Antimicrobial Salvage Therapies for the Treatment of Methicillin-Resistant Staphylococcus aureus Infective Endocarditis

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Pharmacy Grand Rounds
September 27, 2016
Objectives

- Describe the pathophysiology of methicillin-resistant *Staphylococcus aureus* (MRSA) infective endocarditis (IE)
- Review current guideline recommendations for the treatment of MRSA IE
- Discuss current literature evaluating antimicrobial salvage therapies
- Examine limitations of current salvage therapy options when considering penetration through the blood brain barrier
Epidemiology

Microbiology in Infective Endocarditis

- **S. aureus**: 43%
- **CoNS**: 11% (Worldwide), 12% (North America)
- **VGS**: 17% (Worldwide), 9% (North America)
- **Enterococcus**: 6% (Worldwide), 13% (North America)
- **HACEK**: 2% (Worldwide), 0.3% (North America)

S. aureus: Staphylococcus aureus
CoNS: Coagulase-negative staphylococci
VGS: Viridans group streptococci

Pathophysiology

Available at: http://www.mayoclinic.org/diseases-conditions/endocarditis/multimedia/endocarditis/img-20006116
Question 1

• What is the most common causative organism of infective endocarditis?
  • *S. aureus*
  • *Enterococcus*
  • Viridans group streptococcus
  • HACEK
Patient Case

• 48 year old female admitted to an outside hospital with acute disorientation, dizziness, and weakness
  • 50 lb unintentional weight loss over the last 5 months with malaise and lethargy
  • Superficial abscesses on scalp, back, and coccyx
• Labs
  • WBC: 21.0 cells $\times 10^9$/L
  • Temperature: 39.0 C
Patient Case

• PMH
  • Recurrent MRSA skin infections
  • T2DM, recently diagnosed

• SH
  • Family members with CA-MRSA skin infections

• Medications: Metformin 500 mg BID

• Allergies: NKDA

CA-MRSA: community-acquired MRSA
Patient Case

• 8/2 CT Abdomen
  • Pyelonephritis and perinephric abscess
  • Nephrostomy tube and percutaneous pigtail catheter placed
• 8/2 Blood cultures
  • Preliminary results: gram-positive cocci in clusters
  • Empiric treatment with vancomycin and ertapenem

CT: computerized tomography
Patient Case

- 8/3 TEE
  - 1.1 x 0.9 cm mass on the mitral valve
  - 1.8 x 0.9 multilobulated mass attached to the cordae on the left ventricle
  - 1.1 x 1.1 cm mass in left atrium

TEE: Transesophageal echocardiogram
Question 2

• According to the American Heart Association guidelines, what is an appropriate initial antibiotic for the treatment of MRSA native-valve infective endocarditis?
  • Continue vancomycin
  • Continue vancomycin and add rifampin plus gentamicin
  • Change to daptomycin 6 mg/kg/day
  • Change to ceftaroline
American Heart Association (AHA)
Infective Endocarditis Guidelines

AHA/IDSA Guidelines

• Goals of treatment
  • Eradicate infection
  • Sterilize vegetations

• Prolonged antibiotic therapy is required
  • Focal infection
  • High bacterial density
  • Slow rate of bacterial growth within biofilms

AHA/IDSA Guidelines

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose</th>
<th>Duration</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>Trough 10-20 mcg/mL</td>
<td>6 weeks</td>
<td>I-C</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>≥ 8 mg/kg/day</td>
<td>6 weeks</td>
<td>IIb-B</td>
</tr>
</tbody>
</table>

I-C: Benefit outweighs risk and treatment should be performed, based on expert opinion
IIb-B: Benefit may be greater than or equal to the risk and treatment may be considered, based on evaluation in limited populations

### Microbiology Results

#### 8/4 Peripheral Blood Culture and Sensitivity

<table>
<thead>
<tr>
<th>Organism: <em>Staphylococcus aureus</em></th>
<th><strong>Oxacillin</strong></th>
<th>&gt;2 R</th>
<th><strong>Ceftaroline</strong></th>
<th>0.5 S</th>
<th><strong>Clindamycin</strong></th>
<th>&lt;=0.5 S</th>
<th><strong>TMP/SMX</strong></th>
<th>&lt;=.5/9.5 S</th>
<th><strong>Vancomycin</strong></th>
<th>2 S</th>
<th><strong>Linezolid</strong></th>
<th>&lt;=2 S</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daptomycin</strong></td>
<td>1 S</td>
<td></td>
<td><strong>Mupirocin</strong></td>
<td>&lt;=256 S</td>
<td><strong>Rifampin</strong></td>
<td>&lt;=0.5 S</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

S: susceptible  
R: resistant  
I: intermediate  
N: not susceptible
**Microbiology Results**

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<td><strong>Oxacillin</strong></td>
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<td><strong>TMP/SMX</strong></td>
</tr>
<tr>
<td><strong>Daptomycin</strong></td>
</tr>
</tbody>
</table>

S: susceptible
R: resistant
I: intermediate
N: not susceptible
Question 3

• Given the culture and sensitivity results, what modification should be made to the patient’s antibiotic regimen?
  • Continue daptomycin
  • Continue daptomycin and add ceftaroline
  • Change to linezolid
  • Change to ceftaroline
Antimicrobial Salvage Therapies for MRSA Infective Endocarditis
MRSA IE Treatment Challenges

- No standard therapies exist for MRSA IE not susceptible to vancomycin
  - hVISA: reduced susceptibility
  - VISA: intermediate resistance
  - VRSA: high-level resistance

hVISA: Heterogeneous vancomycin-intermediate Staphylococcus aureus
VISA: Vancomycin-intermediate Staphylococcus aureus
VRSA: Vancomycin-resistant Staphylococcus aureus
MRSA IE Treatment Challenges

• MRSA strains with reduced susceptibility to vancomycin have reduced susceptibility to daptomycin
  • Correlated with cell wall thickness

AHA/IDSA Guidelines

- Salvage therapies
  - Trimethoprim/sulfamethoxazole
  - Trimethoprim/sulfamethoxazole plus daptomycin
  - Linezolid
  - Daptomycin plus β-lactam
  - Ceftaroline

Use of Antistaphylococcal β-Lactams to Increase Daptomycin Activity in Eradicating Persistent Bacteremia Due to Methicillin-Resistant *Staphylococcus aureus*: Role of Enhanced Daptomycin Binding

Study Design

• Case series (n=7) of patients with persistent MRSA bacteremia
• DAP-ASBL after treatment with standard therapy
• Results: rapid clearance of bacteremia within 48 hours
  • Restoration of DAP susceptibility
  • Increases in DAP membrane binding
  • Reduction in membrane surface charge

DAP: daptomycin
DAP-ASBL: daptomycin plus anti-staphylococcal β-lactam

Ceftaroline fosamil

- Fifth generation cephalosporin
  - High affinity for PBP 2A
- FDA approved for SSTI and CAP
  - Dose: 600 mg IV Q12H
- Used off-label to treat severe MRSA infections

PBP: penicillin binding protein
SSTI: skin and soft tissue infections
CAP: community-acquired pneumonia

In Vivo Efficacy of Ceftaroline (PPI-0903), a New Broad-Spectrum Cephalosporin, Compared with Linezolid and Vancomycin against Methicillin Resistant and Vancomycin-Intermediate Staphylococcus aureus in a Rabbit Endocarditis Model

Study Design

• Rabbit endocarditis model
• Efficacy against methicillin-resistant and vancomycin-intermediate S. aureus
  • Ceftaroline
  • Linezolid
  • Vancomycin
  • No treatment (control)

Results

The Use of Ceftaroline Fosamil in Methicillin-Resistant *Staphylococcus aureus* Endocarditis and Deep-seated MRSA Infections

Ceftaroline fosamil

• Case series (n=10) of ceftaroline for MRSA NVE and other MRSA infections after treatment failure with vancomycin
  • Ceftaroline 600 mg IV Q8H

• 5 cases with MRSA NVE
  • 4 cases had clear blood cultures after 3-7 days
  • 3 cases had clinical cure

NVE: native valve endocarditis

Treatment Course

- **Daptomycin**
  - 8/6
  - 8/11
  - First negative blood culture
- **Ceftaroline**
  - 8/15
  - Repeat TEE
Treatment Course

- **Daptomycin**
- **Ceftaroline**

- **8/17**
  - Transfer to Mayo Clinic, blood cultures positive

- **8/19**
  - Negative blood culture

- **8/22**
  - CPK: 960 mcg/L

CPK: creatine phosphokinase
Additional Testing

• 8/19 MRI Brain
  • Numerous septic emboli with ring-enhancing abscesses in the right parietal lobe and left centrum semiovale
Question 4

What modification to the antibiotic regimen would be appropriate to improve penetration into the central nervous system?

- Continue ceftaroline
- Add linezolid
- Add rifampin
- Add minocycline
Central Nervous System Penetration of Antimicrobial Agents for MRSA
CNS Penetration

- Drug delivery to the CNS
  - Molecular size
  - Lipophilicity
  - Plasma protein binding
  - Affinity of active transport mechanisms
  - Meningeal inflammation

### MRSA brain abscess, subdural empyema, spinal epidural abscess

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV vancomycin for 4-6 weeks</td>
<td>B-II</td>
</tr>
<tr>
<td>Some experts recommend the addition of rifampin 600 mg daily or 300-450 mg twice daily</td>
<td>B-III</td>
</tr>
<tr>
<td>Alternatives:</td>
<td></td>
</tr>
<tr>
<td>Linezolid 600 mg PO/IV twice daily and</td>
<td></td>
</tr>
<tr>
<td>TMP-SMX 5 mg/kg/dose IV every 8-12H</td>
<td>B-II C-III</td>
</tr>
</tbody>
</table>

**B-II:** Moderate evidence, based on results of non-randomized, controlled clinical trials  
**B-III:** Moderate evidence, based on expert opinion  
**C-III:** Poor evidence, based on expert opinion

Ceftaroline CNS Penetration

- Ceftaroline in a rabbit meningitis model against *E. coli* and *K. pneumoniae*


**Inflamed Meninges**

- **Penetration (%)**: 15.1 ± 9.7

**Non-Inflamed Meninges**

- **Penetration (%)**: 3.17 ± 1.29
## Antibiotic CSF penetration

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>AUC&lt;sub&gt;CSF/AUC&lt;sub&gt;S&lt;/sub&gt;</th>
<th>Acceptable CSF:MIC?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>0.14</td>
<td>0.3</td>
</tr>
<tr>
<td>Linezolid</td>
<td>0.9</td>
<td>Not available</td>
</tr>
<tr>
<td>Rifampin</td>
<td>0.22</td>
<td>Not available</td>
</tr>
<tr>
<td>Tetracycline (doxycycline)</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**AUC**: area under the curve  
**CSF**: cerebrospinal fluid  
**S**: serum  
**MIC**: minimum inhibitory concentration  

Nau et al. *Clin Microbiol Rev.* 2010;23(4):858-83
Treatment Course

Ceftaroline

8/19

8/20
CPK: 960 mcg/L

8/22

8/26
WBC: 2.0 x10⁹/L
Platelets: 140 x10⁹/L

8/27

8/30
Discharge

Linezolid
Minocycline

8/30

CPK: creatine phosphokinase
WBC: white blood cell
Patient Case Recommendations

- MRSA NVE treatment
  - Initial treatment with vancomycin
  - Daptomycin
  - Daptomycin plus ceftaroline
  - Ceftaroline

- Septic emboli to the brain
  - Initial treatment with linezolid
  - Minocycline
Conclusions

• MRSA is a highly virulent organism and is associated with high morbidity and mortality

• Vancomycin is recommended as first line-therapy for MRSA NVE

• No standard therapies exist for MRSA IE not susceptible to vancomycin

• Treatment of septic emboli requires careful consideration of antimicrobial CNS penetration
Questions & Discussion