

**Cook Children's Medical Center  
Clinical Excellence Committee**

**Evidence based pathway for the diagnosis and management of *Staphylococcus aureus* bacteremia**

**Inclusion Criteria:**

- Children and adolescents, birth – 18 years of age, with *Staphylococcus aureus* bacteremia

**Exclusion Criteria:**

- Older than 18 years

**Background:**

*Staphylococcus aureus* is a leading cause of both community- and healthcare-associated bacteremia in children. *S. aureus* bacteremia (SAB) is associated with increased morbidity and mortality, even with appropriate therapy. Fifty to 60% of SABs are healthcare associated and 40-50% are community associated. [1, 2] Pediatric mortality ranges from 2-8%. [3]

All episodes of SAB in children should be considered clinically significant. [1-4] Outcomes are improved with Infectious Diseases consultation and optimal antimicrobial therapy. [3, 5, 6]

**Risk Factors:**

Risk factors for increased mortality in children include age less than 1 year, central venous catheters, concurrent pneumonia, sepsis syndrome, endocarditis, or if no focus is identified. [4-6] Mortality may be as high as 15% in children with risk factors. [6] Risk factors within these groups may be additive.[4]

The source of infection in children often differs from that of adults. The approach to treatment of SAB in pediatrics depends on the likely source and severity of infection, and whether it is community associated or healthcare associated. The local prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the community is important to know if it is a community associated infection.[2, 4] According to the Cook Children's Medical Center (CCMC) [2021](#) Antibigram, 32% (306/956) of *S. aureus* isolates were resistant to methicillin (MRSA).

## Infection Source:

Although SAB can occur in 5-7% of patients without a focus of infection, most SAB in children are associated with a localizing infection source.[2, 4, 7]:

- Bone and joint infections
- Pneumonia
- Skin and soft tissue infections
- Invasive devices (e.g., central venous catheters)

## Clinical Features of Complicated SAB [4]:

- Positive blood cultures > 48-72 hours on therapy
- Fever > 3 days while on appropriate antibiotic therapy
- Multiple sites of infection
- Endocarditis
- Complex local disease involving multiple adjacent tissue structures (e.g., Deep venous thrombosis (DVT) and bone)

## Diagnosis:

*S. aureus* isolated from the blood should always be considered clinically significant and treated with appropriate antibiotic therapy. [4]

Positive blood cultures demonstrating gram-positive cocci in clusters on Gram stain will be tested by the Verigene Gram-Positive Blood Culture Panel, which includes targets for *S. aureus* and the *mecA* gene.

- If *S. aureus* and *mecA* are detected, a presumptive identification of “*Staphylococcus aureus* (MRSA)” will be reported. Verigene is 99% accurate in determining if the *mecA* gene is present
- If *S. aureus* is detected but *mecA* is **not** detected, a presumptive identification of “*Staphylococcus aureus*” will be reported until antimicrobial susceptibility testing is performed to determine if MSSA or MRSA
- Identification will be confirmed and full susceptibility testing will be performed once the isolate grows on solid media

Transthoracic echocardiogram (TTE) is recommended in patients **with 1 or more** of the following: [4]

1. Structurally abnormal hearts (including pacemakers)
2. Sustained bacteremia ( $\geq 2$  days while on active antibiotics)
3. Persistent fever ( $\geq 7$  days)
4. Clinical features suggestive of endocarditis (eg, new or changing murmur, septic emboli, positive repeat blood cultures, multiple sites of infection)

## Management:

- At CCMC, an **Infectious Diseases (ID) consultation is strongly recommended** for all *S. aureus* bacteremia infections. Patients with SAB will also need follow up in the outpatient setting.
  - Meta-analyses have shown that ID consultation for SAB results in increased adherence to best practices, with lower rates of mortality and recurrent bacteremia. Studies including only children have also demonstrated improvement in investigation, management, and outcome of SAB with ID consultation.[3-6]
  - Infectious Diseases consultant can help to determine the need for additional evaluation such as an immunology referral in those patients with severe and fulminant presentations
- Removal of Infectious Foci [7, 8]:
  - Intravascular catheter removal
    - For catheter-related SAB, optimal management includes removal of the infected catheter. However benefits of catheter removal must be weighed against the difficulties of obtaining alternative venous access. Treatment with antibiotics without catheter removal is reasonable if the child is not in shock, fever resolves, bacteria clears, and has no evidence of infected thrombus or distant sites of infection
    - Indwelling catheters with obvious tract infection require removal
    - If catheter remain in place, both systemic and antibiotic lock therapy may be warranted (See Antibiotic Lock Therapy Policy PS 701)
- Surgical intervention
  - Surgical intervention is often warranted in children with infectious foci (e.g., osteomyelitis, septic arthritis, skin abscesses)

## Empiric Antibiotic Treatment [4]:

Empiric treatment is largely based on severity and source of infection.

First Line Empiric for Life-Threatening Infection with Suspected SAB: IV Vancomycin plus IV Beta-lactam (e.g., Oxacillin or Cefazolin)

- Cefazolin is considered equivalent to anti-staphylococcal penicillins
- Cefazolin has limited central nervous system (CNS) penetration and should not be used if concerned with CNS infection

**Table 1 Comparison of Oxacillin and Cefazolin for Treatment of MSSA Bacteremia [9]**

	<b>Oxacillin</b>	<b>Cefazolin</b>
<b>Advantages</b>	<ul style="list-style-type: none"> <li>• Gold standard of therapy</li> <li>• Not susceptible to inoculum effect</li> <li>• Good CNS penetration</li> <li>• Narrower spectrum of activity</li> </ul>	<ul style="list-style-type: none"> <li>• Lower rate of adverse reactions</li> <li>• Less frequent dosing regimen</li> <li>• Less expensive</li> </ul>
<b>Disadvantages</b>	<ul style="list-style-type: none"> <li>• Higher rates of adverse reactions</li> <li>• More frequent dosing regimen</li> <li>• More expensive</li> </ul>	<ul style="list-style-type: none"> <li>• Susceptible to inoculum effect</li> <li>• Poor CNS penetration</li> <li>• Broader spectrum of activity</li> </ul>

**Table 2 Empiric Treatment of SAB\***

<b>Empiric Antibiotics</b>	<b>Allergy/Alternative to immediate or delayed severe Penicillin allergy or intolerance</b>	<b>Comments</b>
Vancomycin 15mg/kg IV q6-8h <sup>^</sup>	Daptomycin IV <ul style="list-style-type: none"> <li>• ≤ 6 years old: 12mg/kg once daily</li> <li>• 7-11 years old: 9mg/kg once daily</li> <li>• 12-17 years old: 7mg/kg once daily</li> <li>• ≥ 18 years old: 6mg/kg once daily</li> </ul>	Do not use Daptomycin if lung involvement because it is inactivated by lung surfactant
Oxacillin 50mg/kg IV q6h Plus Vancomycin 15mg/kg IV q6-8h <sup>^</sup>	or Ceftaroline <ul style="list-style-type: none"> <li>• 15mg/kg IV q8h (max dose 600mg)</li> </ul>	Ceftaroline is restricted to ID
Cefazolin 50mg/kg IV q8h Plus Vancomycin 15mg/kg IV q6-8h <sup>^</sup>	or Linezolid IV/PO <ul style="list-style-type: none"> <li>• &lt;12 years 10mg/kg q8h (max dose 600mg)</li> <li>• ≥12 years 10mg/kg q12h (max dose 600mg)</li> </ul>	Recommend to avoid use of Linezolid in complicated bacteremia or in immunocompromised patients

\*IV Vancomycin plus IV Beta-lactam recommended life-threatening infections with SAB (e.g., sepsis, admitted to PICU, on pressers)

<sup>^</sup>Refer to CCMC Vancomycin Dosing Guidelines

## **Definitive Antibiotic Treatment [4]:**

### **Methicillin-susceptible *Staphylococcus aureus* (MSSA)**

- Stop Vancomycin
  - Inferior outcomes are reported in MSSA bacteremia treated with vancomycin compared with beta-lactams[10]
- Continue/start Oxacillin or Cefazolin
  - If allergy to beta-lactams, continue Vancomycin
  - Additional options may include Daptomycin or Ceftaroline if not able to tolerate Vancomycin due to allergies, renal issues, or unable to reach therapeutic levels

### **Methicillin-resistant *Staphylococcus aureus* (MRSA)**

- Stop Oxacillin or Cefazolin
- Continue Vancomycin (preferred)
  - Daptomycin is an alternative if not able to tolerate Vancomycin due to allergies, renal issues, or unable to reach therapeutic levels
  - Daptomycin should not be used if SAB is associated with a lung infection because lung surfactant inactivates Daptomycin.
- Consider using double coverage as salvage therapy or for complicated bacteremia with Daptomycin and Ceftaroline
  - Combination therapy may not be needed for entire duration (e.g., combination therapy for high inoculum phase followed by monotherapy for consolidation phase)[11]

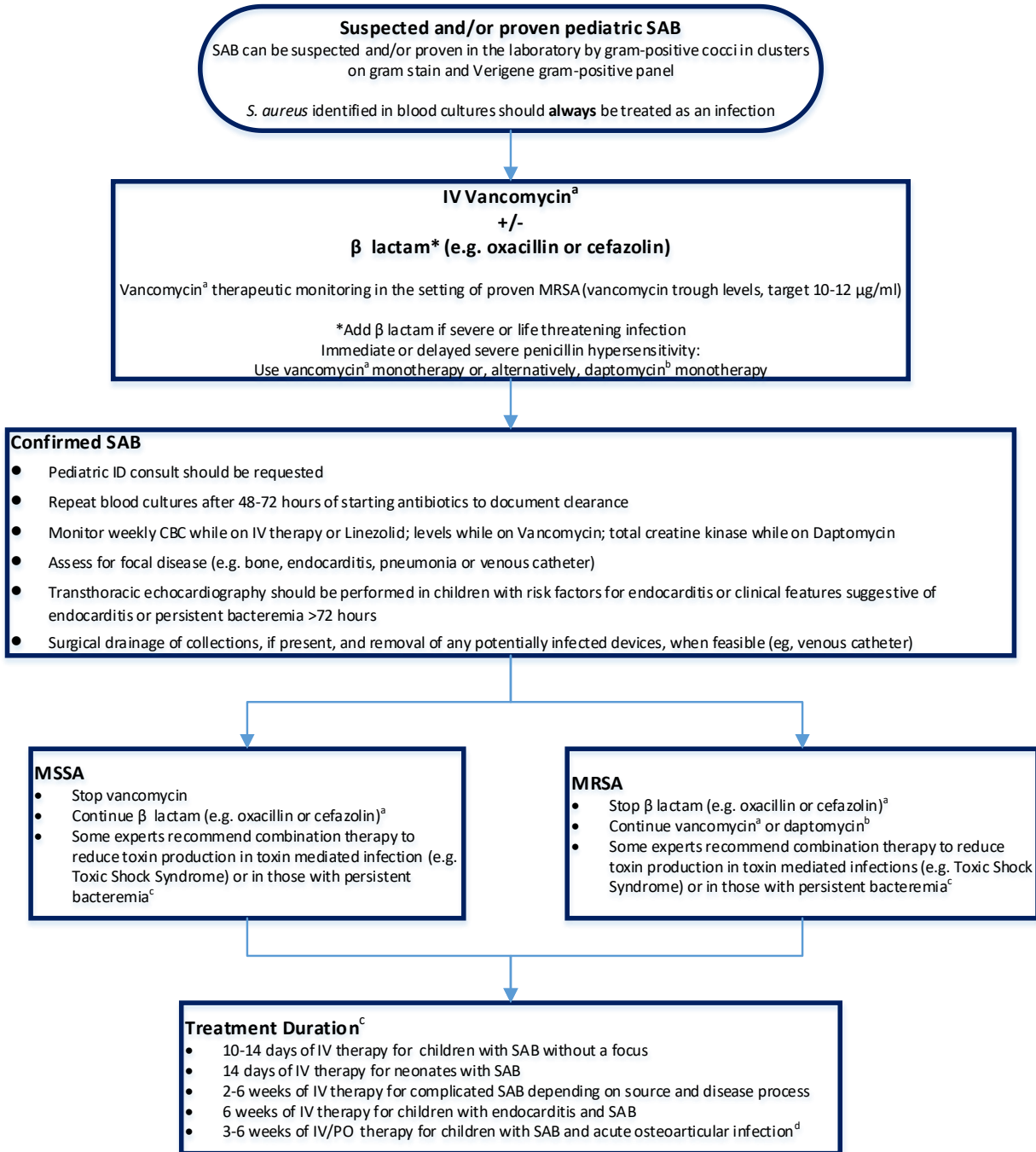
## **Other Alternatives for MRSA [4, 12, 13]:**

Bacteriostatic agents are not recommended if there is a concern for endocarditis or an endovascular source due to higher rate of relapse or failure. Some experts recommend using bactericidal agents in immunocompromised patients with SAB.

- Ceftaroline
  - Bactericidal cephalosporin with activity against MRSA
  - FDA approved for Skin and soft tissue infections (SSTI) and Community acquired pneumonia (CAP) in 2010, later approved for SAB with SSTI in 2015
  - Has been used in salvage therapy or as part of combination therapy in persistent MRSA
- Linezolid
  - Bacteriostatic antibiotic with high bioavailability and tissue penetration that is available as oral or parenteral formulations
  - Evidence for SAB is limited to case reports and series, may consider if bacteremia rapidly clears and is not related to an endovascular source (e.g., osteomyelitis with rapidly cleared bacteremia)

- Toxicity may include bone marrow suppression and, uncommonly, peripheral or optic neuropathy. Toxicities more likely to occur after 2 weeks of treatment
- Clindamycin
  - Bacteriostatic antibiotic with high bioavailability and tissue penetration (limited CNS penetration) that is available as oral or parenteral formulations
  - Has not been studied in randomized controlled trials (RCTs) for SAB and is not recommended for monotherapy due to higher rate of relapse/failure in bacteremia/endocarditis
  - May consider in clinically stable patients with uncomplicated bacteremia if bacteremia rapidly clears and is not related to an endovascular source (e.g., pneumonia or musculoskeletal infections with rapidly cleared bacteremia)
  - May be useful in suspected toxin-mediated disease or as part of combination therapy in persistent MRSA bacteremia
- Rifampin
  - No RCTs have been reported on the adjunctive use of rifampin for SAB in children and routine use in SAB is not recommended
  - Standard of care with other antibiotics in patients with prosthetic material in endocarditis

# Algorithm for Pediatric SAB



<sup>a</sup> In the setting of renal failure, dose adjustment may be required.

<sup>b</sup> Do not use daptomycin to treat SAB with pneumonia or lung involvement.

<sup>c</sup> There are no randomized clinical trials (outside the neonatal period) to inform treatment duration or the value of combination therapy for SAB in children.

<sup>d</sup> There is evidence to support switching to oral therapy as soon as patient is clinically stable with clearance of SAB.

**Duration [4]:**

There are no RCTs (outside of neonatal period) to inform treatment duration. Recommendations are based largely on historical practice and expert opinion.

Consider PICC line placement to complete IV therapy after 2 consecutive sterile blood cultures.

- 10-14 days of IV therapy for children with SAB without a focus
  - In consultation with an Infectious Diseases Specialist, may consider switching to oral therapy to complete course based on clinical presentation and labs
- 14 days of IV therapy for neonates with SAB
- 2-6 weeks of IV therapy for complicated SAB depending on source and disease process (e.g., multifocal sites of infection, DVT)
- 6 weeks of IV therapy for children with SAB with acute endocarditis
- 3-6 weeks of IV/PO therapy for children with SAB with acute osteoarticular infection
  - There is evidence to support switching to oral therapy as soon as the patient is clinically stable with clearance of SAB and symptom resolution is achieved

[MRSA-Decolonization 2022.pdf](#)

[MRSA-Decolonization Maintenance 2022.pdf](#)

**Monitoring [4]:**

1. Repeat blood culture 48-72 hours after initial positive blood culture once to document clearance of bacteremia as SAB may persist even when fever has resolved
  - a. In complicated bacteremia, blood culture should be repeated until negative x3.
2. If persistent bacteremia, when source localization is not possible, consider imaging to identify a focus of infection
3. Refer to CCMC Vancomycin guidelines for dosing and monitoring of Vancomycin
4. Weekly CBC should be monitored while on IV therapy and every 2-3 weeks while on oral therapy to monitor for hematologic adverse reactions such as eosinophilia, leukopenia, thrombocytopenia. Add renal function if on a potentially nephrotoxic medication
5. Total creatine kinase should be monitored weekly with Daptomycin
6. CBC should be monitored weekly if on linezolid > 2 weeks to monitor for hematologic adverse reactions such as leukopenia and thrombocytopenia

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