

Staphylococcal Infections

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Author Disclosure
Dr Todd did not disclose any financial relationships relevant to this article.

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

1. Describe the major clinical syndromes of *Staphylococcus aureus* infection.
2. Know the key laboratory tests for *S aureus*.
3. Discuss the treatment of *S aureus* infection.
4. Recognize the key components of therapy for toxic shock syndrome.

Definitions

Staphylococci are hardy aerobic bacteria that are present in the environment and as normal flora of humans and animals. They are resistant to heat and drying and may be recovered from the environment months after contamination. These organisms are gram-positive cocci that grow in characteristic grapelike clusters. Staphylococci are distinguished from streptococci by a positive catalase (H_2O_2) test. Species are classified as *Staphylococcus aureus* if they are coagulase-positive or as one of many species of coagulase-negative staphylococci (eg, *S epidermidis*, *S saprophyticus*). *S aureus* is the most common cause of pyogenic infection of the skin; it also may cause osteomyelitis, septic arthritis, wound infection, abscess, pneumonia, empyema, endocarditis, pericarditis, meningitis, and toxin-mediated diseases, including food poisoning, staphylococcal scarlet fever, scalded skin syndrome, and toxic shock syndrome (TSS). Coagulase-negative staphylococci tend to be less pathogenic unless a foreign body (eg, intravascular catheter) is present.

Epidemiology

Many neonates are colonized with *S aureus* within the first postnatal week. Thereafter, up to 50% of healthy individuals carry at least one strain of *S aureus* in the anterior nares at any given time. The organisms may be transmitted from the nose to the skin, where colonization seems to be more transient. Persistent umbilical perianal and vaginal carriage has been described. *S aureus* generally is transmitted by direct contact, primarily on the hands. Autoinfection is common. Handwashing by caretakers between contacts with patients decreases the spread of staphylococci from patient to patient. Many different strains of *S aureus* are capable of causing a wide variety of diseases (Fig. 1); these strains, and the diseases they commonly cause, may change in a community over time.

Pathogenesis

Strains of *S aureus* are identified best by the virulence factors they produce (Fig. 1). These factors have four different roles: protecting the organism from host defenses, localizing infection, causing local tissue damage, and acting as toxins affecting noninfected tissue sites.

Many staphylococci produce a loose polysaccharide capsule, or slime layer, that may interfere with phagocytosis. Coagulase causes plasma to clot by interacting with fibrinogen, which may play an important role in localization of infection (ie, abscess formation) – a hallmark of *S aureus* infection. Clumping factor interacts with fibrinogen to cause the formation of large clumps of organism that interfere with effective phagocytosis. Production of coagulase and clumping factor differentiates *S aureus* from *S epidermidis* and other coagulase-negative staphylococci. Another important enzyme elaborated by staphylococci is penicillinase (or beta-lactamase), which inactivates penicillin.

Many strains of *S aureus* produce substances that destroy local tissue. A number of

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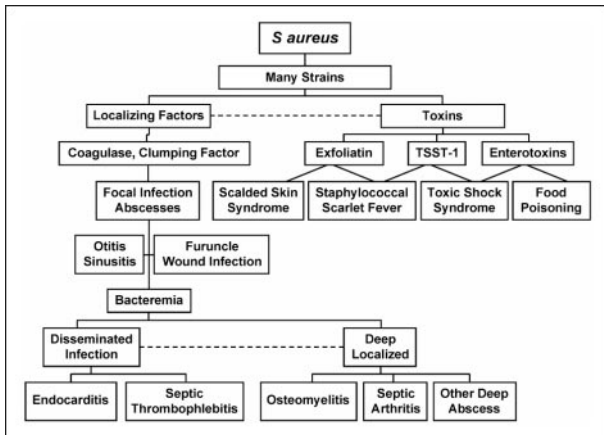


Figure 1. Correlation of staphylococcal virulence factors with disease. Strains may have differing virulence factors that predispose to localized or toxigenic disease and sometimes both.

immunologically distinct hemolysins have been identified. Alpha-toxin acts on cell membranes and causes tissue necrosis. Panton-Valentine leukocidin, which is produced by some virulent strains of *S aureus*, combines with the phospholipid of the phagocytic cell membrane, producing increased permeability, leakage of protein, and eventual death of the neutrophil and macrophage.

Many strains of *S aureus* release exotoxins. Exfoliatin A and B are two serologically distinct proteins that produce skin separation by splitting the desmosome and altering the intracellular matrix in the stratum granulosum, resulting in localized (eg, bullous impetigo) or generalized (eg, scalded skin syndrome, staphylococcal scarlet fever) rashes (Fig. 2). One or more staphylococcal enterotoxins (types A, B, C₁, C₂, D, E) are elaborated by most strains of *S aureus*. Ingestion of preformed enterotoxin is associated with vomiting and diarrhea and is a principal cause of food poisoning. Toxic shock syndrome toxin-1 (TSST-1) is associated with TSS related to menstruation and focal staphylococcal infection. TSST-1 induces production of interleukin-1 and tumor necrosis factor, resulting in hypotension, fever, and multisystem involvement. Enterotoxin A and enterotoxin B also may be associated with nonmenstrual TSS. Epidemiologic and in vitro studies suggest that these toxins are produced selectively in the clinical environment commonly found in abscesses and in the vagina with tampon use during menstruation. The risk factors for symptomatic disease require a nonimmune host colonized with a toxin-producing organism that is exposed to focal growth conditions (eg, menstruation plus tampon use or abscess), which induce toxin production.

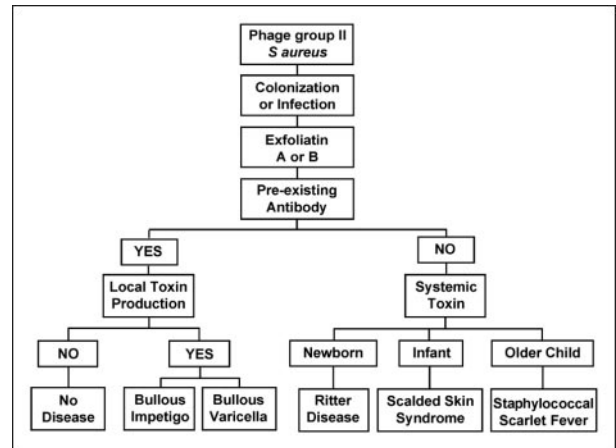


Figure 2. Pathogenesis of staphylococcal scalded skin syndrome.

The development of staphylococcal disease is related to resistance of the host to infection and to the virulence of the organism. The intact skin and mucous membranes serve as barriers to invasion by staphylococci. Defects in the mucocutaneous barriers produced by trauma, surgery, foreign surfaces (eg, sutures, shunts, intravascular catheters), and burns increase the risk of infection.

Infants may acquire type-specific humoral immunity to staphylococci transplacentally. Antibody to the various *S aureus* toxins appears to protect against those specific toxin-mediated diseases but not necessarily focal or disseminated *S aureus* infection with the same organisms.

Individuals who have congenital defects in chemotaxis (Job, Chédiak-Higashi, and Wiskott-Aldrich syndromes), defective phagocytosis, and defective humoral immunity (antibodies required for opsonization) are at increased risk of infection with staphylococci. Patients who have chronic granulomatous disease, in which phagocytosis proceeds normally but killing of ingested catalase-positive bacteria is severely impaired, are particularly susceptible to staphylococcal disease. Local host defense compromise (eg, surgical wound, cystic fibrosis) often is complicated by *S aureus* infection.

S aureus is identified by its growth on blood agar and a positive catalase and coagulase test. Antibiotic susceptibility testing has become increasingly important. In the past, most strains were resistant to penicillin but susceptible to methicillin and the cephalosporins and termed methicillin-susceptible *S aureus* (MSSA). An increasing number have acquired the *mecA* gene that alters beta-lactam antibiotic binding to the staphylococcal cell wall, causing them to become methicillin

(and cephalosporin)-resistant *S aureus* (MRSA). For many years, MRSA strains were seen primarily in hospitals and often were resistant to other antibiotics. Rare resistance to vancomycin also has been reported. In the past few years, community-associated methicillin-resistant *S aureus* (CA-MRSA) strains have become

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more common. In some locales, these strains remained susceptible to clindamycin and trimethoprim-sulfamethoxazole, but erythromycin-induced clindamycin resistance has become increasingly common. Most strains continue to be susceptible to trimethoprim-sulfamethoxazole.

Direct Infection

The signs and symptoms of *S aureus* infection vary with the specific strain and the location of the infection, which although located most commonly on the skin, may involve any tissue (Fig. 1). The classic manifestation of staphylococcal infection is a localized abscess. Disease states of various degrees of severity generally result from local tissue injury, systemic dissemination with metastatic infection, or systemic effects of toxin production. Although the nasopharynx may be colonized with *S aureus*, disease due to this organism is relatively uncommon. Lesions, especially those of the skin, are considerably more prevalent among persons living in low socioeconomic circumstances and particularly among those in tropical climates.

Skin

Pyogenic skin infections may be primary or due to wound infection with *S aureus*. *S aureus* infection is the most common cause of both crusted impetigo and bullous impetigo. *S aureus*, group A streptococci, or both may cause crusted impetigo. Bullous impetigo commonly occurs in the diaper area and is due to exfoliatin-producing *S aureus* strains that cause bullae in locally infected lesions (see scalded skin syndrome). Folliculitis, hydradenitis, furuncles (boils), carbuncles, and wound infections are all different manifestations of localized

infections caused by *S aureus*. Recently, necrotizing fasciitis has been described associated with CA-MRSA.

Respiratory Tract

Infections of the upper respiratory tract due to *S aureus* are uncommon, considering the frequency with which this area is colonized. Otitis media and sinusitis due to *S aureus* occasionally may occur. Staphylococcal tonsillopharyngitis is rare in otherwise healthy children. Unilateral cervical lymphadenitis is caused commonly by *S aureus*, especially in young children. A membranous tracheitis that complicates viral croup may be infected with *S aureus* but also by other organisms. Treatment requires antibiotics and careful airway management.

Staphylococci may cause a necrotizing pneumonitis with empyema. Pneumatocoles, pyopneumothorax, and bronchopleural fistulas develop frequently. Hematogenous pneumonia may be due to septic emboli, right-sided endocarditis, or the presence of infected intravascular devices.

Muscle

A localized staphylococcal abscess in muscle associated with elevation of muscle enzyme concentrations but without septicemia has been called tropical pyomyositis. Although this disorder has been reported most frequently from tropical areas, it also has occurred in the United States in otherwise healthy children. Multiple abscesses occur in 30% to 40% of cases. Surgical drainage and appropriate antibiotic therapy are essential.

Central Nervous System

Meningitis due to *S aureus* is not common; it is associated with cranial trauma and neurosurgical procedures (eg, craniotomy, cerebrospinal fluid shunt placement) and, less frequently, with endocarditis, parameningeal foci (eg, epidural or brain abscess), diabetes mellitus, or malignancy. Coagulase-negative *Staphylococcus* (CONS) is not ordinarily as virulent as *S aureus*, but it has a high affinity for attaching to foreign materials and is the most common cause of shunt-related infections.

Heart

Acute bacterial endocarditis may follow staphylococcal bacteremia. *S aureus* is a common cause of acute endocarditis on native valves. Perforation of heart valves,

Table. Definition of Toxic Shock Syndrome

Major Criteria (all required)	plus	Minor Criteria (any three)
Acute fever Hypotension (orthostatic or shock) Rash (late desquamation)		Mucous membrane inflammation Liver abnormalities Renal abnormalities Muscle abnormalities Central nervous system abnormalities Low platelets
Exclusionary Criteria		
Absence of other explanation Negative blood cultures (except for <i>S aureus</i>)		

myocardial abscesses, heart failure, conduction disturbances, acute hemopericardium, purulent pericarditis, and sudden death may ensue. CONS is a frequent cause of endocarditis affecting prosthetic heart valves.

Kidney

S aureus is a common cause of renal and perinephric abscess, usually of hematogenous origin. Urinary tract infection due to *S aureus* is unusual but more commonly may be caused in males by *S saprophyticus*.

Sepsis

Staphylococcal bacteremia may be associated with any localized infection (Fig. 1). The onset may be acute and marked by nausea, vomiting, myalgia, fever, and chills. Organisms may localize subsequently at any site but are found especially in the lungs, heart, joints, bones, kidneys, and brain. *S aureus* is the most common cause of osteomyelitis and suppurative arthritis in children.

In some instances, especially in young adolescent males, disseminated staphylococcal disease occurs, characterized by fever, persistent bacteremia despite antibiotics, and focal involvement of two or more separate tissue sites (eg, skin, bone, joint, kidney, lung, liver, heart). Endocarditis and septic thrombophlebitis must be ruled out.

Toxin-mediated Infection

Toxic Shock Syndrome

TSS is an acute multisystem disease characterized by high fever, hypotension, vomiting, diarrhea, myalgias, nonfocal neurologic abnormalities, conjunctival hyperemia, strawberry tongue, and an erythematous rash with subsequent desquamation on the hands and feet (Table). Many cases occur in menstruating women 15 to 25 years

of age who use tampons or other vaginal devices (eg, diaphragm, contraceptive sponge) in the presence of vaginal colonization or infection with TSST-1-producing strains of *S aureus*. TSS, however, also occurs in children, nonmenstruating women, and men. Nonmenstrual TSS has been associated with wound infection, nasal packing, sinusitis, tracheitis, pneumonia, empyema, abscesses, burns, osteomyelitis, and primary bacteremia.

Complications include acute respiratory distress syndrome, myocardial failure, and renal failure and are commensurate with the degree of shock. Recovery occurs within 7 to 10 days and is associated with desquamation, particularly of palms and soles. Hair and nail loss also have been observed after 1 to 2 months. Many cases of apparent scarlet fever without shock may be caused by TSST-1-producing *S aureus* strains.

Group A *Streptococcus* can cause a similar TSS-like illness, termed streptococcal TSS, which often is associated with streptococcal bacteremia or a focal streptococcal infection such as necrotizing fasciitis or pneumonia.

Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome represents a spectrum of clinical entities mediated by exfoliatin-producing *S aureus* strains (Fig. 2). Patients who do not have antibody to the toxin develop generalized disease due to hematogenous dissemination of the toxin. The rash is characterized by a painful erythroderma with a positive Nikolsky sign, but signs are more severe in newborns (Ritter disease) and milder in older children (staphylococcal scarlet fever).

Food Poisoning

Food poisoning may be caused by ingestion of enterotoxins that are preformed by staphylococci contaminating foods. Sudden, severe vomiting begins approximately 2 to 7 hours after ingestion of the toxin. Watery diarrhea may develop, but fever is absent or low. Symptoms rarely persist longer than 12 to 24 hours. Rarely, shock and death may occur.

Diagnosis

The diagnosis of staphylococcal infection depends on isolation of the organisms from normally noncolonized

sites, such as skin lesions, abscess cavities, blood, or other sites of infection. Isolation from the nose or skin does not necessarily imply causation because these are normally colonized sites. The organisms can be grown readily on solid media. After isolation, identification is made on the basis of Gram stain and catalase, coagulase, or clumping factor reactivity. Patterns of susceptibility to antibiotics should be assessed in serious cases because resistance to penicillin is common and resistance to the penicillinase-resistant beta-lactam antibiotics is increasing (MRSA).

Management

The increasing resistance of *S aureus* to multiple antimicrobials both in the hospital and the community and another common cause of soft-tissue or toxin-mediated infection (group A *Streptococcus*) being resistant to

decisions. Antibiotic therapy alone rarely is effective for individuals who have undrained abscesses or infected foreign bodies. Loculated collections of purulent material should be drained. Foreign bodies should be removed, if possible.

Therapy for serious infection determined to be caused by MSSA usually is successful with a penicillinase-resistant antibiotic (eg, nafcillin, oxacillin, or a first- or second-generation cephalosporin).

Intravenous treatment is recommended for most patients who have serious staphylococcal infection until the patient has been afebrile for 72 hours and other signs of infection have disappeared. Oral treatment may be provided in milder infections or to complete the course of treatment when parenteral therapy has been discontinued. Dicloxacillin is penicillinase-resistant, absorbed well orally, and clinically effective, although many children do not like its taste. The first-generation cephalosporins, amoxicillin combined with the beta-lactamase inhibitor clavulanic acid, clindamycin, or trimethoprim-sulfamethoxazole administered orally may be effective, depending on antimicrobial susceptibilities. Skin and soft-tissue

infections and minor upper respiratory tract infections often may be managed by oral therapy alone, but in areas that have an increasing incidence of CA-MRSA, culture and susceptibility are necessary to optimize antimicrobial selection.

For TSS, initial parenteral administration of a beta-lactamase-resistant antistaphylococcal antibiotic (eg, nafcillin or a first-generation cephalosporin) or vancomycin in locales where MRSA is increasingly prevalent is recommended after appropriate cultures have been obtained. The addition of clindamycin in severe or unresponsive cases may terminate toxin production. Drainage of the vagina, by removal of any retained tampons in menstrual TSS, and of focally infected sites in nonmenstrual TSS is important for successful treatment. Fluid replacement should be aggressive to prevent or treat hypotension, renal failure, and cardiovascular collapse. Inotropic agents may be needed to treat shock; corticosteroids and intravenous immune globulin may be helpful for severe cases.

trimethoprim-sulfamethoxazole make it imperative to initiate antimicrobial therapy likely to be effective for both organisms in serious infections (eg, sepsis, endocarditis, TSS, necrotizing fasciitis). The combination of vancomycin with the addition of clindamycin for toxin-mediated disease is a reasonable choice for such infections because clindamycin has been shown to reduce TSST-1 production by 90% in culture. Rare vancomycin-resistant strains of both *S aureus* and enterococci have been reported mostly in patients being treated with vancomycin. Vancomycin should be continued only in children who have proven MRSA infections. Linezolid and quinupristin-dalfopristin may be useful for serious *S aureus* infections highly resistant to other antibiotics. The combination of nafcillin (or vancomycin), gentamicin, and rifampin has been recommended for the initial treatment of *S aureus* endocarditis.

The antibiotic used, as well as the dose, route, and duration of treatment, depend on the site of infection, the response of the patient to treatment, and the susceptibility of the organisms recovered from blood or local sites of infection. Appropriate cultures always should be obtained so the causative organism can be identified and susceptibility testing performed to optimize therapeutic

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Prognosis

Untreated staphylococcal septicemia is associated with a high fatality rate. Fatality rates have been reduced dra-

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matically by appropriate antibiotic treatment. Prognosis also may be influenced by numerous host factors, including nutrition, immunologic competence, and the presence or absence of other debilitating diseases. In most cases of abscess formation, surgical drainage is required.

Prevention

Staphylococcal infection is transmitted primarily by direct contact. Strict attention to handwashing techniques is the most effective measure for preventing the spread of staphylococci from one individual to another. Use of a soap containing an iodophor, chlorhexidine, or hexachlorophene is recommended. In hospitals or other institutional settings, all persons who have acute staphylococcal infections should be isolated until they have been treated adequately. Surveillance for nosocomial staphylococcal infections should be constant within hospitals. When MRSA is recovered, isolation of affected patients has been shown to be the most effective method for preventing nosocomial spread of infection. It also may be necessary to identify colonized hospital personnel and eradicate carriage in affected individuals. Strains of *S aureus* resistant to vancomycin that have limited treatment options have been reported, emphasizing the need for restricting the prescription of unnecessary antibiotics and the importance of isolating the causative organism and susceptibility testing in serious infections.

The low risk of acquiring TSS (1 to 2 cases per 100,000 menstruating women per year) may be reduced by not using tampons or by using them intermittently during each menstrual period. If a fever, rash, or dizzi-

ness develops during menstruation, any tampon should be removed immediately and medical attention sought.

Suggested Reading

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

5. You are teaching an infectious disease course to nursing students who soon will begin to care for pediatric patients. In your discussion, you stress the risks of the transmission of *Staphylococcus aureus* infections. You caution them that the *most* common route for *S aureus* to spread to their patients is:
 - A. Airborne.
 - B. Fecal–oral.
 - C. Fomites.
 - D. Hands.
 - E. Vomitus.
6. Pediatricians are seeing an increased incidence of children who have abscesses from *S aureus* in their outpatient practices. Many of these children require incision, drainage, multiple antibiotic treatment, and often inpatient treatment with intravenous antibiotics. *S aureus* organisms generate many factors that contribute to their ability to produce abscesses. The *S aureus*–produced factor *most* likely to facilitate abscess formation is:
 - A. Beta–lactamase.
 - B. Coagulase.
 - C. Enterotoxin A.
 - D. Exfoliatin A.
 - E. Slime layer.
7. An array of clinical illnesses are due to *S aureus* infections. In advising your new intern team, you tell them that the clinical condition *most* likely caused by *S aureus* is:
 - A. Bullous impetigo.
 - B. Laryngotracheal bronchitis.
 - C. Meningitis.
 - D. Otitis media.
 - E. Pharyngitis.
8. A 5–year–old girl presents to the emergency department with a history of 4 days of fever, anorexia, and multiple sores on her arms and legs. Physical examination reveals a temperature of 103°F (39.5°C), pulse of 140 beats/min, and blood pressure of 50/30 mm Hg. She is drowsy and unable to respond to your questions. She has multiple crusted sores on both her arms and legs and two large fluctuant red areas on her buttocks. You obtain specimens of blood and aspirate from one of the fluctuant areas, sending them to the laboratory for culture and sensitivity testing. In addition to establishing venous access and administering several boluses of intravenous fluids, your *best* choice for initial antibiotic treatment is:
 - A. Clindamycin and vancomycin.
 - B. Linezolid.
 - C. Methicillin and gentamicin.
 - D. Vancomycin.
 - E. Trimethoprim–sulfamethoxazole.
9. In the United States, the incidence of community acquired methicillin–resistant *S aureus* (CA–MSRA) infections has been rising. The clinical illnesses caused by CA–MRSAs have included all the typical sites commonly infected by *S aureus*. However, a major problem with CA–MSRA has been multiple skin abscesses (“boils”) in otherwise asymptomatic children. The *most* appropriate action for affected patients is:
 - A. Admission, cultures, and intravenous vancomycin.
 - B. Cephalosporin orally and monitoring of the clinical course.
 - C. Dicloxacillin orally and monitoring of the clinical course.
 - D. Drainage, culture, and choice of antibiotic based on sensitivities.
 - E. Trimethoprim–sulfamethoxazole orally.