Methicillin-Resistant Staphylococcus aureus Infective Endocarditis

What to do with Resistance?

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PGY1 Resident
Objectives

• Identify limitations with current guideline recommended therapies for MRSA Infective Endocarditis

• Describe the seesaw effect of beta-lactam combination therapy for MRSA Infective Endocarditis

• Discuss appropriate indications for salvage therapy with β-lactams based on literature evaluated
AL is a 55-year-old male has been recently admitted for continued fever and generalized fatigue over the past 7 days

Allergies: NKDA

PMH: IV drug use, alcohol abuse

Physical Examination:
• (+) Splinter hemorrhages
• (+) Janeway lesions

Vitals
• Blood Pressure: 152/78 mmHg
• Temperature: 102.9 °F
• Pulse: 115 bpm

Labs
• WBC 23
• SCr 1.9
• CrCl 45
Patient Case

• Day 1
  • Patient is then admitted and started on Vancomycin and Piperacillin/Tazobactam empirically

• Day 2
  • Blood cultures (+) S. aureus pending susceptibilities
  • TTE: vegetation measuring 0.8cm x 1.4cm in the mitral valve with severe regurgitation
Patient Case

- Day 3
  - Susceptibilities return → MRSA (Vancomycin MIC = 1)
  - Piperacillin/Tazobactam discontinued and repeat blood culture drawn
  - Kidney function continue to decline

- Day 5: Patient continues to clinically deteriorate, repeat culture returns
Patient Case

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• Day 5: Patient continues to clinically deteriorate, repeat culture returns

### Repeat Blood Culture Day 5

<table>
<thead>
<tr>
<th>Staphylococcus aureus</th>
<th>Antibiotic</th>
<th>SYS</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>2</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&lt;4</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Oxacillin</td>
<td>&gt;2</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>&gt;4</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Amp/Sub</td>
<td>&lt;8/4</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Trimeth/Sulfa</td>
<td>&lt;2/38</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>&gt;2</td>
<td>R</td>
<td></td>
</tr>
</tbody>
</table>
Why the Concern for S. aureus IE?

• Compared with IE* caused by other pathogens, S. aureus IE has shown to have higher correlation
  • Clinical debilitation
  • Severe sepsis
  • Major neurological events
  • Multiple organ failure
  • Mortality

*IE= Infective Endocarditis

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose and Route</th>
<th>Duration, wk</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxacillin-resistant strain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st Line Vancomycin</td>
<td>30 mg/kg /24 hr IV in 2 equally divided doses</td>
<td>6</td>
<td>Cl</td>
</tr>
<tr>
<td>2nd Line Daptomycin</td>
<td>≥6 mg/kg/dose</td>
<td>6</td>
<td>BII</td>
</tr>
</tbody>
</table>

Baddour et al. Circulation. 2015;132:1435-1486
When to Consider Salvage Therapy?

- MRSA IDSA Guidelines
  - For isolates with a vancomycin MIC ≤ 2 µg/mL, the patient’s clinical response should determine continued use of vancomycin, independent of the MIC

- Persistent bacteremia ~7 days
  - Earlier if clinical deterioration is present

Limitations of Standard Therapy

- Poor outcomes among isolates with higher MICs, within the susceptible range (> 1mg/L)

Vancomycin and Daptomycin Correlation

- In MRSA, hVISA* strains demonstrate thicker cell walls with binding sites that sequester the drug
  - May decrease ability of Daptomycin to reach binding sites

* hVISA= Heterogeneous Vancomycin intermediate S. aureus

Now what if there is resistance to both Vancomycin and Daptomycin?
See-Saw Effect

### Objective
Evaluate whether combination therapy regimens of Daptomycin-Oxacillin (DAP-OX) would enhance the in vitro efficacy over Daptomycin resistant strains of MRSA

### Methods
- n=6
- Population analysis of the strain sets
- In vitro time-kill curves

### Results
Combination of DAP and OX was found to increase the early in vitro bactericidal activity relative to that of DAP or OX alone in DAP\(^r\) strains

### Conclusion
Suggests that combination therapy regimens of DAP and OX has enhanced in vitro efficacy relative to DAP monotherapy in DAP\(^r\) strains which exhibit the DAP-OX seesaw phenomenon in vitro.

<table>
<thead>
<tr>
<th>Objective</th>
<th>Evaluated possible synergy activity of antibiotics against <em>meca</em>-positive hVISA and VISA isolates using beta-lactams, and vancomycin</th>
</tr>
</thead>
</table>
| Methods   | n=154  
- (n=61) VISA; (n=93) hVISA  
- Susceptibility testing; Time-kill synergy assays |
| Results   | Vancomycin + Ceftarolone  
- Synergy against 5/5 VISA and 4/5 hVISA strains  
Vancomycin + Oxacillin  
- Synergy against 3/5 VISA isolates and 1/5 hVISA strains |
| Conclusion| Ceftarolone may be more consistently synergistic than traditional antistaphylococcal beta-lactams with vancomycin |
Vancomycin + β-lactam
**Objective**  
Examine the impact of combination therapy with Vancomycin and a β-lactam on the microbiological eradication of MRSA bacteremia compared to Vancomycin alone

| Methods          | Retrospective cohort study, n=80  
|------------------|-----------------------------------
|                  | • n=50 combination group vs n=30 Vancomycin alone  
|                  | • β-lactam choice varied  
|                  | • Had to have at least one positive blood culture for MRSA with a Vancomycin MIC of 2mg/L |
### MIC of MRSA Isolates for Endocarditis patients

<table>
<thead>
<tr>
<th></th>
<th>Combination (11/50)</th>
<th>Vancomycin alone (11/30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Vancomycin MIC (mg/L)</td>
<td>2 (1.5-2)</td>
<td>1.5 (1.5-2)</td>
<td>0.066</td>
</tr>
</tbody>
</table>
### Results

Microbiological eradication
- 48(96%) Combination therapy vs 24(80%) in the Vancomycin alone ($P=0.021$)
- Infective endocarditis ($n=22$), 11/11 (100%) combination vs. 9/11 (81.8%) treated with Vancomycin alone ($P=0.20$)
- Mean duration of bacteremia
  - 3 days standard therapy vs 1.94 days combination group

### Author’s Conclusion

Combination therapy with Vancomycin and β-lactam is more likely to achieve microbiological eradication among patients with MRSA bacteremia than treatment with Vancomycin.
## Objective
Review cases of refractory MRSA bacteremia treated with the combination of Vancomycin and Ceftaroline
- Persistent bacteremia or deterioration of patient clinical status on Vancomycin alone

## Methods
Case series, n=5
- Vancomycin MIC’s within range (≤1 mcg/mL)
- Dosing for Ceftaroline 600mg q8hr
- 2 cases = endocarditis
- 2 cases = epidural abscess
- 1 case = psoas abscess
Results

4/5 microbiologic cure, 1 transitioned to palliative care

- Successful endocarditis patient

<table>
<thead>
<tr>
<th>Duration of Bacteremia (days)</th>
<th>Vancomycin MIC (mcg/L)</th>
<th>Daptomycin MIC (mcg/L)</th>
<th>Ceftaroline MIC (mcg/L)</th>
<th>Previous Therapy</th>
<th>Ceftaroline Dose and Duration</th>
<th>Duration of combination therapy with Ceftaroline</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>1</td>
<td>N/A</td>
<td>0.38</td>
<td>Vancomycin 15mg.kg IV q12</td>
<td>Ceftaroline 400mg IV q12h (CrCl between 30-50mL/min) for 14 days;</td>
<td>6</td>
</tr>
</tbody>
</table>

Author’s Conclusion

Combination may be considered when Vancomycin monotherapy does not lead to microbiological and/or clinical improvement inpatients with metastatic MRSA bacteremia.
How to Increase Vancomycin Efficacy?

• Ensure therapeutic levels
  • Target trough 15-20 mg/L

• Vancomycin Combinations
  • Greater bactericidal activity
  • See-Saw Effect

• Concern for MIC creep
Daptomycin + β-lactam
Dhand, et al.

<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>Determine whether the addition of an ASBL* to Daptomycin would increase activity in eradicating MRSA bacteremia</th>
</tr>
</thead>
</table>
| **Methods**   | • Case series (n=7)  
  • Nafcillin or Oxacillin 2g IV q4hr to Daptomycin 8–10 mg/kg/day  
  • Time Kill curves  
  • Daptomycin (10mg/L) +/- Oxacillin (20 mg/L) |

*ASBL= anti-staphylococcal B-lactam*
Time Kill Curve

Daptomycin Susceptible Strains

Daptomycin Resistant Strains

DAP= Daptomycin
OXA= Oxacillin

## Results

7/7 cases showed addition of high-dose ASBLs resulted in rapid bacteremia clearance
- 2/7 experienced relapsed

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<th>Author’s Conclusion</th>
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<tbody>
<tr>
<td>• Rapid clearance of bacteremia within 24-48 hours</td>
</tr>
<tr>
<td>• Restoration of DAP susceptibility</td>
</tr>
<tr>
<td>• Increases in DAP membrane binding</td>
</tr>
<tr>
<td>• Reduction in membrane surface charge by ASBLs that was more pronounced in the DAP-R strain</td>
</tr>
</tbody>
</table>

*ASBL = anti-staphylococcal B-lactam*
### Objective
Evaluate the use of Daptomycin and Ceftaroline as a salvage antimicrobial regimen in the treatment of refractory staphylococcal bacteremia

<table>
<thead>
<tr>
<th>Methods</th>
<th>Case study, n=26</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Endocarditis 54% (14/26)</td>
</tr>
<tr>
<td></td>
<td>MRSA 20/26</td>
</tr>
<tr>
<td></td>
<td>Daptomycin 8mg/kg/day + Ceftaroline 600mg q24hr</td>
</tr>
<tr>
<td></td>
<td>In vitro (synergy studies, binding assays, cathelicidin LL-37 killing assays)</td>
</tr>
<tr>
<td>Results</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------</td>
</tr>
<tr>
<td>• Bacteremia persisted for a median of 10 day on previous therapy</td>
<td></td>
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<tr>
<td>• After Daptomycin + Ceftaroline was started</td>
<td></td>
</tr>
<tr>
<td>• Median time to bacteremia clearance was 2 days</td>
<td></td>
</tr>
<tr>
<td>• In vitro studies</td>
<td></td>
</tr>
<tr>
<td>• Ceftaroline synergy against MRSA and enhanced MRSA killing by cathelicid in LL-37and neutrophils</td>
<td></td>
</tr>
<tr>
<td>• Induced Daptomycin binding in MSSA and MRSA to a comparable degree as Nafcillin</td>
<td></td>
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<tr>
<td>Author’s Conclusion</td>
<td>Ceftaroline + Daptomycin may be an option to hasten clearance of refractory staphylococcal bacteremia.</td>
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How to Increase Daptomycin Efficacy?

• High Dose Daptomycin
  • Difficult to treat infections and high bacterial burden
  • Pharmacokinetics – concentration dependent killing
  • Guideline recommendation >6mg/kg/day
    • Consider 8-10 mg/kg/day

• High Dose Daptomycin Combination with β-lactam
  • Greater bactericidal activity
  • Avoid development of resistance
  • See-Saw Effect
What makes Ceftaroline the better β-lactam option?

- Possesses anti-MRSA activity
  - Penicillin Binding Protein 2

- In-vitro evidence regarding superiority over other β-lactams in combination with Vancomycin
### Combination Antibiotic Therapy for Methicillin Resistant Staphylococcus Aureus Infection

**CAMERA-2**

<table>
<thead>
<tr>
<th><strong>Primary Outcome:</strong> Complication-free 90 day survival</th>
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<tr>
<td>• Composite outcome at 90 days of:</td>
</tr>
<tr>
<td>• All-cause mortality</td>
</tr>
<tr>
<td>• Persistent bacteraemia at day 5 or beyond</td>
</tr>
<tr>
<td>• Microbiological relapse</td>
</tr>
<tr>
<td>• Microbiological treatment failure</td>
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**Standard of Therapy**
- Daptomycin 6-10 mg/kg IVPB daily
- Vancomycin 15-20 mg/kg IVPB adjusted dose per site protocol

**Experimental Arm**
- Standard Therapy +
  - IV Flucloxacillin 2g q6hrs OR
  - IV Cloxacillin 2g q6hrs

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*Tong SY, et al. Trials. 2016 Mar 31;17:170*
Patient Case

• Day 3
  • Susceptibilities return → MRSA (Vancomycin MIC =1)
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<td><strong>Daptomycin</strong></td>
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Patient Case

At this point in the patient case, what modification to therapy would you consider making?

A. Continue Vancomycin because patient has not had enough time on therapeutic therapy
B. Discontinue Vancomycin and start Bactrim + Gentamicin
C. Continue Vancomycin and add on Ceftaroline
D. Discontinue Vancomycin and switch to Daptomycin+ Nafcillin
Patient Follow-Up

• Day 6: CrCl 28 - Vancomycin is discontinued, Daptomycin at 10mg/kg q48hrs + Ceftaroline 300mg q12hrs is started, repeat blood cultures drawn

• Day 9: MRSA bacteremia continues, repeat blood cultures

• Day 13: Patient WBC downtrending, afebrile, blood cultures are no growth to date

• Day 17: Latest blood cultures finalized – clear of bacteremia
Key Takeaways

- Consider escalation to salvage therapy when
  - 7 days of therapeutic antibiotics
    - Persistent bacteremia
    - MIC $\geq 2$ for Vancomycin
    - Resistance to Daptomycin
    - Consider sooner if clinical deterioration
  - For salvage therapy consider Daptomycin or Vancomycin with Ceftaroline
    - Other $\beta$-lactams shown in-vitro success as well
Methicillin-Resistant Staphylococcus aureus Infective Endocarditis

What to do with Resistance?

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