Staphylococcus aureus Bacteremia (SAB)

The 18 Most Important Questions Identified by the IDSA Guidelines Committee

Attempted answers courtesy of Henry F. Chambers, MD

I have nothing to disclose
1. What clinical features define whether a patient has complicated S. aureus bacteremia?

- Prolonged bacteremia on therapy, >48-72h (Odds ratio = 5.6)
- Community-onset (OR 3.1)
- Fever > 3 days on therapy (OR 2.2)
- Skin findings c/w systemic infection (OR 2.0)
- Persistent or secondary focus of infection
- Endocarditis, prosthetic valve
- (Elderly patient: age > 60 years)
- (MRSA)

2. In patients with S. aureus bacteremia should follow-up blood cultures be obtained until negative?
Persistent S. aureus Bacteremia/Treatment Failure Risk Factors

- Definitions vary: >3d or >5d or >7d
- What factors are consistently identified as being correlated?
  - Endocarditis, endovascular source
  - Metastatic infection
  - Retained catheter or foreign body
  - Use of vancomycin instead of β-lactam for MSSA


2. In patients with S. aureus bacteremia should follow-up blood cultures be obtained until negative?

YES
3. In patients with S. aureus bacteremia what is the role of echocardiography and what modality should be used?

IE SUSPECTED

- Low risk patient & low clinical suspicion: Initial TTE
  - Neg: TEE
  - Pos: TEE after TTE asap
  - Rx: Look for other source

- High risk patient or moderate to high clinical suspicion, difficult imaging candidate: TEE after TTE asap
  - Neg: TEE
  - Pos: Rx

- High risk features on TTE: Yes
  - Pos: Look for other source
  - No: TEE

- TEE

Circulation. 132:1435-86, 2015
What is High Risk?

• High risk patients (examples)
  • Prosthetic valve
  • Congenital heart disease
  • Previous endocarditis
  • New murmur, heart failure, heart block, stigmata of IE

• High risk TTE (examples)
  • Large or mobile vegetations, anterior MV leaflet veg
  • Valvular insufficiency, perivalvular extension, valve perforation
  • Ventricular dysfunction

Circulation. 132:1435-86, 2015

Considerations in Risk Assessment of SAB

• Up to 25% of SAB is complicated by endocarditis
• Even low risk SAB (e.g., line-associated SAB) ~5% risk
• Adherence to recommendations to obtain ECHO by clinicians is poor
  • Of 877 cases of SAB any ECHO in 43%, TTE 37%, TEE 27%
    (Khatib 92:182, 2013)
• No study has demonstrated that ECHO improves outcomes
3. In patients with S. aureus bacteremia what is the role of echocardiography and what modality should be used?

Depends on the pre-test probability

- Consider TTE in all patients with SAB
  - Possible exception: HCA + no intracardiac devices + no signs IE + negative BC @ 48-72h
- Obtain TEE in high risk patients
  - Embolic events, intracardiac device, IVDU, prior IE


4. In patients with MSSA bacteremia should an antistaphylococcal, penicillinase-resistant penicillin or a cephalosporin be used?
### MSSA Bacteremia

**Beta-Lactams vs. Vancomycin**

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimens compared</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fowler (CID 1998, 27: 478)</td>
<td>Vanco vs beta-lactam</td>
<td>Lower cure rate and higher death rate with vanco</td>
</tr>
<tr>
<td>Schweizer (BMC ID 2011,11:279)</td>
<td>30d mortality with MSSA (1) Naf or cefazolin vs (2) Vanco then naf or cefazolin vs (3) Vanco</td>
<td>1 vs 2 vs 3 mortality: 3% vs. 7% vs 20%</td>
</tr>
</tbody>
</table>

---

### Beta-lactam vs. Vancomycin for MSSA Bacteremia (122 VA hospital study) – Multivariable Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mortality, Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-lactam vs vancomycin</td>
<td>0.65 (0.52-0.80)</td>
</tr>
<tr>
<td>ASP or cefazolin vs vancomycin</td>
<td>0.57 (0.46-0.71)</td>
</tr>
</tbody>
</table>

*Clin Infect Dis 61:361, 2015*
Penicillin for Treatment of Staph. aureus Endocarditis per AHA guidelines

…the current laboratory screening procedures for detecting penicillin susceptibility may not be reliable.

<table>
<thead>
<tr>
<th>Pen MIC (µg/ml)</th>
<th>Tested for blaZ</th>
<th>PCR + for blaZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.015</td>
<td>1 (100)</td>
<td>0</td>
</tr>
<tr>
<td>0.03</td>
<td>24 (100)</td>
<td>0</td>
</tr>
<tr>
<td>0.06</td>
<td>370 (100)</td>
<td>14 (3.4)</td>
</tr>
<tr>
<td>0.12</td>
<td>53 (100)</td>
<td>17 (32.1)</td>
</tr>
</tbody>
</table>

J Clin Micro 54:812, 2016

MSSA Bacteremia: Cefazolin vs. Antistaphylococcal Penicillins

• Efficacy:
  • Penicillinase inoculum effect on cefazolin MICs – does it matter?

• Safety:
  • Adverse events due to ASPs
Mortality and Adverse Events

- Six studies found no difference in treatment failure and/or mortality and half reported cefazolin had non-significant lower mortality
- Four of five studies reported higher adverse drug events in ASPs groups, mainly due to nephrotoxicity and hypersensitivity reactions, often requiring the discontinuation of antibiotics.

Loubet, Clin Micro Infect, 2017, in press

The US Veterans Administration 119 Hospital Study of 3167 Patients

- Patients treated with cefazolin
  - 37% reduction in 30d mortality (HR: 0.63, 95% confidence interval [CI] 0.51–0.78)
  - 23% reduction in 90-day mortality (HR: 0.77, 95% CI 0.66–0.90)
  - Rates of recurrence similar (OR, 1.13; 95% CI 0.94–1.36)

McDaniel, Clin Infect Dis 2017, 65:100
# Cefazolin vs Nafcillin

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratios (95% CI)</th>
<th>Cefaz [79] vs Naf [163]</th>
<th>Cefaz [79] vs Naf [79]*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>0.43 (0.24-0.76)</td>
<td>0.45 (0.23-0.86)</td>
<td></td>
</tr>
<tr>
<td>--Mortality @ 30 d</td>
<td>0.30 (0.07-1.36)</td>
<td>0.38 (0.07-2.04)</td>
<td></td>
</tr>
<tr>
<td>--Change for clinical failure</td>
<td>0.98 (0.48-2.05)</td>
<td>1.22 (0.51-2.91)</td>
<td></td>
</tr>
<tr>
<td>--Recurrence</td>
<td>0.68 (0.13-3.45)</td>
<td>1.00 (0.14-7.28)</td>
<td></td>
</tr>
<tr>
<td>--AE, drug discontinuation</td>
<td>0.35 (0.17-0.73)</td>
<td>0.33 (0.15-0.75)</td>
<td></td>
</tr>
<tr>
<td>Mortality @ 3 mo.</td>
<td>0.15 (0.04-0.65)</td>
<td>0.18 (0.04-0.85)</td>
<td></td>
</tr>
<tr>
<td>Persistent bacteremia</td>
<td>--</td>
<td>0.42 (0.14-1.26)</td>
<td></td>
</tr>
</tbody>
</table>

*Propensity matched cohort Lee, Clin Micro Infect 2017, in press

---

# Outcome for MSSA Bacteremia with Cefazolin: Inoculum Effect

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cefazolin Inoculum Effect</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=13)</td>
<td>No (n=45)</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>8 (61.5%)</td>
<td>13 (28.9%)</td>
</tr>
<tr>
<td>--Change, clinical failure</td>
<td>5 (38.5%)</td>
<td>5 (11.1%)</td>
</tr>
<tr>
<td>--Recurrence</td>
<td>1 (7.7%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>--Mortality @ 1 mo.</td>
<td>2 (15.4%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Lee, Clin Micro Infect 2017, in press
Summary: MSSA Bacteremia

• Cefazolin is better tolerated than ASPs
• Overall mortality no worse, may be better with cefazolin compared to ASPs
• Clinical failure rates and recurrences similar
• Anxiety over the inoculum effect, which may adversely impact outcome in a subset of cefazolin-treated patients

4. In patients with MSSA bacteremia should an antistaphylococcal, penicillinase-resistant penicillin or a cephalosporin be used?

YES
5. In patients with MRSA bacteremia should vancomycin or daptomycin be used?

First Line Choices for MRSA Bacteremia

• Vancomycin
• Daptomycin

Holland et al: JAMA 312:1330, 2014
Daptomycin Endocarditis Trial

• Non-inferior to comparator overall
  • Cure rate MRSA: 44.4 v 31.8%
  • Duration of MRSA bacteremia: no difference v comparator
• Microbiologic failure:
  • Daptomycin 6 mg/kg q24h (n=120) = 16%
  • Vancomycin 30-60 mg/kg as 2-3 divided doses (n=53) = 17%
  • Nafcillin 2 gm q4h (n=62) = 3%
  • 6 of 19 isolates from daptomycin failures (5 MRSA) had rising MICs (often mprF mutants)


Vancomycin, Daptomycin Alternatives

• Low-quality evidence suggests that linezolid, trimethoprim-sulfamethoxazole, dalbavancin, ceftaroline, quinupristin-dalfopristin, and telavancin may be useful for patients who have not responded to first-line therapy.
• Tigecycline should be avoided.
• No data are yet available for tedizolid or oritavancin.

5. In patients with MRSA bacteremia should vancomycin or daptomycin be used? 

YES

6. In patients with MRSA bacteremia for which the isolate has a vancomycin MIC = 2 μg/ml should vancomycin or some other agent be used?
Vancomycin MICs by Method


Duration of Staph. aureus Bacteremia
SFGH Data

Duration of Initial S. aureus Bacteremia Based on First and Last Positive Blood Cultures with an Index Culture Vancomycin MIC=0.5

Duration of Initial S. aureus Bacteremia Based on First and Last Positive Blood Cultures with an Index Culture Vancomycin MIC=2
- Meta-analysis, 38 studies, 8291 episodes
- MIC < 1.5 μg/mL (low) versus MIC ≥ 1.5 μg/mL (high)
- Mortality low = 25.8%, high = 26.8%
- Adjusted risk difference = 1.6% (-2.3 to 5.6%), p = 0.43


6. In patients with MRSA bacteremia for which the isolate has a vancomycin MIC = 2 μg/ml should vancomycin or some other agent be used?

- Vancomycin MIC = 2 μg/ml not a reliable predictor of clinical failure and not a reason to alter therapy.
- Vancomycin MIC > 2 μg/ml is a reliable predictor of nonsusceptibility and clinical failure and another agent should be used.
7. In patients with S. aureus bacteremia or native valve endocarditis should monotherapy or combination therapy be used routinely?

AHA Guidelines Therapy of S. aureus endocarditis

- Native valve
  - MSSA
    - Nafcillin (or Oxacillin) 2 gm q4h x 4-6 weeks
    - Cefazolin 2 gm q8h x 4-6 weeks, allergic or intolerant to naf
    - No aminoglycoside
  - MRSA
    - Vancomycin 30-60 mg/kg/d divided q8-12h to achieve trough of 15-20 μg/ml x 4-6 weeks
    - Daptomycin 6-10 mg/kg q24h x 4-6 weeks
    - No aminoglycoside

### Open-label RCT of Vancomycin vs. Vancomycin + Flucloxacillin (7d) for MRSA Bacteremia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vanco (N=28)</th>
<th>Vanco + fluclox (N=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of bacteremia (mean ± s.d.)</td>
<td>3.0 ± 3.4</td>
<td>1.9 ± 1.8</td>
</tr>
<tr>
<td>Mortality @ 90 d (n)</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>+ BC &gt; 3/7 days</td>
<td>7/3</td>
<td>5/1</td>
</tr>
<tr>
<td>Relapse (n)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>ICU, shock (n)</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Metastatic complication (n)</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>


### Vancomycin Monotherapy versus Beta-lactam Combination Therapy for MRSA Bacteremia

- Retrospective study of 110 patients, single center
  - 47 monotherpay, 63 combination therapy
- Treatment failure
  - Clinical failure (36% mono v 21% combo)
    - Change in therapy (20% v 10%), Mortality (11% v 8%), Readmission (4% v 3%)
  - Microbiological failure (23% v 24%)
- Results of multivariable analysis: Odds ratio (95% CI)
  - Combo: 0.377 (0.142-0.997)
  - Vancomycin MIC > 1: 4.018 (1.297-12.444)

Adjunctive rifampicin for *Staphylococcus aureus* bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial


- 758 patients, 388 SOC and 370 SOC + rifampin
  - 40% deep tissue, 30% diabetics, 1y% IVDU, 6% MRSA, Mean of 62h pre-randomization antibiotics
- Primary outcome composite of treatment failure, recurrence, death at 12 weeks


---

**Composite Primary Outcome**

**Death**

![Graph showing event rates for composite primary outcome and death over time]

Event (%) vs. Number at risk (events)
7. In patients with S. aureus bacteremia or native valve endocarditis should monotherapy or combination therapy be used routinely?

• No high quality RCT has ever demonstrated improved outcomes of combination antimicrobial therapy over monotherapy.
• Studies suggesting a possible benefit of combination therapy are low quality, retrospective, and based on subjective outcomes not mortality, recurrence, metastatic infections.

8. What is the appropriate duration of therapy for patients with uncomplicated versus complicated bacteremia?
## Duration of therapy for SAB

<table>
<thead>
<tr>
<th>Duration</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 days</td>
<td>• Fever resolves by day 3&lt;br&gt;• Sterile blood culture after 2-3 days&lt;br&gt;• Easily removed focus of infection&lt;br&gt;• No metastatic infection (e.g., osteo)&lt;br&gt;• Negative echo, no evidence of endocarditis&lt;br&gt;• No predisposing valvular abnormalities&lt;br&gt;• No implanted prosthetic devices&lt;br&gt;• (No DM, immunosuppression)</td>
</tr>
<tr>
<td>4-6 weeks</td>
<td>• Failure to meet one or more of above criteria&lt;br&gt;• Osteomyelitis, endocarditis, epidural abscess, septic arthritis, pneumonia, complicated UTI</td>
</tr>
</tbody>
</table>

8. What is the appropriate duration of therapy for patients with uncomplicated versus complicated bacteremia?

- 2 weeks for uncomplicated SAB
- 4-6 weeks for complicated SAB
- Recommendations are empirical
9. Is there a role for oral step-down therapy in treatment of S. aureus bacteremia?

- Poorly studied, limited data
- Should work in principal with active, highly bioavailable drug
- Some examples
  - Oral therapy of R-sided MSSA endocarditis with Ciprofloxacin + Rif
  - Oral dicloxacillin (~4 gm/d) step-down therapy of MSSA TCV IE in IVDUs
  - Treatment of vertebral osteomyelitis (several)
  - Treatment of osteo-articular infections in children with oral clindamycin, high-dose oral cephalosporin
    - Peltola, Clin Microbiol Infect 18:582, 2012
10. What is the appropriate duration of therapy for S. aureus bacteremia complicated by vertebral abscess?
Risk Factors Associated with Recurrence

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-stage renal disease</td>
<td>6.58 (1.63-26.5)</td>
</tr>
<tr>
<td>MRSA infection</td>
<td>2.61 (1.16-5.87)</td>
</tr>
<tr>
<td>Undrained paravertebral/psoas abscess</td>
<td>4.09 (1.82-9.19)</td>
</tr>
</tbody>
</table>

Probability of Recurrence-Free Survival

No risk factor

1 or more risk factors
10. What is the appropriate duration of therapy for S. aureus bacteremia complicated by vertebral abscess?

- MSSA
  - 6 weeks if no abscess or drained abscess
  - 8 weeks if undrained abscess
- MRSA
  - At least 8 weeks

11. Should ID consultation be obtained for all patients with S. aureus bacteremia?
11. Should ID consultation be obtained for all patients with S. aureus bacteremia?

- J Infect 59:232, 2009
- Clin Microbiol Infect 16:1783, 2010
- Emerg Infect Dis 18:1072, 2012
- Clin Microbiol Infect. 21:779, 2015

YES!

Time permitting…..

Other Guidelines Questions Listed in the Syllabus
12. In patients with prosthetic valve S. aureus endocarditis should monotherapy or combination therapy be used routinely?

- Prosthetic valve
  - TEE to assess valve ring abscess; abscess is an indication for surgery
  - MSSA Nafcillin 2 gm q4h x 6 wks + Rifampin 300 mg q8h x 6 wks + Gentamicin 1 mg/kg q8h x 2 wks
  - MRSA: As above with Vancomycin 30-60 mg/kg 3 divided dose instead of Nafcillin
- Endocarditis with implantable cardiac devices
  - Device removal associated with improved 1-year survival, especially if valve is also infected
  - Therapy as above


13. In patients with persistent S. aureus bacteremia and negative echocardiography, no retained foreign body, what are the next steps?

Beware: expert opinion below
- Repeat ECHO
- MRI of the spine
- CT of the abdomen
- PET-CT
14. In patients with *S. aureus* bacteremia and back pain should a CT-scan or MRI be obtained?

- MRI is the test of choice because of better sensitivity, better specificity, and better visualization of epidural space and surrounding tissues.
- CT-scan recommended only if MRI not available or cannot be performed.

15. Should patients with *S. aureus* endocarditis complicated by meningitis receive standard of care therapy or should additional agents be added to the regimen?

- No studies or good data to answer this question.
- An antistaphylococcal penicillin (MSSA) or vancomycin (MRSA) are SOC choices.
  - Some authorities recommend adding rifampin to vancomycin, but data to support benefit are lacking.
  - DO NOT USE cefazolin because of its poor CNS penetration.
16. In patients with persistent MRSA bacteremia on vancomycin what should be used as salvage therapy?

- Options include: ceftaroline, daptomycin + ceftaroline, telavancin
- Do not add rifampin or gentamicin to a failing regimen

17. What is the role of biomarkers (IL-10, CRP, PCT) in assessing response to therapy and determination of duration of therapy?

- Certain biomarkers correlate with disease severity and/or mortality
- Utility in assessing response to therapy or duration of therapy unproven and use of biomarkers for this purpose not recommended
18. Should patients with S. aureus bacteremia and septic thrombophlebitis be treated with systemic anticoagulation?

- Benefit uncertain
  - But recommended in cavernous sinus thrombosis
- For extracranial septic thrombophlebitis consider if there is extension of thrombus on therapy