# Clinical Management of *Staphylococcus aureus* Bacteremia in Neonates, Children, and Adolescents

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*Staphylococcus aureus* is a common cause of community and health care–associated bacteremia, with authors of recent studies estimating the incidence of *S aureus* bacteremia (SAB) in high-income countries between 8 and 26 per 100 000 children per year. Despite this, <300 children worldwide have ever been randomly assigned into clinical trials to assess the efficacy of treatment of SAB. A panel of infectious diseases physicians with clinical and research interests in pediatric SAB identified 7 key clinical questions. The available literature is systematically appraised, summarizing SAB management in children in relation to these priority clinical questions. The management of neonates, children, and adolescents with SAB is predominantly based on clinical experience and trial data extrapolated from adult studies, with limited high-quality evidence available to guide management. The optimal, comprehensive management strategies for SAB in children will remain unknown until the questions outlined are answered through prospective observational cohorts and inclusion of children with SAB in clinical trials.

*Staphylococcus aureus* is a common cause of community- and health care–associated bacteremia, with the incidence of *S aureus* bacteremia (SAB) in high-income countries estimated between 8 and 26 per 100 000 children per year.[1,2] It is also one of the most frequent reasons a pediatric infectious diseases physician is consulted.[3] Despite this, critical questions regarding diagnostic investigations and management of SAB in childhood remain unanswered (Table 1). We systematically appraised the literature to summarize the current available evidence informing SAB management in children. An overview of randomized controlled trials (RCTs) and prospective observational studies (Tables 2 and 3), as well as a management algorithm for pediatric SAB (Fig 1), is provided. We highlight several gaps in knowledge and provide directions for future research.

## SEARCH STRATEGY AND SELECTION CRITERIA

A panel of 6 infectious diseases physicians with clinical and research interests in pediatric SAB noted that advice available for adults on this topic, such as in the article by Thwaites et al,[15] was lacking for children. This was taken as a starting point for a Delphi method–inspired process with several meetings to identify and rank prioritized clinical questions (Table 1).

Literature reviews, by using a systematic approach (see the Supplemental Information), were conducted, and the available literature

## abstract

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**TABLE 1** Questions, Summary, and Future Research Priorities for Children With SAB

| Question | Summary | Recommendations for Future Research |
|---|---|---|
| What are the epidemiological risk factors for acquiring SAB in children? | Young age (especially <1 mo), socioeconomic factors, and CVC are important risk factors for SAB in children. Medical comorbidities also appear to be SAB risk factors for children and adults. | Risk factors within these groups are uncertain and may be additive.<br>Understanding of pathogen and host factors in children with SAB, which contribute to disease severity, is needed. |
| In children, are all episodes of SAB clinically significant? | All episodes of SAB in children should be considered clinically significant. | Further research directed at SAB without clinical focus and asymptomatic SAB, including long-term outcome data, is required. |
| How should complicated pediatric SAB be defined? | Complicated SAB for children may include persisting bacteremia and/or fever beyond 72 h of targeted therapy, multifocal sites of infection, endocarditis, and complex local disease involving multiple adjacent tissue structures (eg, DVT and bone). | Further validation through prospective observational studies is required to accurately define complicated SAB and children at risk for poor outcomes. |
| Do all children with SAB require an IDC, echocardiography, imaging, and repeat follow-up blood cultures? | An IDC is recommended for all pediatric SAB. We recommend TTE in children with SAB and one or more of the following: (1) structurally abnormal hearts (including pacemakers), (2) sustained bacteremia (bacteremia ≥2 d), (3) persistent fever (fever ≥7 d), or (4) clinical features suggestive of endocarditis.<br>Given that persistent bacteremia is one criterion for echocardiography and may influence the duration of treatment, we recommend obtaining clearance blood cultures for all children with SAB.<br>In children with persisting bacteremia, when source localization is not possible clinically, consideration should be given to imaging to identify an occult musculoskeletal source. | The role of other imaging technologies in children with SAB, such as fluorodeoxyglucose positron-emission tomography, requires further research. |
| Are cephalosporins, glycopeptides or newer agents equivalent to ASPs for MSSA-B in children? | For MSSA-B in children, cefazolin is likely equivalent to ASP.<br>For MSSA-B in children, glycopeptides are likely inferior to ASP. Empirical antibiotic therapy that is inclusive of an ASP is therefore recommended for SAB in children with severe illness when susceptibilities are unknown. | Prospective clinical trials are required to definitively answer these questions for children.<br>Evidence is lacking for the efficacy of newer agents compared with β-lactams for treatment of MSSA-B in children.<br>Further prospective comparative trials to assess optimal treatment strategies for MRSA-B are required. |
| What are the optimal management strategies for those children with organisms resistant to β-lactams (MRSA), and what is the role of combination therapy? | Vancomycin is a first-line recommended therapy for SAB in children with immediate hypersensitivity reactions to β-lactams or with MRSA-B.<br>Alternative therapeutic options include daptomycin, linezolid, and clindamycin. Ceftaroline may be considered as salvage therapy in SAB.<br>Trimethoprim-sulfamethoxazole and adjunctive rifampicin are not routinely recommended for the treatment of SAB. | Therapeutic targets for trough monitoring in children require further research.<br>Alternative agents may be used for SAB in children with the provisos listed above.<br>Evidence in pediatrics is limited for newer agents.<br>The efficacy and safety of combination therapy in children with SAB is unknown. |
| Duration of IV therapy for children with SAB: are children and adults different? | On the basis of current evidence and practice, we recommend 7–14 d of IV therapy for most children with SAB and 14 d for neonates, with longer therapy for those children with endocarditis (4–6 wk).<br>Children with SAB in the context of OAIs should generally be treated for a total duration of 4–6 wk, although patients may be able to switch to oral therapy before 7 d, depending on the clinical response. | Whether duration of IV therapy for MRSA-B needs to be longer than that for MSSA-B and the role of oral antibiotics for endocarditis in children are unknown. |

DVT, deep vein thrombosis.

**TABLE 2** Summary of Children ($N$ = 292) With SAB Randomly Assigned Into Clinical Trials

| Author, Year, Country | $n$[a] (Total = 292) | Clinical Trial Question | (1) Primary and (2) Secondary Outcomes | Clinical Efficacy Findings | Safety Findings |
|---|---|---|---|---|---|
| Arrieta et al,[4] 2018, United States | 82/82 | Randomized, evaluator-blinded, multicenter, phase 4 trial of IV daptomycin versus SOC (primarily vancomycin or cefazolin) for SAB | (1) Evaluate daptomycin safety in children receiving ≥1 dose; (2) compare daptomycin efficacy to SOC: trial not powered to assess noninferiority | Clinical success (measured by complete or partial resolution of bacteremia signs and symptoms 7–14 d after the end of treatment) rates were similar for daptomycin (88%) and SOC (77%; 95% CI for difference 9%–31%). | Fifteen percent of patients had drug-related adverse events (diarrhea: 4% daptomycin, 8% SOC; raised CK: 4% daptomycin, 0% SOC). |
| Peltola et al,[5] 2012, Finland | 130/265 | Prospective, quasi-randomized trial comparing clindamycin with first-generation cephalosporins in children with acute OAIs aged 3 mo to 15 y. IV therapy was given for the first 2–4 d, then oral therapy with the same equivalent agent was continued | (1) Full recovery defined as the patient free of symptoms or signs of OAI with no antimicrobial agents being readministered for this indication after the treatment course during the 12-mo follow-up; (2) time to normalization of laboratory indices between the clindamycin and cephalosporin recipients and hospital LOS | All patients recovered with an ∼3-wk (mostly oral) course of clindamycin or first-generation cephalosporin; no treatment failures in both groups; no MRSA in this cohort and limited surgical interventions; question the generalizability of these results. | Loose stools were reported slightly less frequently in the clindamycin group than in the cephalosporin group (1% [95% CI 0%–4%] vs 7% [95% CI 4%–14%], respectively). Two clindamycin recipients developed a rash. |
| Chowdhary et al,[6] 2006, India | 14/120 | Neonates ≥32 wk and ≥1500 g with blood culture–proven sepsis without meningitis or deep-seated foci who were clinically remitted by day 5 were randomly assigned to either 7 d or 14 d of IV antibiotic therapy | (1) Treatment failure within 28 d defined as a positive blood culture result, clinical signs, CRP level >12 mg/L, or expert opinion; (2) common adverse effects related to antibiotic usage evaluated on the seventh and 14th d, including skin rashes, deranged LFT and EUC | Of the 14 neonates with SAB, in the 7-d group, 4 of 14 (28.6%) had treatment failure, whereas in the 14-d group, all had successful treatment ($P$ = .02). Thirty-nine patients were excluded before randomization because they were still symptomatic on d 6 and 7 of antibiotic therapy. *S aureus* constituted 61.5% of culture isolates of neonates who were still symptomatic on d 6 and 7 ($P$ = .0001). | No subjects developed deranged LFT and EUC or skin rash in either group. |
| Kaplan et al,[7] 2003, United States | 66/321 with *S aureus* infection (unknown number with SAB) | Children with Gram-positive infections were randomly assigned 2:1 to receive IV linezolid or vancomycin followed by an appropriate oral agent for a total duration of 10–28 d | (1) Clinical efficacy was assessed by evaluating clinical outcome. Cure was defined as a resolution of the baseline clinical signs and symptoms of infection by d 5 and after 15 doses of treatment. Failure was defined as the persistence of signs and symptoms of infection after 2 d and 6 doses of treatment | Clinical cure rates were 79% linezolid and 74% vancomycin ($P$ = .36). Pathogen eradication rates in microbiologic evaluable patients were high for linezolid (94%) and vancomycin (95%) ($P$ = .82). | Significantly fewer patients treated with linezolid had drug-related adverse events compared with those treated with vancomycin (19% vs 34%, respectively; $P$ = .003). Hematologic events were uncommon and similar between treatment groups. |

CK, creatine; CRP, C-reactive protein; EUC, electrolytes, urea, and creatinine; LFT, liver function test; LOS, length of stay; SOC, standard of care.
[a] $n$ represents the number of children aged ≤18 y with SAB enrolled in the clinical trial.

was appraised. PubMed and Medline (January 1960 to December 31, 2018) were interrogated by using specific Medical Subject Headings stems in combination with search terms for each question.

The search was limited to studies published in English. Bibliographies were searched for secondary references. Each question was answered by using a prespecified hierarchy of evidence from systematic reviews to RCTs, case-control and cohort studies, case series, and case reports. When there were limited pediatric studies available, adult data were also reviewed. Each section was appraised by one author and

**TABLE 3** Summary of Children With SAB in Prospective Clinical Studies

| Author, Year, Country | Pediatric Case No. | Patients | SAB Incidence or Rate | *S aureus* Focus | Antibiotics, d | ICU | Community Acquired | MSSA | Mortality | Median LOS | Key Take-home Points |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Shane et al,[8] 2012, United States | 305 | VLBW neonates | 316/8444 VLBW infants (3.7%) | Meningitis and/or SAB | Unknown | Unknown | Unknown | 228/316 (72%) | 78/316 (25%) all-cause mortality measured at 120 d | 68 d | For VLBW neonates with SAB, most episodes occurred as late-onset sepsis ≥72 h ($n$ = 311/316; 98%), and there was no difference in mortality for MRSA (26%) versus MSSA (24%) (0.96; 95% CI 0.63–1.46). Risk of SAB and/or meningitis increased with decreasing gestational age and birth wt. |
| Hill et al,[9] 2001, New Zealand | 125 | Children: 51% were <7 y | 16.9 cases per 100 000 y | IV catheter: 23 (17%); SSTI: 6 (5%); skeletal: 19 (14%); lung: 12 (9%); unknown: 53 (39%); other 12 (9%) | 21 d | Unknown | 88/125 (70%) | 117/125 (9%) | 4/134 (3%) 30-d attributable mortality | 14 d | Peak incidence in New Zealand Pacific children <1 y was high: 105 per 100 000 population per y; community-acquired infection predominated. |
| Jacobsson,[10] 2007, Sweden | 13 | Children and adults with invasive *S aureus* (141 had SAB) | 10.4 cases per 100 000 per y | SSTI: 47 (27%); no focus: 32 (19%); arthritis: 25 (15%); line associated: 24 (14%) | Unknown | Unknown | 49% | 100% | Unknown | Unknown | In a predominantly adult cohort of patients with SAB, 25% of patients had no history of fever. The most common predisposing illness was hemodialysis. |
| Fortuin-de Smidt,[11] 2015, South Africa | 82 patients <24y | Children and adults with SAB | 1.9–3.7 cases per 1000 admissions | No focus: 78 (55%); lung: 19 (13.5%); meningitis: 3 (2.1%); SSTI: 11 (7.8%); skeletal: 3 (2.1%); unspecified: 26 (18.5%) | Unknown | Unknown | 46/113 (40%) | 152/240 (63%) | 46/140 (32%) (method not stated) | 29 d | In a South African cohort, strongest associations with MRSA were HIV (OR 4.89; 95% CI 1.05–22.9) and previous hospitalization (OR 15.74; 95% CI 2.49–99.48). MRSA was not significantly associated with mortality (OR 3.7; 95% CI 0.50–27.6). |
| McMullan et al,[2] 2016, Australia and New Zealand | 1153 | Children with SAB | 8.3 cases per 100 000 per y | Bone and joint: 348 (32.4%); sepsis or no focus: 221 (20.6%); device infection: 169 (15.8%) | Unknown | 154/1073 (14.4%) | 761/1073 (70.9%) | 931/1073 (86.7%) | 28/1073 (2.6%) 7-d all-cause mortality; 50/1073 (4.7%) 30-d all-cause mortality | 17d MRSA,14 d MSSA | In this large prospective Australian and New Zealand pediatric cohort, risk factors for mortality were age younger than 1 y; Māori or Pasifika ethnicity; IE, pneumonia, or sepsis; and receiving no treatment or treatment with vancomycin. MRSA infection was associated with increased LOS but not mortality. |

**TABLE 3** Continued

| Author, Year, Country | Pediatric Case No. | Patients | SAB Incidence or Rate | *S aureus* Focus | Antibiotics, d | ICU | Community Acquired | MSSA | Mortality | Median LOS | Key Take-home Points |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Friedland,[12] 1995, South Africa | 36 | Children admitted to hospital with SAB and had echocardiography performed | Unknown | Skin: 22 (66%); lung: 12 (36%); skeletal: 10 (36%); heart: 6 (35%) | 20 d | Unknown | 30/47 (63%) | 20/31 (64%) | 6 (15%) 7-d mortality (method not stated) | Unknown | Incidence of IE was 11% among children with SAB. Clinical signs of endocarditis were absent from children with IE. |
| Valente,[13] 2005, United States | 51 | Children with SAB who had echocardiography performed | Unknown | Catheter: 30 (73%); definite or possible IE: 10 (20%); premature: 16 (31%) | Unknown | Unknown | 18/41 (44%) | 27/41 (66%) | Overall: 18% (1-y all-cause mortality); IE: 40% (1-y all-cause mortality) | Unknown | Incidence of definite IE was 12% among children with SAB. Risk factors for IE included the presence of congenital heart disease and multiple positive blood culture results. |
| McNeil et al,[14] 2013, United States[a] | 44 | Children with invasive *S aureus* infection and CHD | Unknown | SSTI: 103 (41.5%); surgical site infections: 70 (28%); definite IE: 13 (5%); skeletal: 8 (3.7%) | Unknown | 72/248 (29%) | Unknown | Unknown | Attributable mortality for IE 4/13 (31%) | 10 d | IE in this cohort was associated with prolonged bacteremia, thrombocytopenia, and CRP level >10 mg/dL. Sensitivity of echocardiography for diagnosis of IE was 76.9%. |

*N* represents the number of children aged ≤18 y with SAB involved in this study. CHD, congenital heart disease; CRP, C-reactive protein; LOS, length of stay; OR, odds ratio; VLBW, very low birth weight.

[a] In this study, isolates were collected by using prospective surveillance, but it should be noted that medical records were reviewed retrospectively.

reviewed independently by a second author and then by all authors. Narrative review was chosen rather than the systematic review style to allow for exploration of the most relevant questions for clinicians managing this condition in children. The available literature is synthesized in response to 7 key questions.

## WHAT ARE THE EPIDEMIOLOGICAL RISK FACTORS FOR ACQUIRING SAB IN CHILDREN?

Approximately 30% of the population may be colonized with *S aureus*, and another 30% may be intermittently colonized.[16] Nasal colonization has been identified as a major risk factor for the development of invasive *S aureus* infections in both community and hospital settings.[16]

Young age is a risk factor for SAB. Infants <1 year of age have consistently been shown to have a higher incidence of SAB compared with older children.[17,18] The incidence in infants has been reported as high as 16.7 per 100 000 population[19] and in neonates as high as 124.8 per 100 000.[20] Within NICU populations, lower birth weight and younger gestational age correlate with frequency of SAB episodes[8]; these same risk factors have also been associated with poorer outcomes of SAB in NICU patients.[21]

Incidence of SAB in children varies with ethnicity in some studies, although published data are conflicting, and these findings may be principally related to social determinants of health: socioeconomic status, household crowding, and/or geographic factors.[22] Australian Aboriginal and Torres Strait Islander, as well as New Zealand Māori and Pasifika children experience more frequent episodes of SAB.[2,9] In the United States, African American ethnicity is associated with a higher incidence of invasive methicillin-resistant *S aureus* (MRSA) infection.[19] In contrast, the authors of

one multicenter study of NICU patients found no difference in incidence of SAB regarding ethnicity, after controlling for regional effects.[8]

The most common source for health care–associated SAB in children is a central venous catheter (CVC). History of previous hospitalization, HIV infection, malnutrition, and residence in a long-term care facility have all been associated with a higher incidence of methicillin-resistant *S aureus* bacteremia (MRSA-B) following community-acquired MRSA skin and soft tissue infections (SSTIs).[23] *S aureus* also frequently produces bacteremia in previously healthy children; in one US multicenter study, 48% of children with MRSA-B lacked any underlying medical conditions.[24]

Question 1 summary: Young age (especially <1 month), socioeconomic factors, and CVC are important risk factors for SAB in children. Medical comorbidities also appear to be a risk; however, further pediatric-specific analysis is required.

## IN CHILDREN, ARE ALL SAB EPISODES CLINICALLY SIGNIFICANT?

SAB can range from mild to severe infection, and apparently asymptomatic detection in the bloodstream (presumed contamination from skin colonization) is rare.[25] Blood culture positivity due to contamination is estimated to be associated with ≤2% of SAB episodes.[15] For children with SAB labeled as contamination and not treated, there are no published data on relapse rates or long-term outcomes. In addition, SAB in children without apparent clinical focus has been associated with higher mortality.[2]

Question 2 summary: SAB infections range widely in severity. Blood culture contamination with *S aureus* is rare. Therefore, we recommend that *S aureus* isolated from a blood culture should always be considered clinically significant and treated with antibiotic therapy (Fig 1).

## HOW SHOULD COMPLICATED PEDIATRIC SAB BE DEFINED?

On the basis of well-designed observational studies, uncomplicated SAB in adults is defined as the absence of endocarditis or prosthetic devices, negative blood culture results at 48 to 72 hours, defervescence within 72 hours of commencing targeted therapy, and absence of metastatic sites of infection.[23] For adults, when the above criteria are met for uncomplicated SAB, intravenous (IV) treatment duration of 2 weeks is recommended[23]; conversely, for complicated SAB, treatment is extended to 4 to 6 weeks.

In contrast, evidence-based consensus definitions for complicated infection are not available for children, and management is not stratified according to these criteria; treatment duration varies with disease severity and is often clinician dependent. In several case series in children,[26,27] definitions for complicated SAB have been proposed; however, validation by using robust outcome measures (eg, death, hospital readmission, and prolonged bacteremia) has not been performed.[28] Observational studies and case series suggest poorer outcomes with SAB and necrotizing pneumonia, sepsis, ICU admission, visceral abscess, endocarditis, multifocal SSTI or osteoarticular infection (OAI), or deep venous thrombosis in children.[2,29,30] Longer duration of MRSA-B has also been associated with poor outcomes[24]; however, MRSA-B, per se, is inconsistently reported as a risk factor for mortality.[27,31,32] Prognostic factors have not been studied by using large prospective data sets in children with robust measures of outcome.

Question 3 summary: A consensus definition for complicated SAB is not currently available for children. Future research should examine potential risk factors, including persisting bacteremia and fever beyond 72 hours of targeted therapy, multifocal or complex local infection, and endocarditis. Defining complicated SAB for children is an important step to inform treatment duration, prognosis, and timing of the IV to oral switch.

## DO ALL CHILDREN WITH SAB REQUIRE AN INFECTIOUS DISEASES CONSULTATION, ECHOCARDIOGRAPHY, IMAGING, AND REPEAT FOLLOW-UP BLOOD CULTURES?

The value of an infectious diseases consultation (IDC) has been demonstrated in a systematic review of adult SAB, in which 30-day mortality was found to be significantly reduced in the IDC group (12.39% vs 26.07%), with a relative risk of 0.53 (95% confidence interval [CI] 0.43–0.65).[33] In smaller pediatric SAB cohorts, the IDC group was more likely to have had echocardiography performed and a removable source of infection identified.[33] Reduced mortality with IDC for children has recently been demonstrated (B.J.M., unpublished observations).

Investigations routinely recommended for adults with SAB include echocardiography and repeat blood cultures to document SAB clearance (Fig 1). Endocarditis rates in adults with SAB vary, influenced by the population and method of detection. In a single-center prospective study of 724 adults with SAB, 12% had infective endocarditis (IE).[28] In contrast, endocarditis is rare in children with SAB and structurally normal hearts, yet it can be present in up to one-third of children with underlying congenital heart disease.[14] Transthoracic echocardiography (TTE), in comparison with transesophageal echocardiography, is the preferred imaging modality in children given that high-quality images can generally be obtained,[34] general anesthesia can

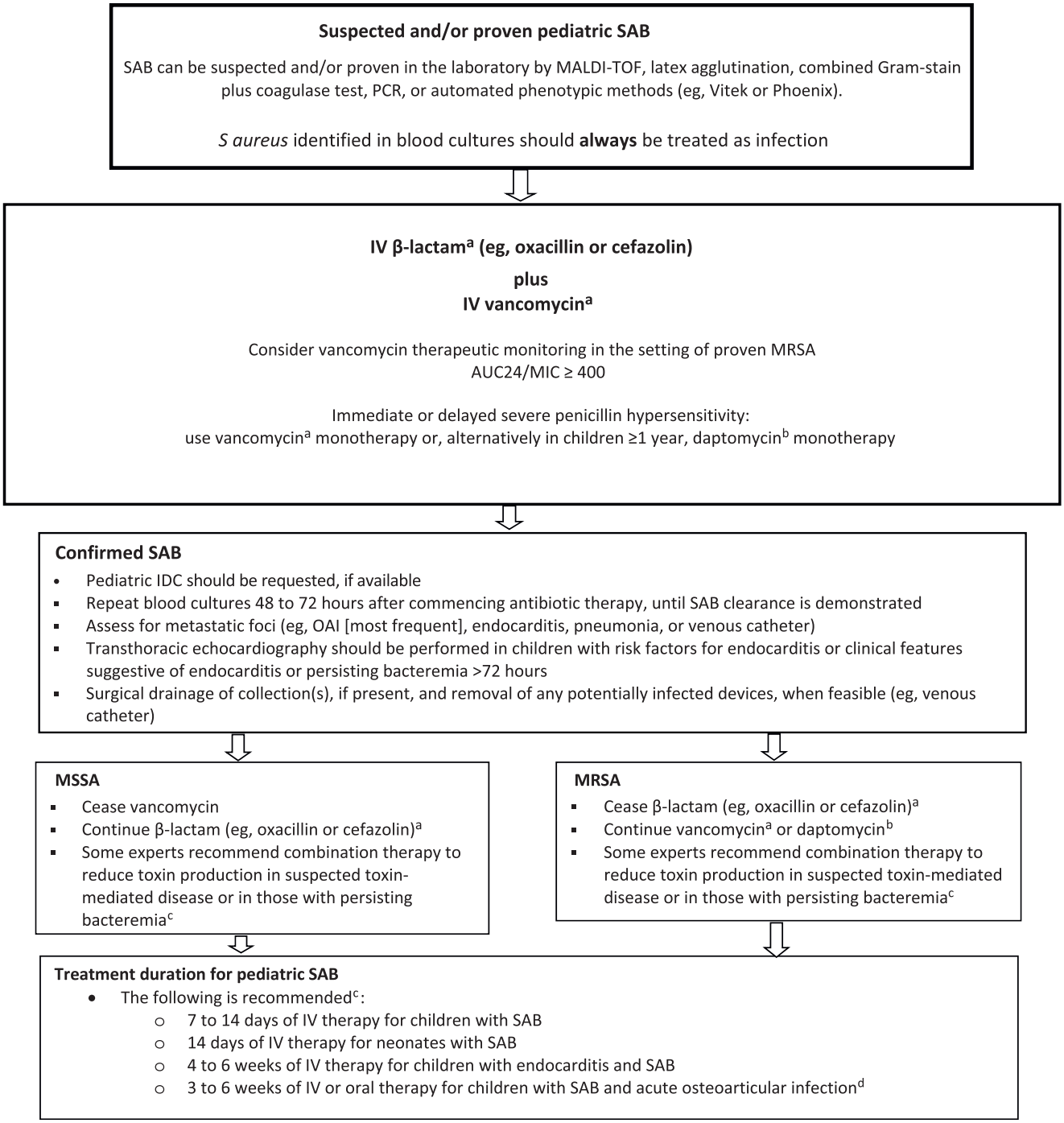


**FIGURE 1**

Algorithm for pediatric SAB. We systematically appraised and summarized the available literature into a clinician management algorithm, addressing key clinical questions for pediatric SAB. [a] In the setting of renal impairment, dose adjustment may be required. [b] Do not use daptomycin to treat SAB with pneumonia or lung involvement. [c] There are no RCTs (outside of the neonatal period) to inform treatment duration or the value of combination antibiotic therapy for SAB in children. The above recommendations are based on expert opinion, available guidelines, and historical practice. Duration of therapy should be discussed with a pediatric infectious diseases specialist or other appropriate expert. [d] A switch to oral therapy after a minimum of 3 days of IV therapy can be considered provided that rapid clearance of SAB and prompt symptom resolution is achieved. MALDI-TOF, Matrix-Assisted Laser Desorption/Ionization-Time Of Flight; PCR, polymerase chain reaction.

be avoided, and there is a low pretest probability for IE in most children.[2]

In prospective studies of children with SAB, persisting bacteremia at 48 to 72 hours is uncommon, and repeat blood cultures are variably performed.[33] In a retrospective cohort study of MRSA-B in children, CVC infections were associated with lower treatment failure, whereas endovascular infections were associated with higher failure.[24] In this study, each additional day of bacteremia was associated with developing infection progression, metastatic foci, or septic emboli.

SAB with a skeletal focus is more common in children,[2] affecting ~30% of children, compared with 16% in adults.[35] OAI may represent occult foci in children with SAB. MRI has the highest sensitivity for detection of OAI and is the imaging modality of choice but often requires sedation or general anesthesia in younger children. Newer technologies, such as fluorodeoxyglucose positron-emission tomography, may be useful in distinguishing active versus inactive inflammation in chronic osteomyelitis, although this has been primarily evaluated in adults.[36] Consideration of radiation exposure is important in the risk/benefit decision for children.[37]

Question 4 summary: An IDC is recommended for all pediatric SAB episodes. Endocarditis is generally rare in children with SAB, and TTE should be performed for those with risk factors (such as congenital heart disease) or clinical features suggestive of endocarditis. Repeat blood cultures to document clearance should be collected to assist in decisions regarding echocardiography and antibiotic treatment length. Imaging may assist in identifying an occult musculoskeletal focus in those with persisting symptoms or bacteremia with an unknown focus.

## ARE CEPHALOSPORINS, GLYCOPEPTIDES, OR NEWER AGENTS EQUIVALENT TO ANTISTAPHYLOCOCCAL PENICILLINS FOR METHICILLIN-SUSCEPTIBLE *S AUREUS* IN CHILDREN?

Inferior outcomes are reported in methicillin-susceptible *S aureus* bacteremia (MSSA-B) treated with glycopeptides compared with β-lactams. In a study of >1000 episodes of SAB in children, 30-day mortality was increased for those receiving glycopeptides, with an adjusted odds ratio of 2.7 (95% CI 1.3–5.8).[2] In 5784 adult veterans treated with either a glycopeptide or β-lactam for MSSA-B, those who received cefazolin or an antistaphylococcal penicillin (ASP) had reduced mortality, compared with patients who received vancomycin, after adjustment for severity of illness, aggregate comorbidities, osteomyelitis, age, β-lactam allergy, and dialysis or end-stage renal disease (hazard ratio: 0.57; 95% CI 0.46–0.71).[38]

No pediatric-specific data are available to inform the choice between β-lactams, including cephalosporins, and ASP for SAB, and few children have been included in published trials evaluating these agents. Practice guidelines, however, often recommend ASPs, such as oxacillin, nafcillin, or flucloxacillin, as first-line agents for the treatment of MSSA-B.[39,40] Authors of a number of recent meta-analyses with data from retrospective and prospective cohort studies have compared outcomes for cefazolin and ASP in adults with MSSA-B. These data demonstrate equivalence[41] or favor cefazolin over ASP.[42,43]

Authors of a number of noninferiority trials in adults have compared newer agents with β-lactams for treatment of SAB (eg, daptomycin[44,45] and telavancin[46]), but small numbers of patients with MSSA-B preclude firm conclusions. Authors of an RCT examining linezolid versus cefadroxil in children with SSTI, which included >200 children with methicillin-susceptible *S aureus* (MSSA), reported similar clinical cure rates at 21 days of 90% and 91%, respectively ($P$ = .737). The number of children with SAB within this trial was not reported, and thus few conclusions can be drawn from these data.[47]

Question 5 summary: β-lactams are superior to glycopeptides for treatment of MSSA-B in children (Fig 1). Evidence is lacking to distinguish between superiority of ASP and cefazolin for treatment of MSSA-B in children. There are no published studies comparing newer antistaphylococcal agents with β-lactams for treatment of MSSA-B in children. Researchers of clinical trials on treating *S aureus* infection should report on numbers and outcomes in those with SAB.

## WHAT ARE THE OPTIMAL MANAGEMENT STRATEGIES FOR THOSE CHILDREN WITH ORGANISMS RESISTANT TO β-LACTAMS (MRSA), AND WHAT IS THE ROLE OF COMBINATION THERAPY?

### Vancomycin

Vancomycin is the first-line recommended treatment option for MRSA-B or for those with β-lactam allergies and has a long history of use in children, often serving as a comparator to newer agents for treating *S aureus* infections (Fig 1).[23] Clinical trial data for vancomycin in children with SAB are limited.[4,7] For optimum vancomycin dosing, a 24-hour area under the curve (AUC24)/minimum inhibitory concentration (MIC) ratio of >400 has been recommended.[48] In general, dosing of 60 mg/kg per day in children is more likely than 40 mg/kg per day to achieve an AUC24/MIC ratio of >400, but correlation between the serum trough level and clinical outcome has not been demonstrated in children.[24,49–51] There is some evidence that trough levels of >15 mg/L in children are associated

with increased risk of nephrotoxicity without improvement in clinical outcomes.[52,53] Although vancomycin-intermediate (MIC 4–8 ug/mL) and vancomycin-resistant (MIC ≥ 16 ug/mL) strains remain uncommon, they should be considered in the setting of persisting SAB with limited or no clinical response to vancomycin.[23] If confirmed with a validated laboratory method, an alternative antimicrobial agent should be used.[23]

### Alternative Antimicrobial Agents

Daptomycin clearance is inversely related to age, with higher elimination rates in younger patients[7,54]; therefore, increased relative doses of daptomycin are required in children. Toxicities include rarely neurologic and muscular effects (eg, rhabdomyolysis), and there is currently insufficient data to inform recommendations for children <12 months of age.[4,7] In addition, daptomycin is inactivated by lung surfactant and is therefore not indicated for SAB with lung involvement.[4] In a clinical trial in children aged 1 to 17 years with SAB ($n$ = 82), researchers found comparable safety and efficacy of daptomycin compared with the standard of care (cefazolin or vancomycin), but the trial was inadequately powered to assess noninferiority.[4]

Linezolid is an oxazolidinone antibiotic with high bioavailability and tissue penetration. There are 2 RCTs with a combined 815 children, mainly with SSTI, in which linezolid at 10 mg/kg per dose every 8 to 12 hours is compared with other active agents.[7,55] Favorable outcomes with linezolid were reported in both; however, outcomes for SAB subgroups were not reported. Evidence supporting linezolid for SAB is limited to case reports and series, although it is commonly used in practice.[56–58] Toxicity may include bone marrow suppression and, uncommonly, peripheral and optic neuropathy, which is more likely to occur beyond the third week of treatment.[59]

Ceftaroline fosamil is a newer cephalosporin with anti-MRSA activity.[60] RCTs for ceftaroline involving pediatric and adult patients with SSTI[60,61] and community-acquired pneumonia have been reported.[60,62,63] Few patients had SAB in SSTI studies, and those with MRSA were excluded in pneumonia studies. Ceftaroline has been used as salvage therapy for patients with MRSA-B (including those with endocarditis) in case series.[64]

Clindamycin was used in a quasi RCT of 99 children for the treatment of OAI[5] and 63 children in an observational study of invasive *S aureus* infections.[65] In both studies, clindamycin was as effective as comparator drugs, with all children who received clindamycin achieving clinical cure. Clindamycin has not, however, been studied in RCTs for SAB and has been recommended not to be used in endocarditis because of higher risk of relapse.[66]

Trimethoprim-sulfamethoxazole (co-trimoxazole) is commonly used for staphylococcal SSTI in children. No clinical trials report on trimethoprim-sulfamethoxazole efficacy in children with SAB. Treatment failure was higher in adults treated with trimethoprim-sulfamethoxazole versus vancomycin in an RCT of MRSA-B.[47] In a small retrospective review in northern Australia, 2 of 8 children with SAB treated with oral continuation on trimethoprim-sulfamethoxazole therapy relapsed.[67]

Some experts recommend consideration of a protein synthesis inhibitor antibiotic, such as clindamycin or linezolid, to reduce toxin production for those with suspected toxin-mediated disease or combination therapy for those presenting with persisting SAB, particularly with MRSA.[23] Currently there are no RCTs that confirm the utility of these practices.

No RCTs have been reported on the use of adjunctive rifampicin for SAB in children. Case series suggesting that rifampicin added to vancomycin may provide benefit in treating children or adults with persistent SAB[68,69] have been challenged by the ARREST trial.[70] This was a multicenter RCT in which adjunctive rifampicin provided no benefit over standard antibiotic therapy in adults with SAB.[70]

Similarly, evidence for combination therapy with gentamicin is lacking; a meta-analysis of 3 RCTs and a prospective study failed to demonstrate improved clinical cure rates or mortality when used in combination with β-lactams in the setting of *S aureus* endocarditis.[71,72] There was also a significantly increased risk of nephrotoxicity.[71,72] Subsequently, adjunctive gentamicin therapy is no longer recommended in the treatment of SAB or native valve IE because of these reasons.[23]

Question 6 summary: Vancomycin is recommended as a first-line therapy for MRSA-B in children at starting doses of 45 to 60mg/kg per day (Fig 1). If therapeutic drug monitoring is performed, an AUC24/MIC ratio of ≥400 should be sought. There are, however, limited data supporting vancomycin therapeutic monitoring for improved efficacy in children. Alternative agents may be used for SAB in children, although further studies into their comparative efficacy is required.

### Duration of IV Therapy for Children With SAB: Are Children and Adults Different?

Little evidence exists to support duration of IV therapy for children with SAB. Historically, treatment in children has been extrapolated from adult data. There has been only one RCT providing information on duration and outcomes, which involved 120 neonates with all-cause

bacteremia.[6] On subgroup analysis of neonates with SAB, 4 of 7 (57%) with 7-day therapy failed treatment compared with 14-day therapy (0 of 7 [0%]; $P$ = .022). Neonates are a high-risk group,[26] and extrapolating these data to older children is challenging. For children with SAB without focus, an IV duration of 7 to 14 days is currently recommended, although earlier transition to oral antibiotics may be possible in those with OAI who have adequate source control and good clinical response.[39,73] In an observational study of 192 children with OAI, those with MRSA-B who received <7 days of vancomycin with appropriate oral antibiotic stepdown did not have increased relapse.[52]

For SAB with endocarditis, 4 to 6 weeks is recommended for children.[39,73] In a recent prospective RCT POET study,[74] researchers examined partial oral versus IV antibiotic treatment of left-sided endocarditis for 87 adult patients with MSSA endocarditis (unknown number with SAB). Changing to oral antibiotic treatment after a minimum of 10 days of IV treatment was noninferior to continued IV antibiotic therapy for the primary composite outcome of all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia (including for *S aureus* endocarditis; odds ratio 0.84 [95% CI 0.15–4.78]).[74] This study did not, however, include children or those with MRSA.

Question 7 summary: Duration of therapy for SAB in children is based largely on historical practice. Until better evidence is available, 7 to 14 days of IV therapy for most children with SAB without focus, ≥14 days for neonates, and at least 4 to 6 weeks for children with endocarditis are recommended (Fig 1). A total antibiotic duration of 3 to 6 weeks for children with SAB and acute OAI is recommended; however, many patients may switch to oral therapy after a minimum of 3 days of IV therapy, although assessing clinical and microbiologic response in practice may take longer than this minimum duration.

## DISCUSSION

Despite the burden of SAB as a common cause of pediatric bacteremia, children are not little adults: they have lower 30-day mortality (5%[16] vs 21%[35]), lower proportions of SAB episodes complicated by endocarditis (1%[16] vs 12%[1]), and higher proportions associated with OAI (32%[16] vs 12%[35]). Experienced pediatricians have well-established knowledge and expertise in caring for children with SAB; for example, prolonged bacteremia is the exception rather than the rule, previously healthy children usually respond well to short-course treatment, and premature neonates have a higher burden of infection and mortality. Despite this knowledge, some aspects of treatment vary markedly between centers, and thus research specific to the treatment of pediatric SAB is urgently required.

Priority questions for future research include defining optimal duration of therapy in children with uncomplicated and complicated SAB and whether combination therapy is beneficial for those with complicated disease. The recent ARREST trial did not reveal an additional benefit of rifampicin compared with the standard of care for adults with SAB.[70] Should this practice be avoided in children also? Without trials involving children in answering these questions, pediatricians remain without equivalent evidence standards.

The limitations of this review are evident by the paucity of pediatric-specific evidence to inform clinical decision-making and clinical trial design. When evidence has been generated in adults, this has been reported on. We have appraised all the studies with available pediatric data to answer these questions.

We have defined the current state of knowledge (or lack thereof) for several key questions relating to SAB in children. The optimal, comprehensive management strategies for SAB in pediatrics will remain unknown until the priority clinical questions outlined are answered through prospective observational cohorts and inclusion of children with SAB in clinical trials.


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## ABBREVIATIONS

ASP: antistaphylococcal penicillin
AUC24: 24-hour area under the curve
CI: confidence interval
CVC: central venous catheter
IDC: infectious diseases consultation
IE: infective endocarditis
IV: intravenous
MIC: minimum inhibitory concentration
MRSA: methicillin-resistant *Staphylococcus aureus*
MRSA-B: methicillin-resistant *Staphylococcus aureus* bacteremia
MSSA: methicillin-susceptible *Staphylococcus aureus*
MSSA-B: methicillin-susceptible *Staphylococcus aureus* bacteremia
OAI: osteoarticular infection
RCT: randomized controlled trial
SAB: *Staphylococcus aureus* bacteremia
SSTI: skin and soft tissue infection
TTE: transthoracic echocardiography

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