Ceftaroline for MRSA Bacteremia

Learning Objectives:

1. Review epidemiology and pathophysiology of methicillin-resistant Staphylococcus aureus bacteremia (MRSAB)
2. Evaluate current therapeutic options for MRSAB
3. Assess ceftaroline as a potential treatment option for MRSAB
4. Evaluate evidence of use of ceftaroline for treatment of MRSAB
I. **Staphylococcus aureus**\(^1\)-\(^2\)
   a. Microbiology: gram-positive cocci in clusters
      i. Golden colonies, catalase positive
      ii. Odor: sweaty gym socks
   b. Natural colonizer of skin and respiratory tract
      i. 3/10 people will grow *S. aureus* in their nares\(^2\)
   c. Types of infections
      i. Skin and soft tissue (SSTI)
      ii. Bacteremia and infective endocarditis
      iii. Bone and joint infections
         1. Osteomyelitis
         2. Prosthetic joint infections
   d. Resistance to antibiotics develops quickly\(^3\)

**Figure 1**

i. Penicillin Resistance: narrow spectrum β-lactamase production
ii. Methicillin-resistant *S. aureus* (MRSA) confers resistance to (almost) all β-lactam antibiotics via alterations in penicillin binding proteins (PBP)
iii. Vancomycin-intermediate *S. aureus* (VISA): increased thickening of cell walls and loss of gene regulator of virulence pathways
iv. Vancomycin-resistant *S. aureus* (VRSA): acquired vanA gene from an Enterococcal plasmid
I. Epidemiology\(^4-7\)
   a. Substantial cause of healthcare associated infections
   b. Historically seen in hospitalized patients or those with healthcare exposure
   c. MRSA prevalence in intensive care units (ICU) doubled from 1992 to 2003\(^7\)

II. Community-acquired MRSA (CA-MRSA)\(^8-9\)
   a. Mid-2000s, MRSA seen in patients without healthcare exposure
   b. Different strain than seen in healthcare-associated MRSA (HA-MRSA)
   c. Typically SSTI in young, otherwise healthy people
   d. Spread by close physical contact: athletes involved in football and wrestling, soldiers kept in close quarters, inmates, childcare workers, and residents of long-term care facilities

III. MRSA Incidence\(^2,10\)
   a. Despite increases previously seen in HA-MRSA and CA-MRSA, the overall incidence of MRSA from 2005 to 2011 has declined by 31%
   b. Largest declines were seen in hospitalized patients (54%)
   c. CA-MRSA infections increased rapidly in the past decade, and while these increases are slowing, they are not on the same downward trend as HA-MRSA

   a. MRSA is classified as a serious threat
      i. 80,461 severe MRSA infections per year in the US
      ii. 11,285 deaths per year in the US
   b. Although overall incidence of MRSA is decreasing, MRSA infections remain common
MRSA Bacteremia

I. Epidemiology

a. MRSA bacteremia and endocarditis are serious diseases
b. Blood stream infections are a leading cause of death in US
   i. *S. aureus* responsible for 20% nosocomial blood stream infections
   ii. MRSA accounts for 50% of *S. aureus* strains in nosocomial infections

c. MRSAB is associated with:
   i. High morbidity and mortality rates
   ii. MRSA endocarditis mortality rates 30-37%
   iii. Increased hospital length of stay
   iv. Increased healthcare costs

d. MRSAB has a greater likelihood of persistence vs MSSA
   i. Median time to clearance: 8-9 days vs 3 days
   ii. Increases likelihood of metastatic infection leading to poorer outcomes

e. Factors associated with increased risk of death in MRSAB
   i. Older age
   ii. Nursing home residence
   iii. Severe bacteremia
   iv. Organ dysfunction

II. Types of MRSA bacteremia

a. Uncomplicated MRSA bacteremia
   i. Exclusion of endocarditis
   ii. No implanted prosthetics
   iii. Clearance of bacteremia within 2-4 days
   iv. Defervescence within 72 hours of therapy
   v. No evidence of metastatic sites of infection

b. Complicated MRSA bacteremia
   i. Bacteremia that does not meet the above criteria for uncomplicated bacteremia

III. Treatment of MRSA bacteremia

Figure 4

- Antibiotic Treatment
- Source Control
- Surveillance Blood Cultures
- Echocardiogram

Table 1

<table>
<thead>
<tr>
<th>MRSA Bacteremia</th>
<th>Treatment Options</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncomplicated</strong></td>
<td>Vancomycin 15-20 mg/kg Q8-12H (target trough 15-20 mcg/mL)</td>
<td>2 weeks</td>
</tr>
<tr>
<td></td>
<td>Daptomycin 6 mg/kg daily</td>
<td></td>
</tr>
<tr>
<td><strong>Complicated</strong></td>
<td>Vancomycin 15-20 mg/kg Q8-12H (target trough 15-20 mcg/mL)</td>
<td>4-6 weeks</td>
</tr>
<tr>
<td></td>
<td>Daptomycin 6 mg/kg daily (some experts recommend higher doses of 8-10 mg/kg)</td>
<td></td>
</tr>
</tbody>
</table>

a. Antibiotic treatment - duration dictated by type of bacteremia
b. Surveillance blood cultures
   i. Additional blood cultures 2-4 days after initial positive blood cultures and as
      needed thereafter until clearance of bacteremia
   ii. Documentation of clearance determines start time of therapy

    c. Source control
       i. Clinical assessment to identify source and extent of infection
       ii. Source control performed if possible

    d. Echocardiogram
       i. Echocardiography is recommended in all patients with bacteremia to evaluate for
          endocarditis
       ii. Transesophageal echocardiogram (TEE) is preferred over transthoracic
          echocardiogram (TTE) as it is a more sensitive test

IV. Vancomycin\(^5,12-15\)
    a. Glycopeptide bactericidal antibiotic that binds to the D-alanyl-D-alanine terminating
       pentapeptide, preventing cross-linking of the cell membrane and inhibiting cell wall
       synthesis, thereby causing cell death
    b. Gold standard for MRSA bacteremia
    c. Dosing: target trough level of 15-20 mcg/mL
    d. Treatment failures and poor outcomes have been seen with vancomycin
       i. Variable dosing/levels
       ii. Limited penetration of bone, lung epithelial fluid, CSF
       iii. Slowly bactericidal, especially a concern with higher innocula
    e. Treatment failures with minimum inhibitory concentration (MIC) > 2 mcg/mL
    f. Resistant strains - VISA, VRSA

V. Daptomycin\(^5,12-16\)
    a. Cyclic bactericidal lipopeptide antibiotic that binds to bacterial cell membranes, causing
       cell death by inducing rapid depolarization of membrane potential and leading to
       disruption of DNA, RNA, and protein synthesis
    b. Emergence of reduced susceptibilities to daptomycin has been observed in several
       patients who experienced treatment failure
    c. Correlations have been seen between daptomycin nonsusceptibility (NS) and increasing
       vancomycin MICs
    d. Concentration dependent killing – may need higher doses up to 8-10 mg/kg

VI. MIC Breakpoints\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>MIC (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>≤ 2</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>≤ 1</td>
</tr>
</tbody>
</table>

VII. MRSA Resistance/Treatment failures\(^5,12-15,17\)
    a. Persistent MRSA bacteremia
       i. Challenging clinical situation, especially if source control is not possible
       ii. Increased risk on individual patient outcomes such as morbidity and increased
           health care utilization
       iii. Selection pressure on bacteria in a persistent high-inoculum focus of infection
           can drive antibiotic resistance
b. Bacteremia that is not cleared at/around day 7 of adequate treatment, should be assessed to determine whether a change in therapy is indicated
   i. Patient's overall clinical response
   ii. Vancomycin trough serum concentrations
   iii. Results of susceptibility testing
   iv. Presence of/ability to remove other foci of infection

c. Vancomycin treatment failures
   i. Slow bactericidal activity
   ii. Emergence of strains with reduced susceptibility
   iii. Inadequate debridement or retention of prosthetic device
   iv. At this time, no alternative regimen has proven to be superior to vancomycin in achieving clinical cure or sterilizing blood cultures

VIII. Alternative treatment options for vancomycin resistant strains\textsuperscript{5, 15, 17}
   a. Recommend change in therapy rather than addition of other agents
   b. Daptomycin
      i. Isolates with vancomycin MIC $\geq 2$ mcg/mL are associated with daptomycin NS strains with MICs $>1$ mcg/mL
      ii. May need to use higher doses of 10 mg/kg/day
      iii. Potential combination with trimethoprim-sulfamethoxazole

IX. Alternative treatment options for vancomycin resistant and daptomycin nonsusceptible strains\textsuperscript{5, 15, 17}
   a. Quinupristin-dalfopristin IV 7.5 mg/kg Q8H
      i. Used successfully as salvage therapy in patients with vancomycin treatment failure, although response rates are lower for patients with endocarditis or bacteremia of unknown source
   b. Trimethoprim-sulfamethoxazole IV 5mg/kg BID
      i. Bactericidal in vitro, but inferior to vancomycin for treatment of \textit{S. aureus}
      ii. Potential combination with daptomycin
   c. Linezolid 600mg PO/IV BID
      i. Has been used with success in MRSA infections, however treatment failures have been seen
   d. Telavancin IV 10 mg/kg daily
      i. One case of MRSA bacteremia and tricuspid valve endocarditis was successfully treated
   e. Vancomycin or daptomycin + $\beta$-lactam
      i. Vancomycin combination has been shown to be synergistic \textit{in vitro} and \textit{in vivo} for VISA and VRSA
      ii. Similar observations have been seen with daptomycin in combination with $\beta$-lactams due to daptomycin nonsusceptible strains

X. Newer MRSA Treatment Options\textsuperscript{14-15, 17}
   a. Ceftaroline
      All have MRSA activity,
   b. Dalbavancin
      however there is little to no
   c. Oritavancin
      data available for their use in
   d. Tedizolid
      bacteremia
Table 3

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Ceftaroline Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl &gt;30-50 mL/min</td>
<td>400mg Q12H</td>
</tr>
<tr>
<td>CrCl 15-30 mL/min</td>
<td>300mg Q12H</td>
</tr>
<tr>
<td>CrCl &lt; 15 mL/min</td>
<td>200mg Q12H</td>
</tr>
<tr>
<td>ESRD on HD</td>
<td>200mg Q12H</td>
</tr>
</tbody>
</table>

VI. Adverse Reactions
   a. Diarrhea, nausea, rash, hypokalemia, ↑ LFTs
   b. Direct Coombs’ seroconversion

VII. Monitoring Parameters: renal function

VIII. Drug Interactions: minimal potential for interactions – not an inducer, inhibitor or substrate of CYP450 enzymes

IX. Resistance is expected to be minimal; however, ~2-3% are nonsusceptible at baseline

X. MIC Breakpoints

<table>
<thead>
<tr>
<th></th>
<th>MIC (mcg/mL)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>≤ 2</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>≤ 1</td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>≤ 1</td>
</tr>
</tbody>
</table>
XI. Pharmacokinetics

**Table 5**

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>21 mcg/mL</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>1 hr</td>
</tr>
<tr>
<td>AUC</td>
<td>56 mcg/mL/hr</td>
</tr>
<tr>
<td>V&lt;sub&gt;d&lt;/sub&gt;</td>
<td>20 L</td>
</tr>
<tr>
<td>Protein binding</td>
<td>20%</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>2.7 hrs</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine (88%); feces (6%)</td>
</tr>
</tbody>
</table>

XII. Pharmacodynamics

a. Bactericidal time-dependent killing
   i. \( f \% T > \text{MIC} = \) percentage of time during the dosing interval that free-drug concentrations remain above MIC
   ii. Goal \( f \% T > \text{MIC} > 50\% \)

b. Van Wart et al<sup>23</sup>
   i. Monte Carlo simulations: evaluated PK-PD target attainment by MIC in simulated patients following IV administration of ceftaroline 600mg Q12H and simulated patients with renal impairment administered various dosing regimens
   ii. Bacterial Reduction Endpoints

**Table 6**

<table>
<thead>
<tr>
<th>( f % T &gt; \text{MIC} )</th>
<th>Bacterial Reduction Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 26</td>
<td>Bacterial stasis</td>
</tr>
<tr>
<td>≥ 36</td>
<td>1-log&lt;sub&gt;10&lt;/sub&gt; CFU reduction</td>
</tr>
<tr>
<td>≥ 51</td>
<td>2-log&lt;sub&gt;10&lt;/sub&gt; CFU reduction</td>
</tr>
</tbody>
</table>

iii. Target attainment for ceftaroline 600mg Q12H for normal renal function (CrCl ≥ 80 mL/min)

**Figure 5**

1. MRSA with an MIC of 1 treated with ceftaroline 600mg Q12H in normal renal function resulted in 97% target attainment of \( f \% T > \text{MIC} \) ≥ 51
2. MIC distribution was based on contemporary surveillance data

iv. Conclusions
   1. Ceftaroline dosed at 600mg Q12H in normal renal function attains appropriate PK-PD targets required for efficacy
   2. Similar results were seen in renally adjusted ceftaroline dosing regimens
XIII. Why even think about using ceftaroline for MRSA bacteremia?
   a. MRSA coverage
   b. Ceftaroline is a \(\beta\)-lactam
   c. Favorable PK/PD
   d. High barrier to resistance
   e. No need to monitor drug levels

XIV. Why are we even talking about ceftaroline? \(^5,24\)
   a. \(\beta\)-lactams have better outcomes in MSSA bacteremia compared to vancomycin
      i. Vancomycin kills staphylococci more slowly than \(\beta\)-lactams
      ii. Per guidelines “clearly inferior to \(\beta\)-lactams for MSSA bacteremia and endocarditis”
      iii. Superior to vancomycin in preventing recurrence of bacteremia
      iv. Associated with lower mortality rates
   b. Ceftaroline is a \(\beta\)-lactam

XV. FDA Approval Trials
   a. CANVAS I & II \(^25\)
      i. Determine noninferiority of clinical cure rate with ceftaroline monotherapy, compared with that achieved with vancomycin plus aztreonam combination therapy for the treatment of complicated SSTIs
      ii. Ceftaroline achieved high clinical cure rates and was efficacious against complicated SSTIs caused by MRSA and other common SSTI pathogens
      iii. Small MRSA bacteremia subpopulation
         1. In pooled analysis: trend towards higher clinical cure rate for vancomycin plus aztreonam arm

<table>
<thead>
<tr>
<th></th>
<th>Cure Rate, n/n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftaroline</td>
<td>6/7 (85.7)</td>
</tr>
<tr>
<td>Vancomycin plus</td>
<td>2/2 (100)</td>
</tr>
<tr>
<td>aztreonam</td>
<td></td>
</tr>
</tbody>
</table>

|                  |                                  |
| MRSA Bacteremia  |                                  |

   b. FOCUS I & II \(^26\)
      i. Ceftaroline was evaluated for treatment of CAP in 2 randomized, double-blinded, multicenter trials versus ceftriaxone
      ii. Ceftaroline was found to be noninferior to ceftriaxone
      iii. No MRSA bacteremia subgroup

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Literature Review – Ceftaroline Monotherapy

I. Ho et al, 2012
   a. Case series of 6 patients in which ceftaroline was utilized as salvage monotherapy for persistent MRSAB or endocarditis

II. Polenakovic et al, 2013
   a. Retrospective chart review of 31 patients with MRSAB treated with ceftaroline

III. Casapao et al, 2014
   a. Retrospective observational multicenter study that analyzed clinical and microbiological outcomes of 527 patients treated with ceftaroline ≥ 72 hours
I. Case series of 6 patients in which ceftaroline was utilized as salvage monotherapy for persistent MRSAB or endocarditis
   a. Therapy was initiated with ceftaroline 600mg Q8H after multiple doses of MRSA-active therapy
      i. Rationale for dosing: PD models and severity of infections
         1. Ensure optimal %T>MIC

<table>
<thead>
<tr>
<th>Source of MRSAB</th>
<th>Days of Prior Therapy (Agent)</th>
<th>Duration of Bacteremia (days)</th>
<th>Ceftaroline Duration of Therapy (weeks)</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Endocarditis</td>
<td>13 (VAN) then 4 (DAP)</td>
<td>18*</td>
<td>6</td>
<td>Resolution</td>
</tr>
<tr>
<td>2 Endocarditis</td>
<td>15 (VAN)</td>
<td>15</td>
<td>3 (LZD x 3)</td>
<td>Resolution</td>
</tr>
<tr>
<td>3 SSTI, uveitis, endocarditis</td>
<td>22 (VAN)</td>
<td>2**</td>
<td>3 (LZD x 3)</td>
<td>Resolution</td>
</tr>
<tr>
<td>4 UTI</td>
<td>11 (VAN)</td>
<td>11</td>
<td>1.5</td>
<td>Death</td>
</tr>
<tr>
<td>5 Uveitis, ethmoid osteomyelitis</td>
<td>12 (VAN)</td>
<td>13</td>
<td>2 (VAN x 3)</td>
<td>Resolution</td>
</tr>
<tr>
<td>6 Prostatitis, septic thrombophlebitis</td>
<td>8 (VAN)</td>
<td>13</td>
<td>3 (DAP for home IV)</td>
<td>Resolution</td>
</tr>
</tbody>
</table>

* Bacteremia cleared after 13 days, but relapsed at day 17. Cleared again on day 18, day 1 of ceftaroline.
** Cleared bacteremia on day 2 of vancomycin, however developed uveitis on day 22 and was switched to ceftaroline

b. Characteristics of ceftaroline therapy
   i. Conversion to ceftaroline
      1. Previous treatment: vancomycin or daptomycin
      2. Median duration of previous therapy: 13.5 days
      3. Short duration of bacteremia after switch to ceftaroline
   ii. Complications
      1. Acute respiratory failure that required intubation, evidence of GI bleed
         → patient expired
         a. Factors not thought to be associated with infection
      2. Limited patient follow-up information suggests clinical and microbiological cure with no relapses or emergence of resistance

c. Take Home Message
   i. First case series to report on use of ceftaroline for MRSAB
   ii. All patients received multiple doses of MRSA-active therapy prior to initiation with ceftaroline and subsequently cleared their bacteremia
   iii. Limited follow-up does not give insight into long-term adverse events related to prolonged duration of therapy with ceftaroline
I. Retrospective chart review of 31 patients with MRSAB treated with ceftaroline
   a. Inclusion/Exclusion

Figure 6

<table>
<thead>
<tr>
<th>Patients receiving ceftaroline (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excluded (n=81)</td>
</tr>
<tr>
<td>- No MRSAB (n=72)</td>
</tr>
<tr>
<td>- Non-evaluable (n=4)</td>
</tr>
<tr>
<td>- &lt; 7 days of therapy</td>
</tr>
<tr>
<td>- Bloodstream co-infection (n=2)</td>
</tr>
<tr>
<td>Patients meeting inclusion criteria (n=31)</td>
</tr>
</tbody>
</table>

II. Sources

Table 9

<table>
<thead>
<tr>
<th>Source of Bacteremia</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central venous catheter</td>
<td>7</td>
</tr>
<tr>
<td>Complicated ABSSSI</td>
<td>6</td>
</tr>
<tr>
<td>IVDU</td>
<td>5</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3</td>
</tr>
<tr>
<td>Arteriovenous graft</td>
<td>2</td>
</tr>
<tr>
<td>Orthopedic implant</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
</tr>
<tr>
<td>Met criteria for endocarditis</td>
<td>9</td>
</tr>
</tbody>
</table>

III. Most common rationales for ceftaroline use
   a. Vancomycin MIC $\geq$ 2 mcg/mL
   b. Persistent bacteremia
   c. Poor clinical response to therapy as documented by treating ID physician

IV. Characteristics of ceftaroline therapy

Table 10

<table>
<thead>
<tr>
<th>Ceftaroline Therapy</th>
<th>Result, n (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of previous MRSA therapy, days</td>
<td>5 (1-30+)</td>
</tr>
<tr>
<td>Median duration of ceftaroline therapy, days</td>
<td>30 (7-60)</td>
</tr>
<tr>
<td>Median total daily dose of ceftaroline, mg</td>
<td>1200 (400-1800)</td>
</tr>
</tbody>
</table>
V. Outcomes

Table 11

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Result, n (%) (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical success</td>
<td>23 (74.2)</td>
</tr>
<tr>
<td>Microbiological cure</td>
<td>20 (64.2)</td>
</tr>
<tr>
<td>Median time to clearance of bacteremia on ceftaroline, days</td>
<td>3 (1-8)</td>
</tr>
<tr>
<td>Mortality</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Recurrent bacteremia</td>
<td>3 (9.7)</td>
</tr>
</tbody>
</table>

VI. Adverse Events

Table 12

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>N (%) (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requiring cessation of treatment</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Antibiotic-associated diarrhea</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Eosinophilic pneumonia</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Peripheral eosinophilia*</td>
<td>2 (6.5)</td>
</tr>
</tbody>
</table>

*resolved without cessation of ceftaroline

VII. Take Home Message

a. Larger case series in which ceftaroline was used successfully as salvage treatment
b. Ceftaroline is a relatively safe drug when used for an extended period of time; however clinicians need to be aware of rare occurrence of eosinophilia pneumonia
I. Retrospective observational multicenter study that analyzed clinical and microbiological outcomes of 527 patients treated with ceftaroline ≥ 72 hours
   a. Exclusion: ceftaroline was used for
      i. Prophylactic therapy
      ii. Infection caused by an agent known to be resistant to ceftaroline alone without MRSA infection

II. Characterization of Types of Infections

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients, n(%) (N=527)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus Infection</td>
<td></td>
</tr>
<tr>
<td>ABSSSI</td>
<td>175 (35.1)</td>
</tr>
<tr>
<td>Bacteria</td>
<td>148 (28.1)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>99 (18.8)</td>
</tr>
<tr>
<td>Bone and joint</td>
<td>81 (15.4)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (2.7)</td>
</tr>
<tr>
<td>Positive Culture Results</td>
<td></td>
</tr>
<tr>
<td>S. aureus</td>
<td>327 (62)</td>
</tr>
<tr>
<td>MRSA</td>
<td>271/327 (89)</td>
</tr>
<tr>
<td>Previous Antibiotic Use</td>
<td></td>
</tr>
<tr>
<td>Vancomycin, daptomycin, or linezolid</td>
<td>422 (80.1)</td>
</tr>
</tbody>
</table>

III. Ceftaroline Usage

<table>
<thead>
<tr>
<th>Rationale for ceftaroline use</th>
<th>Patients, n(%) (N=527)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease progression on prior therapy</td>
<td>253 (48)</td>
</tr>
<tr>
<td>Simplified regimen for multiple indications</td>
<td>95 (18)</td>
</tr>
<tr>
<td>Anticipated risk of toxicity</td>
<td>79 (15)</td>
</tr>
<tr>
<td>Ceftaroline dosing</td>
<td></td>
</tr>
<tr>
<td>600mg Q12H or renally adjusted equivalent</td>
<td>452 (85.5)</td>
</tr>
<tr>
<td>600mg Q8H</td>
<td>76 (14.4)</td>
</tr>
</tbody>
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IV. S. aureus Bacteremia Subpopulation

<table>
<thead>
<tr>
<th>S. aureus Bacteremia Subpopulation</th>
<th>Patients, n/n (%) or n (range) (N=133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus bacteremia</td>
<td>133/148 (90)</td>
</tr>
<tr>
<td>MRSA bacteremia</td>
<td>123/133 (92.5)</td>
</tr>
<tr>
<td>Off-label dosing (600mg Q8H)</td>
<td>44 (33.1)</td>
</tr>
<tr>
<td>Median duration of ceftaroline treatment during hospitalization, days</td>
<td>9 (4-16)</td>
</tr>
<tr>
<td>MRSA treatment prior to ceftaroline</td>
<td>143/148 (96.6)</td>
</tr>
<tr>
<td>Time to switch to ceftaroline, days</td>
<td>6 (3-11)</td>
</tr>
<tr>
<td>Time to clearance of bacteremia on ceftaroline, days</td>
<td>2.5</td>
</tr>
</tbody>
</table>
V. Outcomes

Table 16

<table>
<thead>
<tr>
<th>Overall Outcomes</th>
<th>Overall</th>
<th>S. aureus Bacteremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical success rate</td>
<td>426/484 (88)</td>
<td>101/129 (78.3)</td>
</tr>
<tr>
<td>Microbiological cure</td>
<td>--</td>
<td>21/148 (14.8)</td>
</tr>
<tr>
<td>Mortality during hospitalization</td>
<td>40/527 (7.6)</td>
<td>109/120 (90.8)</td>
</tr>
</tbody>
</table>

VI. Outcomes by Dosing Strategy in Bacteremia Subgroup

Figure 7

VII. Adverse Reactions

Table 17

<table>
<thead>
<tr>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experienced any adverse reaction, n/n (%)</td>
</tr>
<tr>
<td>Patient in bacteremia subgroup with adverse reaction, n/n (%)</td>
</tr>
<tr>
<td>Patients receiving off-label dosing with adverse reaction, n/n (%)</td>
</tr>
<tr>
<td>Median duration of ceftaroline to onset of adverse reaction, days</td>
</tr>
<tr>
<td>Most common adverse reactions</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*adverse reaction more common and occurred in patients receiving off-label dosing

VIII. Take Home Message

a. Large observational analysis of patients receiving ceftaroline with a high MRSA bacteremia population
b. Similar success rates and time to clearance of bacteremia to those in previous case reports/series
c. No difference in clinical cure in MRSA bacteremia using standard or off-label dosing
d. Ceftaroline was also well tolerated with low frequencies of adverse events
   i. More adverse events were seen in off-label dosing
   ii. No reports of treatment cessation
e. A longer duration of ceftaroline therapy is warranted to fully evaluate tolerability
f. Use of off-label dosing, 600mg Q8H, may have potential in treatment of severe infections but deserves further investigations, especially in bacteremia
Ceftaroline and Daptomycin Combination Therapy

I. Daptomycin plus β-lactam synergy
   a. Guidelines mention combination of daptomycin and anti-staphylococcal β-lactams as an option for salvage therapy
   b. *In vitro* studies have shown enhanced killing using the combination
   c. Daptomycin plus ceftaroline — *In vitro* data shows that the combination appears to be potent, with rapid and sustained bactericidal activity

II. Sakoulas et al
   a. Retrospective analysis of 26 cases of refractory staphylococcal bacteremia treated with daptomycin and ceftaroline as salvage therapy
   b. Types of Infections

<table>
<thead>
<tr>
<th>Infection Characteristics</th>
<th>Results, n (%) or median (range) (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staphylococcal Infection</strong></td>
<td></td>
</tr>
<tr>
<td>MRSA</td>
<td>20 (76)</td>
</tr>
<tr>
<td>MSSA</td>
<td>2 (8)</td>
</tr>
<tr>
<td>VISA</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Methicillin-resistant S. epidermidis</td>
<td>2 (8)</td>
</tr>
<tr>
<td><strong>Patients with MRSAB and endocarditis</strong></td>
<td>10/20 (50)</td>
</tr>
<tr>
<td><strong>Daptomycin + ceftaroline salvage therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Second-line therapy</td>
<td>8 (31)</td>
</tr>
<tr>
<td>Third-line therapy</td>
<td>13 (50)</td>
</tr>
<tr>
<td>Fourth-line therapy</td>
<td>5 (19)</td>
</tr>
<tr>
<td><strong>Bacteremia duration prior to combination therapy, days</strong></td>
<td>10 (3-23)</td>
</tr>
</tbody>
</table>

c. Ceftaroline Usage

<table>
<thead>
<tr>
<th>Ceftaroline Usage</th>
<th>Results, n (%) or median (range) (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftaroline dosing</td>
<td></td>
</tr>
<tr>
<td>Q8H</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Q12H</td>
<td>19 (73)</td>
</tr>
<tr>
<td>Q24H</td>
<td>2 (8)</td>
</tr>
<tr>
<td><strong>Duration of combination therapy, days</strong></td>
<td>16 (3-16)</td>
</tr>
<tr>
<td><strong>Duration of combination therapy plus follow-up antibiotics, days</strong></td>
<td>42 (8-132)</td>
</tr>
<tr>
<td><strong>Duration of bacteremia after combination therapy, days</strong></td>
<td>2 (1-6)</td>
</tr>
</tbody>
</table>

d. Outcomes
   i. Survival: 25/26 patients (96%)
   ii. Adverse Effects
      1. No adverse effects attributed to ceftaroline
      2. Eosinophilic pneumonia attributed to daptomycin
   iii. *In Vitro* Testing:
      1. Combination demonstrated considerable synergy over each drug alone
      2. Ceftaroline induces daptomycin binding in MSSA and MRSA comparably to nafcillin
      3. Significantly enhances neutrophilic killing of MRSA

e. Take Home Message
   i. Combination therapy with daptomycin and ceftaroline appears to rapidly clear bacteremia in two days
      1. Results are similar to those seen in ceftaroline monotherapy case series
   ii. No adverse effects were attributed to ceftaroline; however, eosinophilic pneumonia was seen in ceftaroline monotherapy
Controversies with Ceftaroline

I. Controversies
   a. Where is ceftaroline’s place in MRSAB therapy?
   b. What is the optimal dose?
   c. When should ceftaroline monotherapy be used versus combination therapy?

II. Pros/Cons

Table 20

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bactericidal agent with good MRSA activity even against vancomycin resistant and daptomycin nonsusceptible strains</td>
<td>Off-label dosing (600mg Q8H)</td>
</tr>
<tr>
<td>Clearance of bacteremia is quick (2-3 days)</td>
<td>Faster clearance of bacteremia was seen after many days of vancomycin or daptomycin, unsure of effect of previous therapy</td>
</tr>
<tr>
<td>Regimens have been well tolerated</td>
<td>Limited follow up data - unknown side effects of prolonged course of therapy required for bacteremia and higher off-label dosing strategy</td>
</tr>
<tr>
<td>Favorable PK/PD profile</td>
<td>Lack of randomized control trials, only case reports/series</td>
</tr>
</tbody>
</table>

III. Where does ceftaroline fit in?
   a. Vancomycin or daptomycin are still first line
   b. Ceftaroline is an option for salvage treatment for MRSAB
      i. Take into account the clinical scenario and condition of the patient
      ii. Bacteremia persists > 7 days and received adequate treatment
      iii. Vancomycin resistance and daptomycin nonsusceptibility
      iv. Allergies or intolerance of vancomycin or daptomycin

IV. What is the optimal dose for ceftaroline?
   a. FDA approved dose is 600mg Q12H for ABSSSI and CAP
   b. Dose was validated by PK-PD studies previously mentioned
   c. However – Vidaillac et al conducted an in vitro PK-PD study comparing Q12H vs Q8H
      i. Target $f\%T>MIC > 50\%$ for bactericidal effect
      ii. 12 hour regimen: $f\%T>MIC = 83\%$
      iii. 8 hour regimen: $f\%T>MIC = 100\%$
      iv. This was in the strains with an MIC = 0.5 mcg/mL
      v. No difference in time-kill curves between Q12H versus Q8H
         1. Except ceftaroline was superior in VISA/VRSA strains

V. Potential for more adverse events with higher dose
   a. Concern with longer treatment durations required for bacteremia and endocarditis
   b. Casapao et al showed higher incidence of adverse events with off-label dosing
   c. Eosinophilic pneumonia
      i. Required treatment cessation in one patient in Polenakovik et al
      ii. Attributed to daptomycin in combination therapy case series
   d. Hematologic toxicities
      i. Jain et al
         1. Retrospective review of 12 cases treated with ceftaroline for refractory staphylococcal infections
         2. 9/12 (75%) discontinued due to adverse effects
3. 7/12 discontinued due to hematologic toxicities – neutropenia or anemia
4. Average time to discontinuation: 22 days

ii. Furtek et al³⁷
1. Retrospective analysis of 41 patients that received at least 7 days of ceftaroline
2. 5 (12%) patients developed neutropenia requiring treatment cessation

iii. Neurotoxicity³⁸
1. Higher doses of cefepime in mild renal impairment leading to higher troughs, was associated with neurotoxicity
2. Will there be similar results with ceftaroline?

VI. Ceftaroline monotherapy versus combination therapy with daptomycin
a. In vitro studies have shown the combination of daptomycin and ceftaroline to be potently bactericidal, more so than using either agent alone
b. No difference in time to clearance of bacteremia using the combination therapy vs ceftaroline alone seen in case series
c. Potential for additive side effects using prolonged therapy with both agents
d. Expensive regimen
e. Would be interesting to see if combination therapy can be used to clear bacteremia and then de-escalate to a single agent

Conclusions

I. Vancomycin or daptomycin remain first line therapies for MRSA bacteremia
II. Ceftaroline is an valid option for salvage therapy in the populations described
   a. Bacteremia persists > 7 days and received adequate treatment
   b. Vancomycin resistance and daptomycin nonsusceptibility
   c. Allergies or intolerance of vancomycin or daptomycin

III. Dosing is controversial as there is potential for increase of adverse events with prolonged duration of high dose therapy
   a. Available data doesn’t seem to show a difference between Q12H and Q8H dosing
   b. Many of the patients in the case series were treated successfully with Q8H
   c. Prefer Q8H dosing, especially in these very ill patients, until there is more data

IV. At this time, I would not recommend use of ceftaroline and daptomycin combination therapy over ceftaroline monotherapy
   a. No advantage over ceftaroline in clearance of bacteremia


18. Teflaro (ceftaroline fosamil) [prescribing information]. St. Louis, MO: Forest Pharmaceuticals Inc; 2013


