, household exposures (ie, close contacts) may play a role in colonization. (54) Therefore, decolonization of household contacts may alter the colonization pattern in the index case, which could result in a successful and sustained reduction of SSSIs. (54)

Summary

- Based on observational and epidemiologic studies, approximately one-third of the population is colonized with *Staphylococcus aureus,* and colonization of the individual and/or household members is a risk factor for *S aureus* infection.
- From evidence-based guidelines, empirical treatment for non–life-threatening infections suspected to be from *S aureus* should include methicillin-sensitive *S aureus* (MSSA) treatment, ideally a β-lactamase–resistant β-lactam (BLRBL). Methicillin-resistant *S aureus* (MRSA) treatment may be included (either with a second drug or more often as clindamycin monotherapy) in geographic areas with high rates of community-acquired MRSA.
- From published clinical guidelines and expert opinion, empirical treatment for life-threatening and invasive *S aureus* infections should cover both MSSA and MRSA. This includes a parenteral BLRBL (for MSSA) and vancomycin (for MRSA) while awaiting culture results and susceptibilities.
- From evidence-based guidelines, the treatment of staphylococcal scalded skin syndrome includes parenteral antibiotics and fluid and electrolyte management.
- Evidence-based guidelines recommend that the treatment of toxic shock syndrome due to *S aureus* includes drainage of the nidus of infection, antibiotics targeted to inhibiting bacterial cell wall synthesis (such as nafcillin/oxacillin or vancomycin), and inhibiting protein synthesis (such as clindamycin).
- On the basis of Cochrane review and expert opinion, decolonization practices have little evidential support. These practices may be used if the patient experiences recurrent skin and skin structure infections despite optimization of hand hygiene and wound care. If decolonization is recommended, all members in the household should also undergo this process.

***To view teaching slides that accompany this article, visit* http://pedsinreview.aappublications.org/content/39/6/287.supplemental.**



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1. A previously healthy 3-year-old boy is brought to the office due to a painful lesion on his right thigh. He has not had fever and is eating well. Mom states that the area started to have whitish drainage this morning. His father has a history of recurrent methicillin-resistant *Staphylococcus aureus* (MRSA) skin infections. There is a 3-cm erythematous area of his right thigh that has purulent drainage. A culture is obtained that grows MRSA. Which of the following is the mechanism of resistance to methicillin and other β-lactam antibiotics?
   A. Alteration of penicillin-binding protein.
   B. β-Lactamase production.
   C. Decreased antibiotic membrane permeability.
   D. Efflux mechanism.
   E. Modification of the ribosomal antibiotic target.
2. A previously healthy 9-month-old girl is admitted to the hospital due to cellulitis of her left buttock that is not improved after 2 days of treatment with cephalexin. She is fussy but consolable. Her temperature is 102.4°F (39.1°C). There is a 12×15-cm tender area of erythema and induration of her right buttock with central fluctuance. Incision and drainage is performed and sent for culture. The hospital antibiogram notes that 36% of *S aureus* isolates were resistant to clindamycin. Which of the following is the most appropriate initial antibiotic treatment regimen?
   A. Ampicillin-sulbactam.
   B. Ceftriaxone.
   C. Nafcillin.
   D. Trimethoprim-sulfamethoxazole (TMP-SMX).
   E. Vancomycin.
3. A 20-month-old boy is admitted to the hospital due to a 3-day history of fever. He started limping 4 days ago and now will not bear weight on his left leg. He has also developed swelling around his left knee. A magnetic resonance image of the left leg bone shows marrow edema of the left distal femur and a subperiosteal fluid collection. The latest antibiogram released by the hospital lists a 26% incidence of MRSA isolated from the community. A blood culture is obtained, and he is started on intravenous (IV) vancomycin and ceftriaxone. He is taken to the operating room for incision and drainage. The blood culture and subperiosteal abscess culture grow *S aureus* susceptible to oxacillin (methicillin susceptible), vancomycin, linezolid, tetracycline, and TMP-SMX. He has no known drug allergies. Transition to which of the following IV antibiotics is most appropriate?
   A. Ampicillin.
   B. Doxycyline.
   C. Linezolid.
   D. Nafcillin.
   E. TMP-SMX.
4. By day 7 of hospitalization the same 20-month-old boy as in question 3 is significantly improved. He has been afebrile for 48 hours and is starting to bear weight on his left leg. A repeated blood culture has no growth after 72 hours. He is discharged on oral cephalexin.

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Which is the most appropriate total duration of antimicrobial therapy if he continues to clinically improve with normalization of his ESR?

A. Fourteen days.
B. Six weeks.
C. Ten days.
D. Twelve weeks.
E. Twenty-one days.

5. A 14-year-old girl with a history of recurrent acute sinusitis is admitted to the PICU after presenting to the emergency department with a 2-day history of fever and diffuse myalgia. Her most recent menstrual period ended 6 days ago. Over the past day she has had 2 episodes of vomiting and 5 watery stools. She has also developed a rash. In the emergency department her temperature was 102.2°F (39°C), heart rate was 112 beats/min, respiratory rate was 28 breaths/min, blood pressure was 96/60 mm Hg, and oxygen saturation was 97%. She was given 2 boluses of IV normal saline and is currently receiving a third bolus. She also received IV vancomycin and IV ceftriaxone. Her blood pressure, after 2 fluid boluses, currently is 111/70 mm Hg, and her heart rate is 84 beats/min. She is tired appearing but can answer questions appropriately. She has conjunctival injection and a diffuse macular erythroderma. Her capillary refill time is 2 seconds. The remainder of her examination findings are normal. Laboratory tests show a white blood cell count of 15,200/μL (15.2×10^9/L), hemoglobin level of 12.4 g/dL (124 g/L), platelet count of $85 \times 10^3/\mu$L (85×10^9/L), aspartate aminotransferase level of 106 U/L (1.8 μkat/L), creatine phosphokinase level of 232 U/L (3.9 μkat/L), blood urea nitrogen level of 15 mg/dL (5.4 mmol/L), and creatinine level of 0.8 mg/dL (70.7 μmol/L). Blood culture is pending. Which of the following is the most appropriate next step in management?

A. Computed tomographic scan of the abdomen and pelvis.
B. Fresh frozen plasma transfusion.
C. IV clindamycin.
D. IV doxycycline.
E. IV phenylephrine.