Guidelines for Management of *Staphylococcus aureus*

Bacteremia and Infective Endocarditis

(December 2014)

Guidelines should not be viewed as rules of practice that require 100% compliance. Rather, they should be used to assist in clinical decision-making. Furthermore, guidelines may not be applicable to all patients. If questions or problems arise, then an Infectious Diseases consultant should be contacted.

Executive summary

The majority of *S. aureus* bacteremia is caused by MRSA. Vancomycin is the drug of choice for treatment of MRSA bacteremia; vancomycin troughs should be maintained at 15-20 µg/mL for bloodstream infections. In addition, proper management of *S. aureus* bacteremia requires removal of infected devices, debridement and abscess drainage. Blood cultures should be repeated every 24 hours until the blood is sterile. Four to six weeks of intravenous antibiotic therapy should be considered for *S. aureus* bacteremia unless there is convincing evidence that a shorter course of therapy is appropriate.

As the management of *Staphylococcus aureus* bacteremia can be complex and can result in serious long-term complications when not managed appropriately, identification of *S. aureus* from a blood culture will, per hospital policy, prompt automatic consultation from Infectious Diseases.

++++++++++++++++++++++++

Purpose

Over the past several years, there have been clinically significant changes in the management of *S. aureus* bacteremia. The purpose of the Guideline is to describe appropriate diagnosis and treatment of *S. aureus* bacteremia and infective endocarditis due to *S. aureus* at the VA West Los Angeles Healthcare Center.

[back to top]

Background

S. aureus bacteremia is a relative common infection:

- It may be either hospital- or community-acquired
- Approximately 70% of hospital- or community-acquired cases are caused by methicillin-resistant *S. aureus* (MRSA)
- Persistent *S. aureus* bacteremia, despite apparently effective treatment, is common; this occurs most often with MRSA, but is occasionally seen with methicillin (oxacillin) susceptible *S. aureus*.

S. aureus bacteremia is most often due to:

- Skin/soft tissue infection, which may be trivial or clinically inapparent
- Infective endocarditis (IE)
- Infected peripheral or central venous catheters (CVC)
- Pneumonia

Antimicrobial and adjunctive therapy

- The term "MRSA" connotes resistance to all β-lactam agents (penicillins, cephalosporins, carbapenems and monobactams)
- Vancomycin remains the 1st line agent of choice for treatment of MRSA bacteremia (other agents may be effective in less serious infections for which oral therapy may be appropriate)
- An increase in the relative resistance of MRSA to vancomycin has developed over the past several years and has been particularly noted at GLA; this translates into a need for more aggressive treatment and diagnostic approaches
- Proper management of *S. aureus* bacteremia requires removal of infected devices and debridement or drainage of abscesses

- Occasionally, the use of use of agents adjunctive to vancomycin (gentamicin and rifampin) or use of other agents in place of vancomycin (e.g., daptomycin or linezolid) may be considered to clear bacteremia in difficult cases

Challenges

- Difficult-to-eradicate (DTE) sites of infection include endovascular infection, infected prosthetic devices (including indwelling vascular catheters) and deep tissue infection (bone, muscle and visceral abscess)
- Persistent bacteremia (defined as positive blood cultures while on effective treatment for >48 hours) suggests either an endovascular infection or infection at another DTE site.
- DTE sites of infection due to *S. aureus* often require intravenous antimicrobial therapy for 4-6 weeks

[back to top]

Treatment

Empiric antimicrobial therapy for patients with suspected *S. aureus* bacteremia:

- Vancomycin to cover MRSA/MSSA until identification and susceptibility data are available

Targeted antimicrobial therapy for patients with proven *S. aureus* bacteremia

- Administer vancomycin until susceptibilities are known
- Change to oxacillin, if the isolate is susceptible; cefazolin should be used in patients with non-anaphylactic penicillin allergies
- Continue vancomycin if organism is determined to be MRSA—vancomycin troughs should be 15-20 µg/mL (get assistance from a clinical pharmacist)

[back to top]

Assessment & initial management of patients with documented *S. aureus* bacteremia:

Search for a focus of infection that may either have led to bacteremia, or be a consequence of bacteremia:

- Evaluate for possible infective endocarditis (EKG to assess for new conduction abnormalities and TTE to assess for vegetations)
- Infected skin entrance sites/tunnels of vascular catheters (physical exam)
- Skin/soft tissue infection (physical exam)
- Bone infection, particularly axial skeleton (CT/MRI, if clinically significant back or neck pain is present)
- Deep abscesses, including kidney, spleen and psoas muscle (consider abdominal/pelvic CT + IV contrast)

Other interventions:

- Repeat blood cultures: Obtain 2 sets of follow-up blood cultures every 24 hours until the blood is sterile, beginning with notification by the laboratory of “gram positive cocci in clusters; on

"effective" treatment, blood cultures may not become positive until 2-3 days after they were collected.
- Remove all intravascular catheters that were present around the time of onset of bacteremia.
- Do NOT change central vascular catheters (CVCs) over a guide wire—select a new site for CVC insertion, if a central catheter is warranted.

Role of echocardiography: Transthoracic echocardiography (TTE) versus transesophageal echocardiography (TEE):

- ALL cases of *S. aureus* bacteremia should prompt echocardiography to evaluate for endocarditis.
- TTE may be an appropriate initial evaluation in most patients, but a TTE that is negative for evidence of endocarditis should be used as evidence to shorten intravenous antibiotic therapy to ≤ 14 days only if all of the following criteria are met in which case NPV of TTE is in excess of 90%:

    - TTE is judged by Cardiology to be of high quality: all valves are clearly visualized
    - No valvular abnormalities (including valve thickening, bicuspid aortic valve, stenosis or regurgitation greater than "trace") are noted
    - Patient has no prior history of endocarditis or intravenous drug use
    - Patient has no prosthetic heart valves or intracardiac devices (pacemaker, ICD, etc.)
    - Patient is not hemodialysis dependent
    - Febrile illness was not present for more than 2 days prior to first blood culture yielding *S. aureus*
    - Bacteremia clears within 48 hours of the onset of appropriate antibiotic therapy
    - Fever resolves within 72 hours of the onset of appropriate antibiotic therapy
    - There is no evidence for metastatic spread of bacteremia or other clinical reasons to suspect IE

- TEE is more sensitive than TTE and should be done to evaluate for endocarditis in the following situations:

    - All cases of *S. aureus* bacteremia with negative TTE that do not meet all of the "negative" criteria above
    - To evaluate for myocardial abscess or pathology requiring valve replacement in patients with IE as diagnosed by TTE,
    - Patients with prosthetic valve-associated IE.

- Absent indications for earlier TEE, test is performed preferably at 5 – 10 days of therapy.

[back to top]

Guidelines for duration of treatment of *S. aureus* bacteremia when IE has not been not diagnosed

SHORT (7-10 days) COURSE THERAPY:

- In ***RARE*** cases of ***MSSA*** bacteremia, in which there is rapid defervescence (<48h), removal of source of infection, and rapid (<48h) clearance of bacteremia, a 7-10 day treatment course of intravenous antibiotics may be considered. Such short course therapy should be done ONLY in consultation with Infectious Diseases

INTERMEDIATE (14 days) COURSE THERAPY:

- *S. aureus* bacteremia that clears promptly (i.e., within 24 – 48 hours) with institution of treatment can be treated for 14 days of intravenous antibiotics if *all* the following conditions are satisfied:

    - No metastatic foci of infection are present (e.g. multiple nodular-cavitating pulmonary lesions, splenic abscess, etc.)
    - No other evidence of endocarditis is present with negative echocardiography as above
    - Low risk for endocarditis or other site of endovascular infection, including absence of prosthetic
    - Absence of intravascular materials [e.g., prosthetic valve, pacemaker, ICD, arteriovenous dialysis graft or femoral- popliteal bypass graft] and absence of purulent phlebitis at the site of a recently removed central venous catheter
    - No recent implantation of intravascular stents, prosthetic joint or other significant surgical hardware
    - Febrile illness was not present for more than 2 days prior to first blood culture yielding *S. aureus*
    - Fever has resolved within 72 hours of the onset of appropriate antibiotic therapy.
    - Follow-up blood cultures draw 2 – 4 days after initial set are sterile

Failure to satisfy all of these conditions indicates the need for more prolonged parenteral therapy (i.e., 4 weeks or more).

LONG (4-6 weeks) COURSE THERAPY:

- Persistent bacteremia (positive blood cultures for >48 hours on effective therapy) is suggestive of endovascular infection and warrants treatment for at least 4 weeks and an aggressive workup for potential occult source of bacteremia
- Longer therapy may be warranted if there is metastatic infection

[back to top]

Guidelines for management of *S. aureus* infective endocarditis (IE)

- *Diagnosis* of *S. aureus* IE, as opposed to persistent *S. aureus* bacteremia, relies heavily on the modified Duke criteria (see Mylonakis and Calderwood [NEJM], cited below).
- *Duration of treatment:* Patients with IE are treated for 4-6 weeks with an effective agent; the treatment clock starts with the 1st negative blood culture
- *Echocardiography*

    - Trans**esophageal** echocardiography (TEE) is indicated to assess for deep-seated myocardial infection in cases of IE diagnosed by TTE, as above
    - A trans**thoracic** echocardiogram (TTE) should be done at end of therapy

[back to top]

Clinical pearls

Key Standards of Care

- Promptly remove intravascular focus of infection & drain abscesses. *Sooner is better!*
- Search for 1° & metastatic (bone & viscera) sites of infection
- Obtain 2 sets of blood cultures every 24° until blood is sterile on treatment—this should be initiated upon preliminary report by the microbiology laboratory of "blood cultures positive for gram-positive cocci in clusters"
- Use IV β-lactam therapy for MSSA
- Administer appropriate dose and duration of therapy

Echocardiography

- Each of the following is a major (echocardiographic) criterion for diagnosis of IE, using the Duke criteria (see Mylonakis & Calderwood, below):
  - an oscillating intracardiac mass or vegetation
  - an annular abscess
  - partial prosthetic valve dehiscence, or
  - new valvular regurgitation (this is a major criterion if detected either by echo or physical exam)
  - vegetations occasionally persist after successful treatment of IE
- IE can occur with a non-diagnostic echocardiogram

Complications of *S. aureus* bacteremia include

- Brain abscess
- Mycotic aneurysm, particularly intracranial
- Multiple pulmonary nodules or infiltrates, often cavitating
- Intra-abdominal abscess (e.g., splenic or renal abscess)
- Osteomyelitis (particularly of the axial spine) and septic arthritis

S. aureus in the urine

- Recovery of *S. aureus* from urine may an important clue (reflecting seeding of the kidneys and urine) to subclinical *S. aureus* bacteremia, or it may as a consequence of GU tract manipulation with ascending infection.

[back to top]

References

1. Cosgrove SE, Fowler VG. Management of methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Infect Dis 46 Suppl 5:S386-93, 2008.
2. Mylonakis E, Calderwood SB. Infective Endocarditis in Adults. N Engl J Med 345:1318, 2001.
3. Chang F-Y, Peacock JE, Musher DM, et al. *Staphylococcus aureus* Bacteremia. Medicine. 82 333-389, 2003.

4. Mohr JF, Murray BE. Point: Vancomycin is not obsolete for the treatment of infection caused by methicillin-resistant *Staphylococcus aureus*. Clin Infect Dis 44: 1536-42, 2007.
5. Holland TL, Arnold C, Fowler VG. Clinical Management of *Staphylococcus aureus* Bacteremia: A Review. JAMA. 2014; 312:1330-1441.
6. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis. 2011; 52:e18-e55.

[back to top]