

Staphylococcus aureus – antimicrobial resistance and the immunocompromised child

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Abstract: Children with immunocompromising conditions represent a unique group for the acquisition of antimicrobial resistant infections due to their frequent encounters with the health care system, need for empiric antimicrobials, and immune dysfunction. These infections are further complicated in that there is a relative paucity of literature on the clinical features and management of *Staphylococcus aureus* infections in immunocompromised children. The available literature on the clinical features, antimicrobial susceptibility, and management of *S. aureus* infections in immunocompromised children is reviewed. *S. aureus* infections in children with human immunodeficiency virus (HIV) are associated with higher HIV viral loads and a greater degree of CD4 T-cell suppression. In addition, staphylococcal infections in children with HIV often exhibit a multidrug resistant phenotype. Children with cancer have a high rate of *S. aureus* bacteremia and associated complications. Increased tolerance to antiseptics among staphylococcal isolates from pediatric oncology patients is an emerging area of research. The incidence of *S. aureus* infections among pediatric solid organ transplant recipients varies considerably by the organ transplanted; in general however, staphylococci figure prominently among infections in the early posttransplant period. Staphylococcal infections are also prominent pathogens among children with a number of immunodeficiencies, notably chronic granulomatous disease. Significant gaps in knowledge exist regarding the epidemiology and management of *S. aureus* infection in these vulnerable children.

Keywords: pediatric, HIV, cancer, transplant

Staphylococcus aureus – antimicrobial resistance and the immunocompromised child

Staphylococcus aureus is among the most common pathogens encountered in pediatric practice and is the most common cause of bacterial skin-and-soft tissue infection (SSTI).¹ While SSTIs are the most common manifestation, *S. aureus* also is responsible for a wide spectrum of invasive infections including musculoskeletal infections, complicated pneumonia, and endocarditis. The emergence of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) led to an evolution of the severity of disease with an increase in invasive infections in some series.^{2–5} Studies of adults have shown that immunosuppression is associated with increased risk of *S. aureus* colonization, putting these fragile patients at risk for infection and further morbidity.⁶

Children with immunocompromising conditions represent a unique group for the acquisition of antimicrobial resistant infections due to their frequent encounters with the health care system, need for empiric antimicrobials, and immune dysfunction. While most pediatricians are familiar with the treatment of staphylococcal infections,

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these vulnerable children pose clinical challenges as a result of poor immune function, frequent antibiotic resistance, and the presence of medical devices and catheters that circumvent normal anatomic barriers. These infections are further complicated in that there is a relative paucity of literature on the clinical features and management of *S. aureus* infections in immunocompromised children, and clinical decisions must be drawn from the very limited available pediatric data or extrapolated from studies of adults. This review seeks to provide an overview of the published literature on the epidemiology, clinical features, antimicrobial susceptibility, and treatment of *S. aureus* infections in immunocompromised children.

Overall epidemiology of pediatric *S. aureus* infections

The past two decades have seen an enormous increase in the incidence of CA-MRSA infections.⁷ Studies from the 1990s and early 2000s revealed that CA-MRSA infections differed from typical health care-associated MRSA (HA-MRSA) in that CA-MRSA infections more often occurred in otherwise healthy patients without typical risk factors for antibiotic resistant infections, including children.^{8,9} In addition, CA-MRSA was more often susceptible to non- β -lactam antimicrobials, carried genes for Panton–Valentine leukocidin (PVL), were staphylococcal chromosome cassette mec type IV, and associated with soft-tissue rather than invasive infections compared to HA-MRSA.⁸ In the 2000s, the USA300 pulsed field gel type emerged as the predominant genotype of CA-MRSA in North America, accounting for anywhere from 50%–97% of isolates.^{1,10–12} During this time, USA300 also emerged as an important cause of HA-MRSA in both children and adults in some centers,^{13–15} thus blurring the distinction between typical CA- and HA-MRSA. Furthermore, some centers have noted an increase in the proportion of methicillin-susceptible *S. aureus* (MSSA) isolates possessing the USA300 genetic background.¹⁶ This is of further import in that the increase in the USA300 clone has been temporally associated with an increase in invasive infections in children, including complicated pneumonia, osteoarticular infections, and pyomyositis.^{2–5}

S. aureus and immune evasion

S. aureus possesses a number of mechanisms to evade immune destruction in the healthy host (Figure 1). Among the most notable of these mechanisms include capsule, staphylococcal surface proteins and PVL. The majority of *S. aureus* possesses a carbohydrate capsule of one of eleven serotypes,

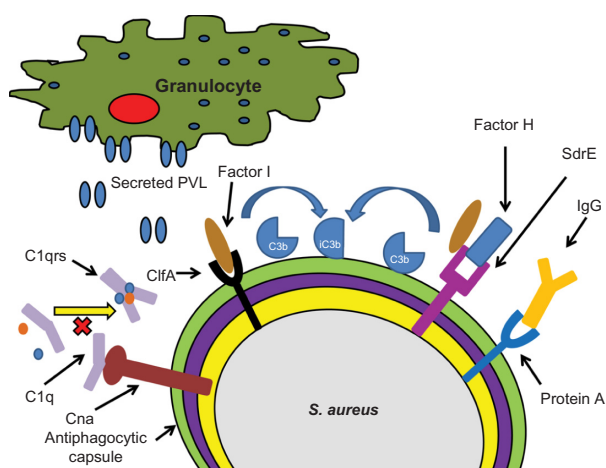


Figure 1 A schematic depiction of selected *Staphylococcus aureus* mechanisms for immune evasion.

Notes: Cna interacts with C1q preventing formation of the C1qrs complex. ClfA and SdrE each promote Factor I mediated conversion of C3b to iC3b. Protein A is depicted binding to the Fc region of IgG preventing immunoglobulin opsonization. **Abbreviations:** ClfA, staphylococcal clumping factor A; Cna, collagen adhesin; IgG, immunoglobulin G; PVL, Panton–Valentine leukocidin; SdrE, *S. aureus* surface protein.

the most common and best studied of which are capsular serotypes 5 and 8. Capsule plays a role in inhibiting phagocytosis by granulocytes as well as promoting adherence to surfaces.¹⁷ In large part because of the presence of capsule, opsonization is required for the enhanced phagocytosis of staphylococci; other means exist for *S. aureus* to avoid opsonization. Staphylococcal protein A, expressed on the cell surface, provides a defense mechanism to staphylococci through binding to the Fc region of immunoglobulin G. This results in an inappropriate orientation of the immunoglobulin for opsonophagocytosis and complement activation.¹⁸ Collagen adhesin (Cna) is a *S. aureus* protein involved in adhesion to extracellular collagen; however, it also has a role in immune evasion. Cna binds to C1q preventing the formation of the C1qrs complex and creating a blockade of the classical complement pathway.¹⁸ Staphylococcal clumping factor A (ClfA), in addition to binding fibrinogen, facilitates the destruction of the complement component C3b. ClfA interacts with complement regulatory factor I, promoting the conversion of C3 to the inactivated iC3b, thus decreasing complement-mediated phagocytosis.^{19,20} An additional *S. aureus* surface protein, SdrE, binds complement factor H and promotes factor I-mediated breakdown of C3b, resulting in less C3b deposition on the organism.²¹ This is particularly notable in that C3 is a common mediator of the classical, alternative, and lectin-mediated complement pathways.

While *S. aureus* elaborates a wide array of extracellular toxins, PVL is the only known toxin that specifically targets leukocytes.²² PVL is a bicomponent toxin encoded by the

genes *lukS-PV* and *lukF-PV* and produces pores in leukocytes, resulting in cell death.²³ There is a clinical association between infection with PVL-positive *S. aureus* and severity of disease;²⁴ however, the exact role that PVL plays in pathogenesis has been conflicting in animal models. Taken together, *S. aureus* exhibits a number of tools for evading the immune system, which can only be accentuated in the immunocompromised host.

Children with human immunodeficiency virus/acquired immunodeficiency syndrome

Research among adults with human immunodeficiency virus (HIV) has revealed higher rates of colonization with *S. aureus* than the general population, reaching as high as 81% during a 1-year study period.²⁵ In addition, HIV-positive adults are known to more often have invasive *S. aureus* infections, notably bacteremia, than HIV-negative controls.²⁶

Furthermore, HIV-positive adults and children often are infected with *S. aureus* isolates exhibiting a multidrug-resistant (MDR) phenotype.²⁷ The MDR-MRSA isolates often exhibit resistance to clindamycin, macrolides, ciprofloxacin, tetracyclines, and mupirocin. Two of the resistance genes in these MDR isolates, *ermC* and *mupA*, are carried on a large conjugative plasmid known as pUSA03.²⁸ *S. aureus* infections in HIV-positive children have high rates of antimicrobial resistance, with over 82% and 40% of isolates resistant to methicillin and clindamycin, respectively, in one small single center study of 28 cases.²⁹ Furthermore, the isolates were also resistant to ciprofloxacin in 47.6% of cases consistent with a MDR phenotype. Resistance to trimethoprim-sulfamethoxazole (TMP-SMX) in these staphylococcal isolates is rather uncommon in the United States (3%), even in the presence of chronic TMP-SMX prophylaxis. In a series from Houston, TX, 19 of 21 (90.5%) isolates available from children with HIV were of the USA300 pulsed field gel electrophoresis type, and 18 (85.7%) isolates possessed the genes for PVL.²⁹

A number of studies in adults have examined the risk factors within the HIV population for *S. aureus* infection. Within HIV-positive adults, described risk factors for *S. aureus* infection include elevated HIV viral load, antiretroviral medication noncompliance, high-risk behaviors, and injection drug use.³⁰ A single center study in children found that recent antibiotic exposure, a \log_{10} HIV viral load ≥ 3 , a CD4 T-cell count ≤ 350 cells/mm³, and a higher Centers for Disease Control and Prevention (CDC) category of disease were associated with *S. aureus* infections in univariate

analyses.²⁹ Another large multicenter study with over 1,800 subjects attempted to determine associations specifically with MRSA infection in pediatric HIV patients.³¹ This work found that a \log_{10} viral load ≥ 3 , African-American race, and residence in a high MRSA prevalence area were all independently associated with MRSA infection. Notably, behavioral acquisition of HIV (ie, high-risk sexual behavior or injection drug use) was not associated with MRSA infection in this population. Among HIV-positive children, SSTIs are the predominant manifestation of *S. aureus* disease (over 80%) although other invasive infections do occur.^{29,31}

Studies among African children with HIV have differed somewhat from those among HIV-positive children in the developed world. Up to 24% of 203 HIV-positive children in a study at Tygerberg Children's Hospital in Cape Town were colonized with *S. aureus*; more importantly, colonization was associated with a greater degree of immune suppression.³² Other work from Johannesburg has shown that the incidence of *S. aureus* bacteremia in South African children is higher than that described in the developed world and is particularly associated with HIV infection.³³ Furthermore, *S. aureus* was more commonly a cause of pneumonia in HIV-positive (15% of cases) compared to HIV-negative (3%) patients in a study of 150 South African children.³⁴ Over 90% of the *S. aureus* isolates in a Cape Town study were resistant to TMP-SMX, and approximately 80% were MRSA.³² In Gaborone, Botswana,³⁵ higher rates of antimicrobial resistance were seen in MRSA compared to MSSA to numerous antibiotics including erythromycin, chloramphenicol, tetracycline, and gentamicin, suggesting the existence of an MDR-MRSA phenotype in this population as well.

While there does appear to be a correlation between viral load, CD4 T-cell count, and *S. aureus* infection, the interaction of *S. aureus* and HIV is complex and incompletely understood. It is possible that depletion of CD4 T-cells during HIV infection affects granulocyte function and predisposes to *S. aureus* infection. Investigations into the pathogenesis of simian immunodeficiency virus in nonhuman primates has revealed that disease progression is associated with depletion of T helper 17 cells.³⁶ Studies in mice deficient in interleukin (IL)-17 producing T-cells have been shown to have impaired neutrophil recruitment and increased severity of cutaneous staphylococcal infections³⁷ as well as surgical site infections.³⁸ Mouse models have also shown *S. aureus* nasal colonization to be a T-cell dependent process,³⁹ suggesting that HIV-mediated T-cell suppression may predispose to *S. aureus* colonization and infection. Alternatively, one may hypothesize that at least some of the clinical findings of

CD4 suppression are the result of temporary fluctuations in control of HIV disease due to an intercurrent infection, as has been well described for other pathogens such as *Treponema pallidum*.⁴⁰

The management of bacterial infections in children with HIV should take into account both the type of infection and the degree of immune suppression. Published guidelines state that children without serious immune compromise (CDC category I) and who are not neutropenic should be treated similarly to HIV-uninfected children.⁴¹ In the Houston series, over 50% of patients were successfully managed as outpatients with incision and drainage and oral antimicrobials.²⁹ Most experts, however, recommend hospitalization and broad spectrum empiric antimicrobials, including the use of bactericidal agents, for those children who are neutropenic or severely immunocompromised.

Children with malignancy

Patients suffering from malignancy are at risk for invasive bacterial infection as a result of receipt of antineoplastic chemotherapy, the need for invasive procedures and central venous catheters, and the intrinsic immune dysfunction of their underlying disease (as is the case with hematologic malignancies). *S. aureus* accounts for 9%–10% of total cases of bacteremia in a series of adults with malignancy. The mortality rates reported in adults, however, range from 15% to as high as 24%;^{42,43} the mortality rate for *S. aureus* pneumonia in adult cancer patients is particularly high at 49.5%.⁴⁴ Furthermore, in a series of 52 nonneutropenic adults with malignancy and *S. aureus* bacteremia, 33% developed metastatic infectious complications.⁴³

As *S. aureus* colonization has previously been associated with an increased risk of staphylococcal infection,⁴⁵ much interest has developed in identifying colonized high-risk patients. The rates of MRSA colonization among adults with malignancy reported in the literature varies widely from 9%–60%.^{46,47} It is known, however, that MRSA colonization has increased overtime among pediatric cancer patients; in one center, MRSA colonization increased from <1% to 3.8% in a seven year period among 1,735 subjects studied.⁴⁸

Bloodstream infections are the most common health care-associated infections (HAI) in pediatric cancer patients with Gram-positive cocci, in particular *S. aureus*, being the most common agents.⁴⁹ In children with malignancy, *S. aureus* accounts for up to 9%–13% of neutropenic bloodstream infections and febrile neutropenia.^{50,51} Moreover, *S. aureus* has been the most commonly reported cause of infectious death in some studies of pediatric febrile neutropenia.⁵² In

contrast to healthy children and even HIV-positive children, the most common manifestation of *S. aureus* infection in children with malignancy is bacteremia with central line-associated bloodstream infection (CLA-BSI) accounting for 84.7% of cases in one study.⁵³ A study of 52 cases of *S. aureus* bacteremia at the St Jude's Children's Research Hospital noted that less than a third of patients with *S. aureus* bacteremia were in remission at the time of infection and that 81% of infections were a result of MSSA.⁵⁴ While the majority of bacteremic events were due to MSSA, MRSA infections were associated with a longer duration of bacteremia and a greater need for catheter removal.⁵⁴ This study also revealed that 46% of pediatric cancer patients with *S. aureus* bacteremia had an absolute neutrophil count less than 500 cells/mm³. Notably MRSA infections are associated with a larger relative proportion of SSTIs,^{53,55} likely a reflection of the dissemination of the USA300 clone of MRSA in the community, with its predilection for causing SSTI.⁵⁶ In Houston, TX, the USA300 clone accounted for a much lower percentage of *S. aureus* infections among pediatric cancer than HIV patients (63 of 171 [36.8%] isolates).^{29,53} Notably, non-USA300 pulsotypes were more often associated with bacteremia than SSTI. Similarly, Srinivasan et al reported that among 88 MRSA infections in pediatric cancer patients, PVL-positive isolates accounted for only 40% of all cases with the majority being USA300.⁵⁵

Complications of *S. aureus* infections have been described to occur in pediatric cancer patients in 10%–18% of all infections and up to 33% of cases of bacteremia.^{53–55} A study at Texas Children's Hospital (TCH) of 213 *S. aureus* infections in children with cancer has shown that complicated *S. aureus* bacteremia is associated with thrombocytopenia and an absolute monocyte count <100 cells/mm³.⁵³ There was additionally a tendency for complications to occur more frequently in hematopoietic stem cell transplant recipients. Described complications of *S. aureus* bacteremia in this population include pulmonary nodules, pneumonia, pleural effusion, lung abscess, thromboses, skin nodules, musculoskeletal infection, central nervous system abscess, and endocarditis.^{53,54} In the TCH series, six patients with pulmonary nodules underwent biopsy and 5 of 6 cultures revealed *S. aureus* alone; the sixth patient showed evidence of metastatic malignancy (Figure 2). The overall survival from *S. aureus* infection is much better among pediatric than adult oncology patients. Mortality from *S. aureus* in this population is described at 2.3% and is associated with a diagnosis of acute myelogenous leukemia and a platelet count <50,000/mm³ at the time of infection.⁵³

The need for alteration of antistaphylococcal therapy in the setting of malignancy is unclear. Some experts recommend a longer duration of therapy than in immunocompetent hosts and/or the use of a bactericidal agent. In the series of *S. aureus* bacteremia from St Jude's, patients were treated for a median of 10 days with either vancomycin or oxacillin; notably, no patient had a recurrence of bacteremia within a year of the treatment.⁵⁴ In the TCH series, 6.8% of neutropenic patients developed relapse of infection following discontinuation of therapy compared to 3.2% of nonneutropenic patients; however, this did not achieve statistical significance.⁵³ Regardless, many experts would recommend use of bactericidal agents and/or a prolonged duration of therapy for neutropenic hosts with a *S. aureus* infection. Furthermore, for patients who have severe or deep-seated infection, some would recommend continuing therapy beyond the usual duration until granulocyte counts have recovered. For CLA-BSI due to *S. aureus*, catheter removal is strongly recommended, particularly in this population.⁵⁷

One of the modalities that has been adopted to decrease the incidence of invasive infections in hospitalized patients, in particular those with hematologic malignancies, is the use of antiseptics such as chlorhexidine gluconate. The use of these agents for decolonization, central line care, and oral rinses has been shown to decrease the incidence of HAIs in adult populations.^{58–64} While there is the potential for tremendous benefit, there are a number of genes in *S. aureus*, notably *qacA/B*, *smr*, and *norA*, which confer higher minimum inhibitory concentration/minimum bactericidal concentration to these agents.^{65–67} These plasmid-borne genes encode efflux pumps which not only confer tolerance to antiseptics but

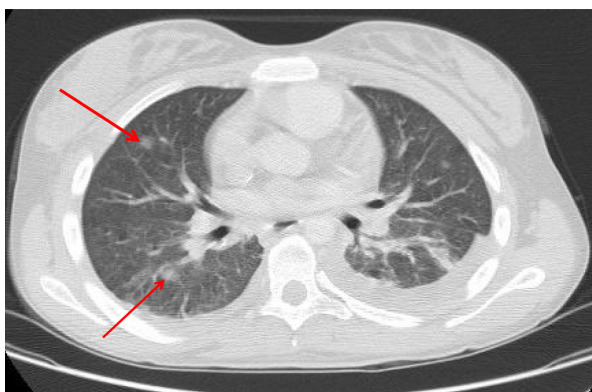


Figure 2 Computed tomography chest image with contrast of a 19-year-old female with relapsed neuroblastoma, *Staphylococcus aureus* bacteremia, and pulmonary nodules (arrows) that were initially concerning for invasive fungal disease.

Notes: The patient was initially started on amphotericin and then underwent biopsy of the lesions. Both culture and histopathology revealed *S. aureus*; Amphotericin was discontinued without the development of other evidence of fungal disease.

also resistance to a number of other systemic antimicrobials including fluoroquinolones. A recent pediatric study revealed an increase in the prevalence of *S. aureus* isolates from oncology patients harboring biocide tolerance genes following an escalation of chlorhexidine use at their institution.⁵³ The isolates with antiseptic tolerance were also more likely to have resistance to ciprofloxacin. Notably, however, there was a decrease in the total number of *S. aureus* infections following implementation of antiseptic prophylaxis, attesting to the potential benefits of their use. In addition, recent laboratory studies have demonstrated that MDR efflux pumps may contribute to *S. aureus*' ability to colonize skin, adding further import to these clinical findings.⁶⁸ While these findings are concerning, the full clinical implications are unclear and are under investigation.

Solid organ transplantation

Patients who have received a solid-organ transplant (SOT) represent a unique population for the acquisition of HAIs given their preoperative organ failure, need for surgery, and often prolonged hospitalization and immunosuppression. The need for anti-T-cell immunosuppressive therapies may predispose to *S. aureus* infection in a manner similar to that described for HIV infection above. In fact, SOT is a known risk factor for *S. aureus* bacteremia in a study of Canadian adults.⁶⁹ Data on *S. aureus* infections in pediatric SOT recipients is extremely limited, and much of what is known was gleaned from larger studies of infection in pediatric SOT in general or from studies in adult populations. Overall, infections among SOT patients can be divided temporally based on the time since transplantation in the early (<1 month), intermediate (1–6 months), and late (>6 months) periods. The early period is typically characterized by infections that are health care associated in nature, including surgical site infections, ventilator-associated pneumonia, and CLA-BSI, of which *S. aureus* is among the principal pathogens.⁷⁰ In fact, among adult liver transplant recipients, recent surgery was associated with an increased risk of *S. aureus* infection in multivariate analyses.⁷¹

The frequency, clinical manifestations, and outcomes of *S. aureus* infection vary considerably with the organ transplanted (Table 1). A single center 11-year review of 345 patients revealed that bacterial infection occurred in 45% of pediatric liver transplant recipients within the first 90 days, with *S. aureus* accounting for 20.4% of infections.⁷² Colonization has further been shown to be a risk factor for MRSA infection in liver recipients.⁷³ Among 596 adult lung transplant recipients, *S. aureus* infection occurred in

18% in the first 90 days posttransplant and was associated with an increased length of hospital stay, risk of subsequent cytomegalovirus disease, graft rejection, and mortality.⁷⁴ By comparison, *S. aureus* is a much less common complication of renal transplant in adults, complicating only 1.3% of cases in one series of 116 subjects.⁷⁵

Specific studies of pediatric SOT recipients with *S. aureus* infection are ongoing, with preliminary data suggesting a rate of clindamycin resistance that is higher than in the general population (McNeil et al, unpublished data). Furthermore, there has been demonstrated a temporal increase in the proportion of MRSA infections among lung transplant recipients.⁷⁴

Given that these patients often have numerous comorbidities, by-and-large treatment must be individualized to the unique circumstances of the patient. Aggressive treatment of any and all infections is essential, particularly in the early posttransplant period, with a goal towards identifying an organism. Patients who are ill-appearing or recently transplanted should be admitted and receive broad spectrum intravenous antimicrobial therapy for both Gram-positive and Gram-negative agents including coverage for MRSA. Once patients are clinically stable and a pathogen identified, therapy can be deescalated to oral agents in many cases. Preliminary data from ongoing pediatric studies suggests that clindamycin can be used successfully to treat nonlife-threatening infection in SOT patients in the late posttransplant period (McNeil et al, unpublished data).

Due to the evidence of increasing frequency of MRSA infection among SOT recipients,⁷⁴ prevention strategies are needed. Numerous centers have implemented surveillance and decolonization measures to curtail the spread of antibiotic-resistant organisms. In one single-center study of 144 adult liver recipients, a protocol was instituted of active surveillance for nasal and rectal colonization, cohorting, and decolonization with intranasal mupirocin.⁷⁶ These measures were associated with a decrease in the rate of newly colonized patients as well as *S. aureus* infections, suggesting a benefit from these measures in this high risk population.

Primary immunodeficiency

Severe or recurrent infections, including skin infections, are among the warning signs of a primary immunodeficiency (PI). While healthy children frequently experience recurrent infections with *S. aureus*,^{77,78} the clinician should consider the possibility of PI particularly when patients are exhibiting other warning signs of immune dysfunction such as failure to thrive, pneumonia, chronic diarrhea, other infections, or generalized lymphadenopathy. Phagocyte defects in particular predispose to staphylococcal infections. The most common primary phagocyte disorder encountered in clinical practice is chronic granulomatous disease (CGD).^{79,80} CGD is caused by any number of mutations in the genes encoding components of the respiratory burst pathway of phagocytes, resulting in impaired production of reactive oxygen species and bacterial killing. Patients with CGD are predisposed to suppurative infections, notably skin abscesses, lymphadenitis, pneumonia/lung abscesses, and osteomyelitis.⁸¹ *S. aureus* is the most common bacterial pathogen isolated in children with CGD, accounting for up to 31% of all positive cultures;^{82,83} other major pathogens in CGD include *Serratia*, *Nocardia*, and *Aspergillus* spp. Long-term prophylaxis with TMP-SMX in addition to itraconazole is helpful at decreasing the frequency of serious infections in patients with CGD.^{84,85} Interferon-gamma injections have also been used successfully to decrease the incidence of major infections in children with CGD. In addition, hematopoietic stem cell transplant has successfully provided cure in patients with CGD.⁸⁶

Leukocyte adhesion defect (LAD) is a phagocyte disorder characterized by failure of neutrophils to extravasate from the peripheral circulation into infected tissues. Patients with LAD experience recurrent infections of the skin, mucosal surfaces, and gastrointestinal tract. The most common infectious agents in these patients are staphylococci as well as *Pseudomonas* spp.; infections in LAD are characterized by extreme leukocytosis but the absence of purulence at the site of infection.⁸⁷ Similar to CGD, TMP-SMX prophylaxis is recommended for children with LAD.

Table 1 Reported types of *Staphylococcus aureus* infection by transplanted organ

Transplanted organ	Bacteremia	Surgical site infection/ deep organ space	Pneumonia/ empyema	SSTI	References
Lung	6–15	7	35–81	7–12	74,107,108
Heart	7–9	20	16	30–85	70
Liver	6–36	30–61	11	22	72,109,110
Kidney	13–16	1–50	16	33	75

Notes: All values are expressed as a percentage of total *S. aureus* infections. The studies referenced varied in the posttransplantation time period for including patients.

Abbreviation: SSTI, skin-and-soft tissue infection.

Hyperimmunoglobulin E syndrome (HIES), also known as Job's syndrome, is an additional increasingly recognized PI. HIES exists in both autosomal dominant and recessive forms with coarse facial features, severe eczema, recurrent cold skin abscesses, recurrent pneumonias, and pneumatocele formation among its many features.^{87,88} Infections in HIES are primarily due to *S. aureus* although other commonly implicated bacterial pathogens include *Streptococcus pneumoniae* and *Haemophilus influenzae*; chronic mucocutaneous candidiasis is an additional common infectious complication of HIES. The molecular basis behind HIES is incompletely understood but involves mutations within STAT3, a transcription factor involved in the expression of a number of cytokines including IL-6, IL-10, and IL-17.⁸⁹ Moreover, STAT3 mutations have been shown to impair the differentiation of T helper 17 cells and thus may impair neutrophil recruitment leading to a predisposition to staphylococcal infections.⁹⁰

Disorders of humoral immunity are also associated with an increased incidence of *S. aureus* infection. *S. aureus*, along with *S. pneumoniae* and *H. influenzae*, are among the most common bacterial pathogens isolated in both X-linked agammaglobulinemia and common variable immunodeficiency.^{87,91} Individuals with common variable immunodeficiency often develop bronchiectasis and chronic lung disease, which may be complicated by staphylococcal infection.

In general all infections in children with PIs should be managed aggressively with a goal towards identifying the pathogen and providing specific therapy. There is a paucity of published data on the antimicrobial susceptibility profiles of staphylococcal isolates in patients with PI. One could reasonably hypothesize, however, that this population would have a high rate of infection with drug-resistant organisms given the frequent need for antimicrobials. Furthermore, once clinical improvement is observed, practitioners should be cautious for relapse of symptoms on discontinuation of therapy. Consultation with an infectious diseases specialist or clinical immunologist is recommended in the management of these patients.

Specific antimicrobial therapy for drug resistant *S. aureus* in children

As a basic principle, empiric use of antimicrobials should be guided by local epidemiology and antimicrobial susceptibility as well as the clinical state of the patient, with final therapy determined by culture and sensitivity data. A brief overview of specific antimicrobial therapy commonly used for pediatric staphylococcal infections is provided with data from immunocompromised hosts reviewed when applicable.

There is a great deal of strong in vitro as well as clinical evidence from adult patients supporting the use of nafcillin or cefazolin over vancomycin for the treatment of MSSA infections.⁹² Thus an antistaphylococcal β -lactam is recommended for both healthy and immunocompromised hosts for disease as a result of MSSA. Moreover, for severely ill patients with suspected staphylococcal disease, empiric combination of an antistaphylococcal β -lactam along with vancomycin pending culture data is recommended by some experts.

Vancomycin remains the drug of choice for the treatment of severe MRSA infections in children, with typical doses ranging from 10–15 mg/kg/dose every 8 hours.⁹³ For critically ill, bacteremic, or patients with central nervous system disease, it is recommended to increase dosing to every 6 hours. The Infectious Disease Society of America (IDSA) recommends early addition of vancomycin if there is suspicion of staphylococcal infection in febrile neutropenic patients.⁹⁴ The need for therapeutic monitoring of vancomycin levels in children is unclear. From studies in adults, primarily with *S. aureus* bacteremia, there is evidence to suggest improved clinical outcomes with vancomycin troughs of 15–20 $\mu\text{g/mL}$.⁹⁵ Many experts recommend similar goal levels in pediatric patients, yet the evidence to support this is limited. Serum vancomycin troughs $>15 \mu\text{g/mL}$ are often difficult to achieve in young children; in an Australian series only 43% of children 1–12 years old achieved goal troughs after 8 days of therapy.⁹⁶

Clindamycin is the most commonly used antimicrobial for the management of mild–moderate CA-MRSA infections.⁹⁷ Previous retrospective series in immunocompetent hosts have shown it to be noninferior to vancomycin in children.⁹⁸ Clindamycin was the most commonly used antimicrobial for the treatment of *S. aureus* infections in a small series of children with HIV, albeit, these were primarily SSTIs and not invasive infections.²⁹ Thus clindamycin could be considered for select patients who are not bacteremic, not severely immune suppressed, and have clindamycin susceptible isolates. Nearly all *S. aureus* isolates exhibit in vitro susceptibility to TMP-SMX, and this agent is endorsed by the IDSA for the treatment of staphylococcal SSTI.⁹³ Pediatric retrospective studies have been conflicting in the efficacy of TMP-SMX for SSTI, with some studies showing equivalence while others showed increased treatment failure compared to clindamycin.^{99,100} Increasing rates of clindamycin resistance have resulted in increased use of TMP-SMX in some centers. There is very limited data for TMP-SMX treatment of invasive infections, particularly in immunocompromised hosts.

Linezolid, a bacteriostatic oxazolidinone, has been shown to be noninferior to vancomycin for Gram-positive bacteremia and hospital-acquired pneumonia in pediatric clinical trials.¹⁰¹ The IDSA also recommends that physicians consider the use of linezolid for empiric treatment of febrile neutropenic adults when Gram-positive organisms are a concern.⁹⁴ A potential concern with linezolid is the occurrence of medication-induced bone marrow suppression; this could be potentially worrisome in the already immunocompromised host. A series of 17 pediatric cancer patients from Athens, Greece sought to evaluate the safety and efficacy of linezolid for Gram-positive infections in this population.¹⁰² All patients achieved microbiologic cure in this small series; 23.5% experienced adverse events; however, chemotherapy induced myelosuppression did not appear to be exacerbated by linezolid.

Other newer antistaphylococcal agents have thus far seen limited use in children. Daptomycin, a cyclic lipopeptide antimicrobial, is approved by the US Food and Drug Administration for the treatment of SSTI and bacteremia in adults. Daptomycin is currently undergoing investigation to establish the optimal dosing as well as its safety in children. A handful of case reports/series have described daptomycin use in children with doses ranging from 4–6 mg/kg/day with good efficacy and few adverse events.^{103,104} Ceftaroline, a new anti-MRSA cephalosporin, is approved in adults for treating SSTI as well as community-acquired pneumonia.^{105,106} Notably, this agent had a similar side effect profile to other cephalosporins and was better tolerated than vancomycin in adults. Clinical trials in pediatric patients are ongoing.

Conclusion

Children with immunocompromising conditions represent a unique group for the development of *S. aureus* infections. While many of the manifestations of staphylococcal disease are similar to that seen in healthy pediatric populations, there is the potential for the development of complications, particularly in those children with malignancy. Furthermore, infections in this population often exhibit high rates of resistance to commonly used antimicrobials. These infections should be managed aggressively, letting local epidemiology, culture, and susceptibility data guide antibiotic choice. There remain significant gaps in knowledge regarding the epidemiology and management of these infections that warrant further investigation.

Disclosure

The author reports no conflicts of interest in this work.

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