Staphylococcal Endocarditis and Bacteremia

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Disclosures

- AstraZeneca – advisory board
- Cubist – research grant, advisory panel
- Genentech – advisory board
- Merck – stock
- Pfizer – advisory board
- Theravance – advisory board
Case 1
Catheter-Associated Bacteremia

38 y/o man, new CHF, alcoholic cardiomyopathy, Hct = 13. He is transfused and on hospital day 3 an upper + lower endoscopy performed. Post-procedure T = 38°C. The site of the previous IV, d/c’d post-procedure is tender and red. Two peripheral blood cultures are drawn. The next day he is afebrile and 1 blood culture is growing GPC in clusters. Cultures are repeated and vancomycin is administered. The following day the organism is identified as MSSA and repeat blood cultures show no growth to date.

Case 1 Catheter-Associated Bacteremia

Which of the following has been shown to improve outcome of S. aureus bacteremia?

1. Treatment with daptomycin instead of vancomycin for MRSA.
2. Echocardiography to rule out endocarditis.
3. Infectious diseases consultation.
4. Gentamicin combination therapy instead of single drug therapy with vancomycin or nafcillin.
Get an Infectious Disease Consult!!

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

Case 1
Catheter-Associated Bacteremia

You would
1. Continue vancomycin pending blood culture results, d/c if those are negative.
2. Switch from vancomycin to cefazolin pending blood culture results, d/c if those are negative.
3. Continue vancomycin pending blood culture results, plan to treat for at least 14 days if those are negative.
4. Switch from vancomycin to cefazolin pending blood culture results, plan to treat for at least 14 days.
Predictors of Complicated *Staphylococcus aureus* Bacteremia

- Community-onset
- Septic shock
- Persistent or secondary focus of infection
- Prolonged bacteremia on therapy (>48-72h)
- Fever > 3 days on therapy
- Elderly patient (age ≥ 60 years)
- MRSA
- Use of vancomycin instead of a β-lactam
- Duration of treatment < 10-14 days

Nafcillin vs. Other β-lactams

- Cefazolin similarly efficacious and better tolerated than nafcillin/oxacillin
  - Clinical Infectious Diseases 59:369, 2014
  - Clin Microbiol Infect 17:1581, 2011
- Ceftriaxone, other β-lactams may be less efficacious
  - Clin Microbiol Infect 17:1581, 2011
  - (But see Int J Clin Pharm 36:1282, 2014)
**Duration of Therapy:**

**S. aureus Bacteremia**

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

*Clin Infect Dis 49:1, 2009; Clin Infect Dis 52:285, 2011*

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Case 1: Catheter-Associated Bacteremia

And if those blood cultures turn positive…

– Obtain an ECHO
– Search for secondary or metastatic focus
– Treat for a minimum of 4-6 weeks

What about Echocardiography?

• Consider obtaining ECHO is all cases of S. aureus bacteremia
• ECHO preferably TEE (more sensitive than TTE) for complicated bacteremia defined as any of the following
  – Positive blood cultures for 3 or more days
  – Intracardiac device (pacer, valve)
  – Secondary/metastatic focus of infection
  – Relapse or recurrence
  – Suspected endocarditis
  – Some say community-onset, HD, h/o IVDU but data less convincing

The Facts about Echocardiography?

- TEE is more sensitive than TTE
- TEE can visualize smaller vegetations: 5 mm
- TEE is better than TTE for prosthetic valve endocarditis
- Few data that it improves outcome
- Compliance is poor
  - 379 ECHOS in 877 SAB cases (43%) in one Michigan hospital*


Case 2: Persistent Bacteremia

Mr. Q is a 53 year old diabetic. He was hospitalized four weeks ago for hyperosmolar coma and was readmitted a week ago for fevers to 39°C. A CT scan showed findings consistent with a 4 cm psoas abscess. Three blood cultures were drawn and empirical therapy begun with vancomycin and piperacillin-tazobactam. All three blood cultures grew MRSA with a vancomycin MIC of 2 by microbroth dilution. TEE is negative. Treatment was de-escalated to vancomycin alone with documented trough concentration of 15 µg/ml. One of two blood cultures obtained on day 5 of therapy now is reported as positive for Gram-positive cocci in clusters. Which of the following is the most likely explanation for the persistently positive blood culture?

1. Vancomycin resistance MRSA strain
2. Treatment failure due to the MIC = 2
3. Undrained psoas abscess
4. Subtherapeutic levels of vancomycin
5. Contamination of the blood culture with coag-neg staph
Recommended Vancomycin Dosing

• For serious infections (pneumonia, bacteremia)
  – 15-20 mg/kg IV q8-12h (loading dose of 25-30 mg/kg)
  – Target trough concentrations of 15-20 µg/ml; target AUC$_{24}$/MIC = 400 (or > 211?)
  – Adjust for renal function, actual body weight
• For less serious infections (SSTI):
  – 15 mg/kg q12h (1 gm q12h)
  – Routine measurement of trough not necessary


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
• Controversy over vancomycin MIC > 1 µg/ml (E-test)

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

Vancomycin MICs by Method

• 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

JAMA 312:1552, 2014.

Management of Persistent MRSA Bacteremia on Vancomycin Therapy

• Median time to clearance of MRSA bacteremia is 7-9 days
• Persistent bacteremia around day 7 of therapy should prompt assessment to determine if a change in therapy is indicated:
  – Search for and remove other foci of infection
  – Evaluate clinical response
  – Assess micro data (vanco MIC, results of f/u bld cx)

Consider change if:
1) Unsatisfactory clinical response, regardless of MIC or
2) Vanco MIC = 2

No change if:
1) Clinically responding and
2) Vanco MIC < 2
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Case 3: Vancomycin Treatment Failure

- 38 y/o woman, injection drug user with TCV endocarditis
- Presented with pleural effusion (exudate, sterile), multiple septic pulmonary emboli, 2/2 blood cultures positive for MRSA (vanco MIC < 0.5 µg/ml, dapto MIC < 1)
- TTE: 2 x 2.4 cm TCV vegetation
- Vancomycin 1.25 g q8h (troughs 15-23 µg/ml)
- Blood cultures:
  - Vanco day 2: 2/2 MRSA
  - Vanco day 3: 2/2 MRSA
  - Vanco day 4: 1/2 MRSA (MIC = 1)
  - Vanco day 5: 2/2 NG
  - Vanco day 9: 2/2 NG
Case 3: Vancomycin Treatment Failure

• Vanco days 11-18
  – Afebrile
  – Slowly declining WBC,
  – Serum creatinine 1.53, GFR ~38 ml/min

• Antibiotic day 18
  – Vancomycin discontinued
  – Daptomycin 500 mg (10 mg/kg) q24 hours started

• Day 19 (dapto day 2)
  – Fever spike to 39C
  – 2 blood cultures drawn, eventually grow MRSA (vancomycin MIC=1, dapto MIC = 1)

What to do when vancomycin is not working?

1. Abandon vancomycin
   – Do not add rifampin
   – Do not add gentamicin

2. Switch to another agent(s)
   – Which?
### VISA and VRSA MICs (µg/ml)

<table>
<thead>
<tr>
<th></th>
<th>VISA (n=33)</th>
<th>VRSA (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>% NS</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>4-8</td>
<td>100</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>1-8</td>
<td>70</td>
</tr>
<tr>
<td>Telavancin</td>
<td>0.25-1</td>
<td>0</td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>0.25-2</td>
<td>15</td>
</tr>
<tr>
<td>Linezolid</td>
<td>0.5-4</td>
<td>0</td>
</tr>
</tbody>
</table>

*Clin Infect Dis 55:582, 2012*
Daptomycin Endocarditis Trial

- Non-inferior to comparator overall
  - Cure rate MSSA: 44.6 v 48.6%
  - Cure rate MRSA: 44.4 v 31.8%
  - Duration of bacteremia: no difference v comparator

- Microbiologic failure:
  - 19/120 daptomycin vs. 11/115 comparator (9/53 vancomycin, 2/62 nafcillin)

- Rising MICs
  - 6/19 isolates from daptomycin failures (5 MRSA) (often mprF mutants)
  - 1/9 (4/9 if local results used) from vancomycin failures


Do we have the right dose for daptomycin?

- Dose was chosen based on concerns for toxicity, not guarantee of efficacy
- Daptomycin has concentration dependent killing
- Higher dose may provide protection against emergence of resistance
- IDSA guidelines committee recommends that if daptomycin is used for treatment failure, it be used at a dose of 10 mg/kg/d
Outcomes in *S. aureus* Bacteremia treated with Ceftaroline

<table>
<thead>
<tr>
<th>Group</th>
<th>Success</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocarditis</td>
<td>23/33 (70%)</td>
<td>8/35 (23%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>21/29 (72%)</td>
<td>6/30 (20%)</td>
</tr>
<tr>
<td>Micro evaluable</td>
<td>109/120 (91%)</td>
<td>n/a</td>
</tr>
<tr>
<td>Evaluable</td>
<td>101/129 (78%)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Duration of bacteremia: 6 days, 2.5 days after starting ceftaroline

US Case Series

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>600 mg q12h (n=452)</th>
<th>600 mg q8h (n=75)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure</td>
<td>3</td>
<td>3</td>
<td>0.04</td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
<td>3</td>
<td>0.02</td>
</tr>
<tr>
<td>Cytopenia</td>
<td>0</td>
<td>2</td>
<td>0.02</td>
</tr>
<tr>
<td>Other</td>
<td>23</td>
<td>5</td>
<td>0.58</td>
</tr>
<tr>
<td>Total</td>
<td>28 (6.2%)</td>
<td>13 (17.3%)</td>
<td>0.004</td>
</tr>
</tbody>
</table>


Ceftaroline Salvage Therapy
MRSA Invasive Disease

- 10 patients, case series, San Diego
  - 5 endocarditis
  - 2 pneumonia (neg BC)
  - 3 bone and joint (1 bacteremia)
- Duration of + BC pre-ceftaroline: 5-19
- Vanco MICs (µg/ml): 0.5 (2); 1(4); 2 (4, 1 by E-test)
- Dose 600 mg q8h
- Time to BC clearance with ceftraoline: 2-7 days
- Cures: 7/10 micro, 6/10 clinical
  - Failures: AICD, PJI, pneumonia (comfort care)

J Infect Chemother July 14, 2012
Ceftaroline: Alone or in Combination for *S. aureus* bacteremia

- 31 patients, 9 endocarditis
- Days of +BC on ceftar: 3.4 (mean), 1-8 (range)
- Ceftaroline alone (n=21)
  - 8 failures
    - 3 toxicity (GI, rash)
    - 3 recurrence (catheter, endocarditis)
    - 2 deaths (osteo/epidural, pneumonia/comfort care)
- Ceftaroline combos (n=10) (5 dapto/dapto+)
  - 10 successes


Ceftaroline Prospective Treatment Trial for *S. aureus* Bacteremia

- Index blood culture positive within 24h (N=15)
- Ceftaroline 600 mg q8h IV
- MRSA 4/6 relapse-free success
- MSSA 3/9 relapse-free success
- Patient with +BC 3 h after first dose also failed
- Time to clearance of bacteremia
  - Median: 3 days
  - Range: 0 to 5 days

Fowler, et al. Abstract L-400, ICAAC 2014
Daptomycin Beta-Lactam Combination

- Seven cases of relapse (n=2) and/or persistent bacteremia (7-22d)
  - 1 endocarditis, 1 cSSSI, 5 unknown
- Prior regimens
  - 7 vanco, 5 dapto, 5 dapto+gent
- Dapto 8-10 mg/kg + Naf or Ox 12 g/day
  - Negative BC @ 24-48h
  - 2 relapsed (1 death)
  - 3 rising dapto MIC (MIC > 1 in 2 cases)


MprF Structure
Treatment of Bacteremia and Other Serious Staph. aureus Infections

- Source control is paramount
- Prefer a β-lactam for MSSA infections
- Vancomycin remains a drug of choice for MRSA but has issues…
  - High clinical and microbiological failure rate (25-50%)
  - Yet, no alternative agent(s) has been shown to be superior to vancomycin (they are non-inferior)
  - May be nephrotoxic at doses to achieve target troughs of 15-20 µg/ml (Lodise, AAC 52:1330, 2008)
  - Switch to other agent(s) for treatment failure