

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

Brendan J. McMullan, BMed (Hons), FRACP, FRCPA,^{a,b,c,*} Anita J. Campbell, MBBS, DCH, DipPID, FRACP,^{d,e,f,*} Christopher C. Blyth, MBBS (Hons), PhD, DCH, FRACP, FRCPA,^{d,e,f,g} J. Chase McNeil, BS, MD,^h Christopher P. Montgomery, BA, MD,^{i,j} Steven Y.C. Tong, MBBS (Hons), PhD, FRACP,^{k,l} Asha C. Bowen, BA, MBBS, PhD, FRACP^{d,e,f,k,m}

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



^aDepartment of Immunology and Infectious Diseases, Sydney Children's Hospital, Randwick, New South Wales, Australia; ^bSchool of Women's and Children's Health, University of New South Wales, Sydney, New South Wales, Australia; ^cNational Centre for Infections in Cancer, University of Melbourne, Melbourne, Victoria, Australia; ^dDepartment of Infectious Diseases, Perth Children's Hospital, Nedlands, Western Australia, Australia; ^eWestfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, Nedlands, Western Australia, Australia; ^fSchool of Medicine, The University of Western Australia, Perth, Western Australia, Australia; ^gDepartment of Microbiology, PathWest Laboratory Medicine, QEII Medical Centre, Nedlands, Western Australia, Australia; ^hSection of Infectious Diseases, Department of Pediatrics, Baylor College of Medicine, Houston, Texas; ⁱCenter for Microbial Pathogenesis, The Abigail Wexner Research Institute, Nationwide Children's Hospital, Columbus, Ohio; ^jDivision of Critical Care, Department of Pediatrics, The Ohio State University, Columbus, Ohio; ^kMenzies School of Health Research, Darwin, Northern Territory, Australia; ^lVictorian Infectious Diseases Service, The Royal Melbourne Hospital, and Doherty Department University of Melbourne, at the Peter Doherty Institute for Infection and Immunity, Victoria, Australia; and ^mThe University of Notre Dame Australia, Fremantle, Western Australia, Australia
*Contributed equally as co-first authors.

Drs McMullan and Campbell were involved in the conception and design, literature review process, appraisal and summary of the literature, independent review by a second author, and drafting and revision process of the manuscript, drove the coordination of this manuscript, and critically reviewed the manuscript for important intellectual content; Drs Blyth, McNeil, Montgomery, Tong, and Bowen were all involved in the conception and design, literature review process, appraisal and summary of the literature, independent review by a second author, and drafting and revision process of the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: <https://doi.org/10.1542/peds.2020-0134>

To cite: McMullan BJ, Campbell AJ, Blyth CC, et al. Clinical Management of *Staphylococcus aureus* Bacteremia in Neonates, Children, and Adolescents. *Pediatrics*. 2020;146(3):e20200134

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. 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. 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. 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, ceftazidime is likely equivalent to ASP. 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. Evidence is lacking for the efficacy of newer agents compared with β -lactams for treatment of MSSA-B in children. 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. Alternative therapeutic options include daptomycin, linezolid, and clindamycin. Ceftaroline may be considered as salvage therapy in SAB. Trimethoprim-sulfamethoxazole and adjunctive rifampicin are not routinely recommended for the treatment of SAB.	Therapeutic targets for trough monitoring in children require further research. Alternative agents may be used for SAB in children with the provisos listed above. Evidence in pediatrics is limited for newer agents. 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). Children with SAB in the context of OAI 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	<i>n</i> ^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 OAI's 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 (<i>P</i> = .02). Thirty-nine patients were excluded before randomization because they were still symptomatic on d 6 and 7 of antibiotic therapy. <i>S aureus</i> constituted 61.5% of culture isolates of neonates who were still symptomatic on d 6 and 7 (<i>P</i> = .0001).	No subjects developed deranged LFT and EUC or skin rash in either group.
Kaplan et al, ⁷ 2003, United States	66/321 with <i>S aureus</i> 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 (<i>P</i> = .36). Pathogen eradication rates in microbiologic evaluable patients were high for linezolid (94%) and vancomycin (95%) (<i>P</i> = .82).	Significantly fewer patients treated with linezolid had drug-related adverse events compared with those treated with vancomycin (19% vs 34%, respectively; <i>P</i> = .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	<i>S aureus</i> 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 \geq 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. Peak incidence in New Zealand Pacific children <1 y was high: 105 per 100 000 population per y; community-acquired infection predominated.
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 <i>S aureus</i> (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	<i>S aureus</i> 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 (65%)	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 <i>S aureus</i> 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 population¹⁹ 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 episodes⁸; 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 $\leq 2\%$ 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 recommended²³; 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 outcomes²⁴; 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

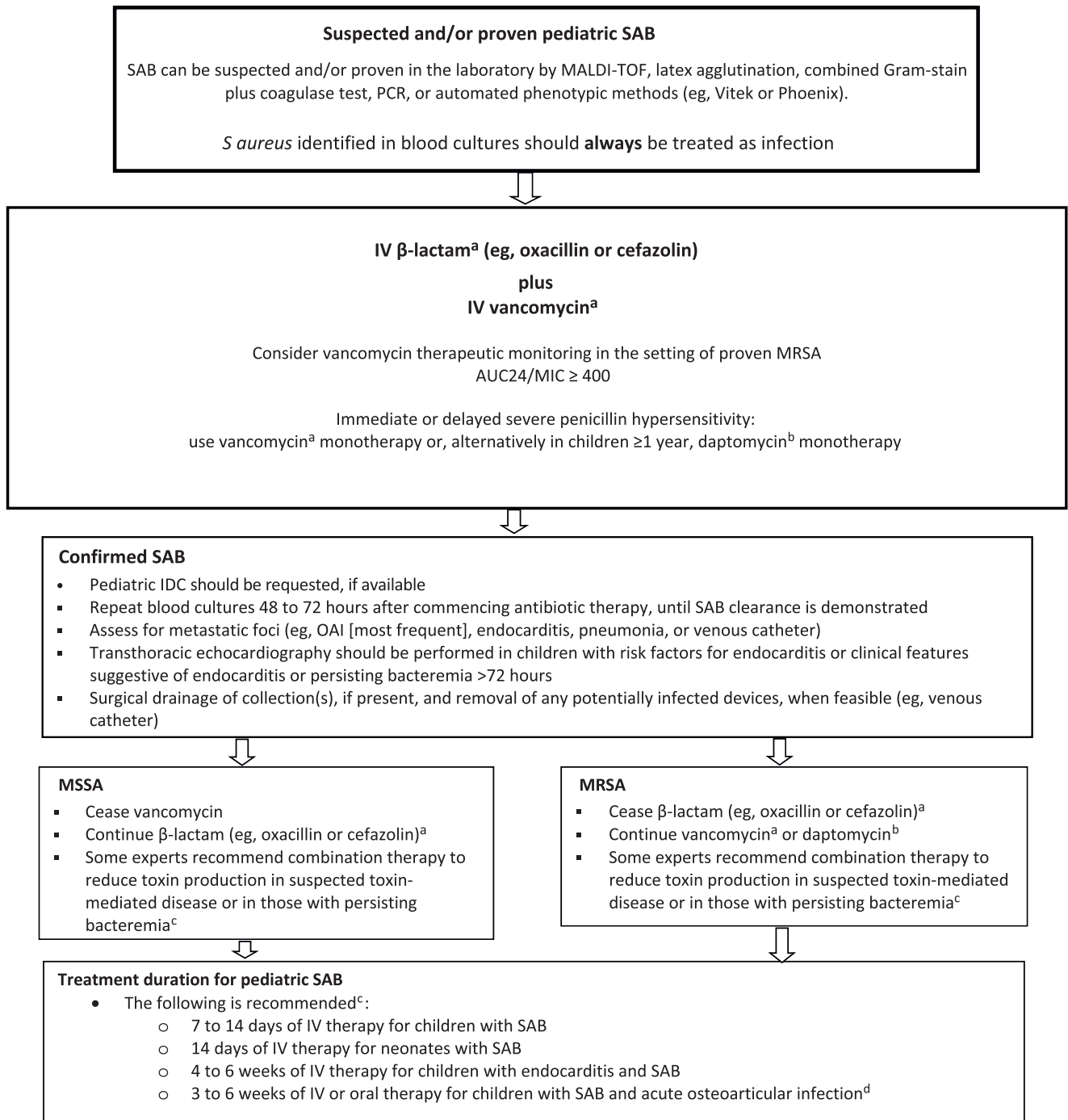


FIGURE 1

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 equivalence⁴¹ 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 telavancin⁴⁶), 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 \geq 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 OAI⁵ 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 \geq 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.

ACKNOWLEDGMENTS

We acknowledge Assistant Professor Michael Z. David for his contributions in the initial process of identifying key questions for the article and initial versions of the article.

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

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No funding was received for this study. Mr McMullan is supported by a PhD scholarship from The University of Melbourne. Drs Blyth, Campbell, Tong, and Bowen are supported by fellowships from the National Health and Medical Research Council of Australia (grant APP1088735 to Dr Blyth; grant APP1133670 to Dr Campbell; grant APP1145033 to Dr Tong; grant APP1111596 to Dr Bowen). Dr McNeil has received funding through the National Institute of Allergy and Infectious Diseases (grant K23AI099159) and The Texas Children's Hospital Pediatric Pilot Research Fund. Dr Montgomery has received funding through the National Institute of Health (grant AI125489).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Groome MJ, Albrich WC, Wadula J, Khoosal M, Madhi SA. Community-onset *Staphylococcus aureus* bacteraemia in hospitalised African children: high incidence in HIV-infected children and high prevalence of multidrug resistance. *Paediatr Int Child Health*. 2012;32(3):140–146
2. McMullan BJ, Bowen A, Blyth CC, et al. Epidemiology and mortality of *Staphylococcus aureus* bacteremia in Australian and New Zealand children. *JAMA Pediatr*. 2016;170(10):979–986
3. Blyth CC, Walls T, Cheng AC, et al. A comparison of paediatric and adult infectious diseases consultations in Australia and New Zealand. *Eur J Clin Microbiol Infect Dis*. 2015;34(8):1589–1592
4. Arrieta AC, Bradley JS, Popejoy MW, et al. Randomized multicenter study comparing safety and efficacy of daptomycin versus standard-of-care in pediatric patients with staphylococcal bacteremia. *Pediatr Infect Dis J*. 2018;37(9):893–900
5. Peltola H, Paakkonen M, Kallio P, Kallio MJT, OM-SA Study Group. Clindamycin vs. first-generation cephalosporins for acute osteoarticular infections of childhood—a prospective quasi-randomized controlled trial. *Clin Microbiol Infect*. 2012;18(6):582–589
6. Chowdhary G, Dutta S, Narang A. Randomized controlled trial of 7-day vs. 14-day antibiotics for neonatal sepsis. *J Trop Pediatr*. 2006;52(6):427–432
7. Kaplan SL, Deville JG, Yogev R, et al; Linezolid Pediatric Study Group. Linezolid versus vancomycin for treatment of resistant Gram-positive infections in children. *Pediatr Infect Dis J*. 2003;22(8):677–686
8. Shane AL, Hansen NI, Stoll BJ, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Methicillin-resistant and susceptible *Staphylococcus aureus* bacteremia and meningitis in preterm infants. *Pediatrics*. 2012;129(4). Available at: www.pediatrics.org/cgi/content/full/129/4/e914
9. Hill PC, Wong CG, Voss LM, et al. Prospective study of 125 cases of *Staphylococcus aureus* bacteremia in children in New Zealand. *Pediatr Infect Dis J*. 2001;20(9):868–873
10. Jacobsson G, Dashti S, Wahlberg T, Andersson R. The epidemiology of and risk factors for invasive *Staphylococcus aureus* infections in western Sweden. *Scand J Infect Dis*. 2007;39(1):6–13
11. Fortuin-de Smidt MC, Singh-Moodley A, Badat R, et al; for GERMS-SA. *Staphylococcus aureus* bacteraemia in Gauteng academic hospitals, South Africa. *Int J Infect Dis*. 2015;30:41–48
12. Friedland IR, du Plessis J, Cilliers A. Cardiac complications in children with *Staphylococcus aureus* bacteremia. *J Pediatr*. 1995;127(5):746–748
13. Valente AM, Jain R, Scheurer M, et al. Frequency of infective endocarditis among infants and children with *Staphylococcus aureus* bacteremia. *Pediatrics*. 2005;115(1):e15–9
14. McNeil JC, Ligon JA, Hulten KG, et al. *Staphylococcus aureus* infections in children with congenital heart disease. *J Pediatric Infect Dis Soc*. 2013;2(4):337–344
15. Thwaites GE, Edgeworth JD, Gkrania-Klotsas E, et al; UK Clinical Infection Research Group. Clinical management of *Staphylococcus aureus* bacteraemia. *Lancet Infect Dis*. 2011;11(3):208–222
16. Perl TM, Golub JE. New Approaches to Reduce *Staphylococcus Aureus* Nosocomial Infection Rates: Treating *S. Aureus* Nasal Carriage. In: *Ann Pharmacother*, vol. 32. 1998:S7–S16
17. Centers for Disease Control and Prevention. *Active Bacterial Core Surveillance Report, Emerging Infections Program Network, Methicillin-Resistant Staphylococcus Aureus, 2015*. Atlanta, GA: Centers for Disease Control and Prevention; 2017
18. Public Health England. *Annual Epidemiology Commentary: Mandatory MRSA, MSSA and E. Coli Bacteraemia and C. Difficile Infection Data 2016/17*. London, England: Public Health England; 2017
19. Kempker RR, Farley MM, Ladson JL, Satola S, Ray SM. Association of methicillin-resistant *Staphylococcus aureus* (MRSA) USA300 genotype with mortality in MRSA bacteremia. *J Infect*. 2010;61(5):372–381
20. Vanderkooi OG, Gregson DB, Kellner JD, Laupland KB. *Staphylococcus aureus* bloodstream infections in children: a population-based assessment. *Paediatr Child Health*. 2011;16(5):276–280
21. Kempley S, Kapellou O, McWilliams A, Banerjee J, McCorquodale A, Millar M. Antibiotic treatment duration and

- prevention of complications in neonatal *Staphylococcus aureus* bacteraemia. *J Hosp Infect.* 2015;91(2):129–135
22. Tong SY, van Hal SJ, Einsiedel L, Currie BJ, Turnidge JD; Australian New Zealand Cooperative on Outcomes in Staphylococcal Sepsis. Impact of ethnicity and socio-economic status on *Staphylococcus aureus* bacteremia incidence and mortality: a heavy burden in indigenous Australians. *BMC Infect Dis.* 2012;12:249
 23. Liu C, Bayer A, Cosgrove SE, et al; Infectious Diseases Society of America. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children [published correction appears in *Clin Infect Dis.* 2011;53(3):319]. *Clin Infect Dis.* 2011;52(3):e18–e55
 24. Hamdy RF, Hsu AJ, Stockmann C, et al. Epidemiology of methicillin-resistant *Staphylococcus aureus* bacteremia in children. *Pediatrics.* 2017;139(6): e20170183
 25. Roediger JC, Outhred AC, Shadbolt B, Britton PN. Paediatric *Staphylococcus aureus* bacteraemia: a single-centre retrospective cohort. *J Paediatr Child Health.* 2017;53(2):180–186
 26. Chuang YY, Huang YC, Lee CY, Lin TY, Lien R, Chou YH. Methicillin-resistant *Staphylococcus aureus* bacteraemia in neonatal intensive care units: an analysis of 90 episodes. *Acta Paediatr.* 2004;93(6):786–790
 27. Le J, Dam Q, Tran T, et al. Epidemiology and hospital readmission associated with complications of *Staphylococcus aureus* bacteremia in pediatrics over a 25-year period. *Epidemiol Infect.* 2017; 145(12):2631–2639
 28. Fowler VG Jr, Olsen MK, Corey GR, et al. Clinical identifiers of complicated *Staphylococcus aureus* bacteremia. *Arch Intern Med.* 2003;163(17):2066–2072
 29. Carpenter SL, Goldman J, Sherman AK, et al. Clinical variables and *Staphylococcus aureus* virulence factors associated with venous thromboembolism in children. *Thromb Res.* 2016;138:69–73
 30. Jung N, Lehmann C, Hellmann M, et al. Necrotizing pneumonia caused by Pantone-Valentine leucocidin-producing *Staphylococcus aureus* originating from a Bartholin's abscess. *Infect Dis Obstet Gynecol.* 2008;2008:491401
 31. Naidoo R, Nuttall J, Whitelaw A, Eley B. Epidemiology of *Staphylococcus aureus* bacteraemia at a tertiary children's hospital in Cape Town, South Africa. *PLoS One.* 2013;8(10):e78396
 32. Storch GA, Rajagopalan L. Methicillin-resistant *Staphylococcus aureus* bacteremia in children. *Pediatr Infect Dis.* 1986;5(1):59–67
 33. Saunderson RB, Gouliouris T, Cartwright EJ, et al. Impact of infectious diseases consultation on the management of *Staphylococcus aureus* bacteraemia in children. *BMJ Open.* 2014;4(7):e004659
 34. Humpl T, McCrindle BW, Smallhorn JF. The relative roles of transthoracic compared with transesophageal echocardiography in children with suspected infective endocarditis. *J Am Coll Cardiol.* 2003;41(11):2068–2071
 35. Turnidge JD, Kotsanas D, Munckhof W, et al; Australia New Zealand Cooperative on Outcomes in Staphylococcal Sepsis. *Staphylococcus aureus* bacteraemia: a major cause of mortality in Australia and New Zealand. *Med J Aust.* 2009;191(7):368–373
 36. Gholamrezaezhad A, Basques K, Batouli A, Matcuk G, Alavi A, Jadvar H. Clinical nononcologic applications of PET/CT and PET/MRI in musculoskeletal, orthopedic, and rheumatologic imaging. *AJR Am J Roentgenol.* 2018; 210(6):W245–W263
 37. van Schuppen J, van Doorn MMAC, van Rijn RR. Childhood osteomyelitis: imaging characteristics. *Insights Imaging.* 2012;3(5):519–533
 38. McDanel JS, Perencevich EN, Diekema DJ, et al. Comparative effectiveness of beta-lactams versus vancomycin for treatment of methicillin-susceptible *Staphylococcus aureus* bloodstream infections among 122 hospitals. *Clin Infect Dis.* 2015;61(3):361–367
 39. Antibiotic Expert Group. Directed Therapy for Infective Endocarditis. In: *Therapeutic Guidelines: Antibiotic. Version 16.* Melbourne, Australia: Therapeutic Guidelines Limited; 2019
 40. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America [published corrections appear in *Clin Infect Dis.* 2010;50(7):1079 and *Clin Infect Dis.* 2010;50(3):457]. *Clin Infect Dis.* 2009; 49(1):1–45
 41. Rindone JP, Mellen CK. Meta-analysis of trials comparing ceftazolin to antistaphylococcal penicillins in the treatment of methicillin-sensitive *Staphylococcus aureus* bacteraemia. *Br J Clin Pharmacol.* 2018;84(6):1258–1266
 42. McDanel JS, Roghmann MC, Perencevich EN, et al. Comparative effectiveness of ceftazolin versus nafcillin or oxacillin for treatment of methicillin-susceptible *Staphylococcus aureus* infections complicated by bacteremia: a nationwide cohort study. *Clin Infect Dis.* 2017;65(1):100–106
 43. Davis JS, Turnidge J, Tong S. A large retrospective cohort study of ceftazolin compared with flucloxacillin for methicillin-susceptible *Staphylococcus aureus* bacteraemia. *Int J Antimicrob Agents.* 2018;52(2):297–300
 44. Rehm S, Champion M, Katz DE, Russo R, Boucher HW. Community-based outpatient parenteral antimicrobial therapy (CoPAT) for *Staphylococcus aureus* bacteraemia with or without infective endocarditis: analysis of the randomized trial comparing daptomycin with standard therapy. *J Antimicrob Chemother.* 2009;63(5):1034–1042
 45. Fowler VG Jr, Boucher HW, Corey GR, et al; S. aureus Endocarditis and Bacteremia Study Group. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus.* *N Engl J Med.* 2006;355(7):653–665
 46. Stryjewski ME, Lentnek A, O'Riordan W, et al. A randomized phase 2 trial of telavancin versus standard therapy in patients with uncomplicated *Staphylococcus aureus* bacteremia: the ASSURE study. *BMC Infect Dis.* 2014;14:289
 47. Paul M, Bishara J, Yahav D, et al. Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by methicillin resistant

- Staphylococcus aureus: randomised controlled trial. *BMJ*. 2015;350:h2219
48. Rybak MJ, Le J, Lodise TP, et al. Executive summary: therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: a revised consensus guideline and review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Pharmacotherapy*. 2020;40(4):363–367
 49. Frymoyer A, Guglielmo BJ, Hersh AL. Desired vancomycin trough serum concentration for treating invasive methicillin-resistant Staphylococcal infections. *Pediatr Infect Dis J*. 2013; 32(10):1077–1079
 50. Kishk OA, Lardieri AB, Heil EL, Morgan JA. Vancomycin AUC/MIC and corresponding troughs in a pediatric population. *J Pediatr Pharmacol Ther*. 2017;22(1):41–47
 51. Frymoyer A, Hersh AL, El-Komy MH, et al. Association between vancomycin trough concentration and area under the concentration-time curve in neonates. *Antimicrob Agents Chemother*. 2014;58(11):6454–6461
 52. McNeil JC, Kaplan SL, Vallejo JG. The influence of the route of antibiotic administration, methicillin susceptibility, vancomycin duration and serum trough concentration on outcomes of pediatric Staphylococcus aureus bacteremic osteoarticular infection. *Pediatr Infect Dis J*. 2017;36(6):572–577
 53. McNeil JC, Kok EY, Forbes AR, et al. Healthcare-associated Staphylococcus aureus bacteremia in children: evidence for reverse vancomycin creep and impact of vancomycin trough values on outcome. *Pediatr Infect Dis J*. 2016;35(3):263–268
 54. Abdel-Rahman SM, Benziger DP, Jacobs RF, Jafri HS, Hong EF, Kearns GL. Single-dose pharmacokinetics of daptomycin in children with suspected or proved gram-positive infections. *Pediatr Infect Dis J*. 2008;27(4):330–334
 55. Wible K, Tregnaghi M, Bruss J, Fleishaker D, Naberhuis-Stehouwer S, Hilty M. Linezolid versus cefadroxil in the treatment of skin and skin structure infections in children. *Pediatr Infect Dis J*. 2003;22(4):315–323
 56. Krzysztofiak A, Bozzola E, Lancella L, et al. Linezolid therapy in a perinatal late-onset Staphylococcus aureus sepsis complicated by spondylodiscitis and endophthalmitis. *Infez Med*. 2015; 23(4):353–357
 57. Miyamoto T, Tomoyasu T, Miyaji K. Successful treatment of pediatric endocarditis and pericarditis due to MRSA with linezolid. *Jpn J Antibiot*. 2011;64(2):109–112
 58. Chen CJ, Chiu CH, Lin TY, Lee ZL, Yang WE, Huang YC. Experience with linezolid therapy in children with osteoarticular infections. *Pediatr Infect Dis J*. 2007; 26(11):985–988
 59. Gould FK. Linezolid: safety and efficacy in special populations. *J Antimicrob Chemother*. 2011;66(suppl 4):iv3–iv6
 60. Cannavino CR, Nemeth A, Korczowski B, et al. A randomized, prospective study of pediatric patients with community-acquired pneumonia treated with ceftaroline versus ceftriaxone. *Pediatr Infect Dis J*. 2016;35(7):752–759
 61. Friedland HD, O'Neal T, Biek D, et al. CANVAS 1 and 2: analysis of clinical response at day 3 in two phase 3 trials of ceftaroline fosamil versus vancomycin plus aztreonam in treatment of acute bacterial skin and skin structure infections. *Antimicrob Agents Chemother*. 2012;56(5):2231–2236
 62. File TM Jr., Low DE, Eckburg PB, et al. Integrated analysis of FOCUS 1 and FOCUS 2: randomized, double-blind, multicenter phase 3 trials of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. *Clin Infect Dis*. 2010;51(12):1395–1405
 63. File TM Jr., Low DE, Eckburg PB, et al; FOCUS 1 investigators. FOCUS 1: a randomized, double-blinded, multicentre, phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. *J Antimicrob Chemother*. 2011;66(suppl 3):iii19–iii32
 64. Polenakovic HM, Pleiman CM. Ceftaroline for methicillin-resistant Staphylococcus aureus bacteraemia: case series and review of the literature. *Int J Antimicrob Agents*. 2013;42(5):450–455
 65. Martínez-Aguilar G, Hammerman WA, Mason EO Jr., Kaplan SL. Clindamycin treatment of invasive infections caused by community-acquired, methicillin-resistant and methicillin-susceptible Staphylococcus aureus in children. *Pediatr Infect Dis J*. 2003;22(7):593–598
 66. Watanakunakorn C. Clindamycin therapy of Staphylococcus aureus endocarditis. Clinical relapse and development of resistance to clindamycin, lincomycin and erythromycin. *Am J Med*. 1976;60(3):419–425
 67. Engelman D, Hofer A, Davis JS, et al. Invasive Staphylococcus aureus infections in children in tropical northern Australia. *J Pediatric Infect Dis Soc*. 2014;3(4):304–311
 68. Faville RJ Jr., Zask DE, Kaplan EL, Crossley K, Sabath LD, Quie PG. Staphylococcus aureus endocarditis. Combined therapy with vancomycin and rifampin. *JAMA*. 1978;240(18):1963–1965
 69. Tan TQ, Mason EO Jr., Ou CN, Kaplan SL. Use of intravenous rifampin in neonates with persistent staphylococcal bacteremia. *Antimicrob Agents Chemother*. 1993;37(11):2401–2406
 70. Thwaites GE, Scarborough M, Szubert A, et al; United Kingdom Clinical Infection Research Group (UKCIRG). Adjunctive rifampicin for Staphylococcus aureus bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. 2018; 391(10121):668–678
 71. Cosgrove SE, Vigliani GA, Fowler VG Jr., et al. Initial low-dose gentamicin for Staphylococcus aureus bacteremia and endocarditis is nephrotoxic. *Clin Infect Dis*. 2009;48(6):713–721
 72. Falagas ME, Matthaiou DK, Bliziotis IA. The role of aminoglycosides in combination with a beta-lactam for the treatment of bacterial endocarditis: a meta-analysis of comparative trials. *J Antimicrob Chemother*. 2006;57(4):639–647
 73. McMullan BJ, Andresen D, Blyth CC, et al; ANZPID-ASAP group. Antibiotic duration and timing of the switch from intravenous to oral route for bacterial infections in children: systematic review and guidelines. *Lancet Infect Dis*. 2016;16(8):e139–e152
 74. Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. *N Engl J Med*. 2019;380(5):415–424

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

Brendan J. McMullan, Anita J. Campbell, Christopher C. Blyth, J. Chase McNeil,
Christopher P. Montgomery, Steven Y.C. Tong and Asha C. Bowen
Pediatrics originally published online August 5, 2020;

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/early/2020/08/03/peds.2020-0134>

References

This article cites 70 articles, 8 of which you can access for free at:
<http://pediatrics.aappublications.org/content/early/2020/08/03/peds.2020-0134#BIBL>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):
Evidence-Based Medicine
http://www.aappublications.org/cgi/collection/evidence-based_medicine_sub
Infectious Disease
http://www.aappublications.org/cgi/collection/infectious_diseases_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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

Brendan J. McMullan, Anita J. Campbell, Christopher C. Blyth, J. Chase McNeil,
Christopher P. Montgomery, Steven Y.C. Tong and Asha C. Bowen
Pediatrics originally published online August 5, 2020;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/early/2020/08/03/peds.2020-0134>

Data Supplement at:

<http://pediatrics.aappublications.org/content/suppl/2020/08/03/peds.2020-0134.DCSupplemental>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2020 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

