Staphylococcus aureus Bloodstream Infection Treatment Guideline

Purpose: To provide a framework for the evaluation and management patients with Methicillin-Susceptible (MSSA) and Methicillin-Resistant *Staphylococcus aureus* (MRSA) bloodstream infections (BSI). The recommendations below are guidelines for care and are not meant to replace clinical judgment. The initial page includes a brief version of the guidance followed by a more detailed discussion of the recommendations with supporting evidence. Also included is an algorithm describing management of patients with blood cultures positive for gram-positive cocci.

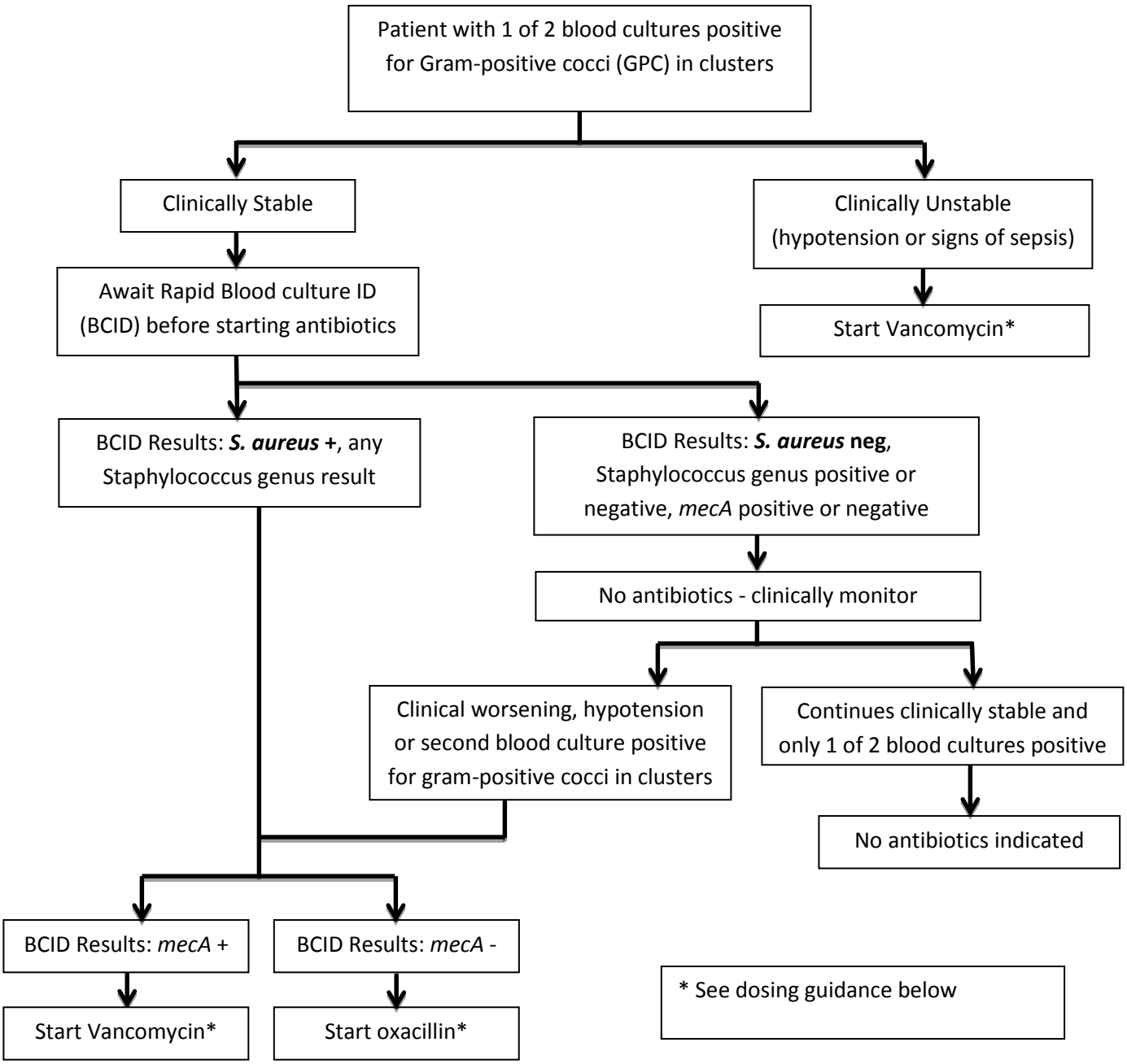
Brief Key Points:

1. **Don't ignore it –** *Staphylococcus aureus* isolated from a blood culture is never a contaminant. All patients with *S. aureus* in their blood should be treated with appropriate antibiotics and evaluated for a source of infection.
2. **Control the source**
    a. **Removing infected catheters and prosthetic devices –** Retention of infected central venous catheters and prosthetic devices in the setting of *S. aureus* bacteremia (SAB) has been associated with prolonged bacteremia, treatment failure and death. These should be removed if medically possible.
        i. Retention of prosthetic material is associated with an increased likelihood of SAB relapse and removal should be considered even if not clearly infected
    b. Evaluate for metastatic infections (endocarditis, osteomyelitis, abscesses, etc.) – Metastatic infections and endocarditis are quite common in SAB (11-31% patients with SAB have endocarditis).
        i. All patients should have a thorough history taken and exam performed with any new complaint evaluated for possible metastatic infection.
        ii. Echocardiograms should be strongly considered for all patients with SAB
        iii. All patients with a prosthetic valve, pacemaker/ICD present, or persistent bacteremia (follow up blood cultures positive) should undergo a transesophageal echocardiogram
3. **Document clearance** – Repeat blood cultures 48-72 hours after initial positive cultures to document clearance of bacteremia as SAB may persist even when fever has a resolved.
    a. Positive repeat blood cultures are a predictor for metastatic infection or endocarditis and should prompt an in-depth investigation for these conditions
    b. If repeat blood cultures are positive do not repeat more frequently than every 48-72 hours

4. **Treat with the right drug at the right dose** – Place patients on the most effective therapy as soon as possible
    - **a.** If Methicillin-susceptible *S. auerus* (MSSA) use a beta-lactam
        - **i.** Oxacillin 2g q4h (preferred)
        - **ii.** Non-severe beta-lactam allergy: Cefazolin 2g q8h
    - **b.** If Methicillin-resistant *S. aureus* (MRSA) use vancomycin routinely
        - **i.** Vancomycin 15 mg/kg q12h
        - **ii.** Do not change therapy based on vancomycin MIC
    - **c.** Patients who are not responding to therapy after 5-7 days may be considered for change to an alternative agent (daptomycin preferred)
5. **Treat for the right duration** – Failure to treat SAB for an adequate duration results in increased rates of relapse and trends toward increased treatment failure
    a. The minimum treatment duration for uncomplicated SAB (see #6 below for definition) is 2 weeks, generally IV, but the majority of patients should receive 4-6 weeks of therapy
6. **Involve Infectious Disease early** – Studies have shown that ID involvement in the management of SAB is associated with improved detection of metastatic infection and adherence to treatment guidelines with decreased relapse rates and mortality

Gram-positive cocci Blood Culture Treatment Algorithm

Patients who have not been initiated on antimicrobials and have a blood culture positive for Gram-positive cocci should be evaluated and treated based upon the algorithm below.



Management of *Staphylococcus aureus* Bacteremia

1. Recommended Therapy for *S. aureus* Bacteremia
    a. **MSSA**: Studies have shown that treatment with vancomycin is associated with increased mortality risk compared to beta-lactam therapy even when therapy was altered after culture results identified MSSA. Convenience of vancomycin dosing does not outweigh the potential benefits of beta-lactams in treatment of MSSA bacteremia. (Schweizer et al. *BMC Infect Dis*. 2011;11:279-286)
        i. Preferred First -line: Oxacillin 2 g IV q4h
            1. Penicillin G 4 million units IV q4h while clinically equivalent should not be used unless the presence of an inducible beta-lactamase has been ruled out by the microbiology lab (available by request)
        ii. Safe in those with non-severe penicillin allergy: Cefazolin 2 g IV q8h
            1. MSSA isolates are considered susceptible to other beta-lactams such as ampicillin/sulbactam, piperacillin/tazobactam, cefepime, ceftriaxone, ertapenem, and meropenem. There is a lack of clinical data supporting the use of these agents in bacteremia, but in mixed infections they are considered active and the addition of another agent such as vancomycin is unnecessary.
        iii. Third-line: Vancomycin 15 mg/kg IV q12h (first line for severe PCN allergy)
    b. **MRSA**:
        i. Preferred First-line: Vancomycin 15 mg/kg IV q12h
            1. Vancomycin should not be avoided based on elevated but susceptible MIC values (see #7 below for when to consider alternative therapy)
            2. Trough levels of 15-20 should be targeted and consultation with pharmacy is recommended.
        ii. Second-line: Daptomycin 6 mg/kg IV q24h

2. Additional antimicrobial agents
    a. The routine addition of agents such as rifampin or gentamicin is not recommended
        i. Gentamicin use provides little clinical benefit and has been associated with increased nephrotoxicity even when only used for a short time (Cosgrove SE, et al. *Clin Infect Dis*. 2009;48:713-21)
        ii. Rifampin use is associated with increased drug interactions and toxicity but it does have a role in infections where prosthetic devices are present such as prosthetic heart valves, pacemakers, or prosthetic joints
            1. Rifampin should not be added without the input of the infectious disease team
            2. Rifampin should **NEVER** be used alone as resistance rapidly develops

3. Repeat blood cultures in 48-72 hours to document clearance of bacteremia

a. Positive repeat blood cultures are a predictor for endocarditis and metastatic infection and should prompt an in-depth investigation for these conditions
b. Continue to repeat blood culture no more frequently than every 48-72 hours until clearance is achieved

4. Catheter and Prosthetic Device Management
    a. *S. aureus* has many virulence factors which allow it to colonize and infect metal and plastic surfaces and catheters and other prosthetic devices are often infected by *S. aureus* without any clinical signs of infection
    b. Any prosthetic device or intra-vascular catheter present at the time of SAB should be considered infected until that infection is ruled out
        i. An attempt should be made to remove all prosthetic devices. In one study the retention of indwelling foreign bodies was associated with an 18-fold increase in the risk of *S. aureus* BSI relapse. (Fowler VG, et al. *Clin Infect Dis*. 1999;179:1157-61.)
    c. Catheter management
        i. Short-term Catheter: All catheters present at the time of bacteremia should be removed immediately if possible
        ii. Long-term Catheter: All catheters should be removed unless there are major contraindications (lack of alternative venous access, patient has significant bleeding diathesis, or quality of life issues take priority over the need for reinsertion of a new catheter at another site)
    d. Other prosthetic material
        i. Due to high rates of infection even when asymptomatic, any patient with persistent SAB should have all retained prosthetic material (prosthetic valve, prosthetic joint, pacemaker/ICD, etc.) removed if possible. In such cases ID consultation is highly recommended. Removal is not always medically possible and in these cases consideration should be given to the addition of rifampin and/or long-term suppression.

5. Echocardiography should be strongly considered for all patients with SAB
    a. There is some debate over the routine use and type of echocardiogram in SAB
        i. Some studies have suggested that patients with low risk bacteremia (known source which is rapidly removed/drained, rapid resolution of fever, no repeat blood cultures positive, no prosthetic valves or intra-vascular devices, no murmur or findings to suggest endocarditis) can avoid an echocardiogram
    b. Patients who do not clearly meet the above criteria should undergo an echocardiogram
        i. Transesophageal echocardiography (TEE) is preferred over transthoracic echocardiography (TTE) due to improved sensitivity for detection of endocarditis and identification of complications such as valve abscess or perforation

ii. TEE is the test of choice in all patients with a prosthetic valve, pacemaker/ICD present, or persistent bacteremia (follow up blood cultures positive)

c. If a TEE is performed, it should generally be performed at least 3-5 days after onset of bacteremia to minimize the possibility of false-negative results.

6. Treatment Duration for *Staphylococcus aureus* Bacteremia
    a. The minimum treatment duration for *S. aureus* BSI is 14 days and duration of therapy is determined by the type of bacteremia (complicated vs. uncomplicated)
    b. **Uncomplicated:** Treat for 14 days from negative blood cultures
        i. Must meet **all** the following:
            1. Exclusion of endocarditis
            2. No evidence of metastatic infection
            3. No implanted prostheses
            4. Negative follow-up blood cultures obtained 48-72 hours after initial set
            5. Resolution of fever within 72 h of initiating effective therapy
            6. Not immunosuppressed or neutropenic
            7. Removal of any indwelling catheter
        ii. It is unknown if transition to oral therapy is safe but in patients with low risk conditions (UTI or skin/soft tissue infection without residual abscess) who meet criteria for uncomplicated BSI transition to active oral agents with good oral bioavailability (TMP/SMX, linezolid, high dose cephalexin (1g TID-QID)) may be considered
    c. **Complicated**: Treat for 28-42 days from negative blood cultures with IV therapy
        i. Defined as: patients with positive blood culture results who do not meet criteria for uncomplicated bacteremia
        ii. Specific duration of therapy defined by complications described (prolonged bacteremia vs. endocarditis vs. osteomyelitis vs. retained prosthesis, etc.)
        iii. ID consultation is strongly recommended
    d. Catheter Tip Culture positive ONLY
        i. While it is not recommended to routinely culture catheter tips, if a catheter tip culture is positive for *Staphylococcus aureus*, and blood cultures are negative patients should receive a 5–7 day course of antibiotics along with close monitoring for signs and symptoms of ongoing infection

7. Persistent *Staphylococcus aureus* Bacteremia
    a. It is not uncommon for SAB to persist for several days after the initiation of appropriate antibiotic therapy and defervescence of the patient (3-5 days).
        i. Metastatic foci and complications become more frequent in bacteremia lasting >3 days.
        ii. Failure to clear the bacteremia should prompt evaluation for metastatic foci of infection

1. Diagnostics tests to consider include TEE, CT of any affected area, MRI of spine, tagged WBC scan, or PET/CT
2. Testing should be based upon symptoms and signs of infection

iii. An Infectious Disease consult is strongly recommended

8. Infectious Disease Involvement
    a. Studies have found that patients with SAB benefit from the involvement of ID specialists
        i. Involvement of ID specialists has been associated with improved adherence to standards of care, better use of diagnostic imaging, increased diagnosis of metastatic disease, longer treatment duration, and decreased mortality (Rieg S, et al. *J Infect*. 2009;59:232-9 and Jenkins TC, et al. *Clin Infect Dis*. 2008;46:1000-8.)
        ii. ID should be consulted at the time of diagnosis of *S. aureus* BSI

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