Objectives:
1. Discuss prevalence, morbidity and mortality associated with *Staphylococcus aureus* (*S. aureus*) bacteremia
2. Identify complications associated with *S. aureus* bacteremia (SAB)
3. Explain difficulties associated with treatment of infections due to methicillin resistant *Staphylococcus aureus* (MRSA)
4. Discuss evidence of linezolid as alternative drug therapy for SAB
I. *Staphylococcus aureus* Bacteremia (SAB)
   a. Epidemiology
      i. One of the leading causes of both community-acquired and hospital-acquired bacteremia\(^1\)\(^-\)\(^3\)
         1. Styers et al\(^3\)
            a. Leading cause of bacteremia from hospital inpatients\(^2\)\(^-\)\(^3\)

   Figure 1: Cause of bacteremia in hospitalized patients

![Bar chart of bacteremia causes in hospitalized patients]

   b. 2\(^{nd}\) leading cause of bacteremia from outpatients\(^2\)\(^-\)\(^3\)

   Figure 2: Causes of bacteremia in outpatients

![Bar chart of bacteremia causes in outpatients]
2. Wisplinghoff et al\textsuperscript{1}
   a. 24,179 cases of nosocomial blood stream infections (BSI)
   b. 2\textsuperscript{nd} most common cause of nosocomial bacteremia after coagulase-
      negative staphylococci (approximately 20% of bacteremias from 1995-
      2002)
   ii. Incidence of has increased in the last several decades\textsuperscript{2}
       1. Increased frequency of invasive surgery
       2. Increased use of intravascular devices
   iii. Sources
       1. Intravascular devices
       2. Pneumonia
       3. Skin and soft tissue infections
       4. Surgery
       5. Urinary tract
b. Morbidity and mortality data
   i. High morbidity and mortality even with appropriate treatment\textsuperscript{3,4}
   ii. Morbidity
       1. Metastatic complications (11-53%)\textsuperscript{5-7}
          a. Incidence
             i. Hospital-acquired SAB: 20%
             ii. Community-acquired SAB: over 40%
          b. Types of complications
             i. Infective endocarditis
             ii. Prosthetic device infection
             iii. Metastatic seeding
                1. Vertebral osteomyelitis
                2. Septic arthritis
                3. Splenic abscess
                4. Thrombophlebitis
                5. Central nervous system
                6. Pulmonary
                7. Soft tissue infections
                8. Bacteriuria
          c. Risk factors for developing complications\textsuperscript{6}
             i. Persistent bacteremia (72-96 hrs after appropriate treatment
                started)
             ii. Community acquisition
             iii. Skin lesions suggestive of distant metastases
             iv. Persistent fever
iii. Mortality
   1. Pre-antibiotic era rates exceeded 80%4
   2. Overall, approximately 18-40%1,7
      a. Cosgrove et al8 performed meta-analysis (1980-2000)
         i. 23.4% MSSA vs 36.4% MRSA
      ii. Limitations
         1. Empiric treatment has changed
         2. Superior treatment for MSSA
   c. Resistance issues of Staphylococcus aureus
      i. Proportion of S. aureus blood isolates that were MRSA has risen significantly1
         1. 22% in 1995 to 57% in 2001 (p < 0.001)
         1. 57% MRSA
         2. 42% MRSA in non-ICU
         3. 26% MRSA in outpatients
      iii. Styers et al and University Hospital data: Increasing trends in MRSA3

Figure 3: MRSA trends 1998-2005 and University Hospital (UH) trends 1999-20093

        d. Duration of therapy
           i. Controversial
              1. Original study by Wilson and Hamburger (1957) revealed high prevalence of endocarditis (64%) in patients with SAB10
              2. Iannini et al11 (1976)
                 a. Retrospective review of 29 patients with SAB with a removable focus
                 b. Mean duration of treatment was 15.2 days (7-29)
                 c. No late complications occurred but follow-up varied from 2 months to six years
3. Ehni et al\textsuperscript{12} (1989)
   a. Prospectively followed 13 patients with catheter-related SAB for at least 3 months
   b. Used short course therapy (≤ 16 day) with mean duration 11.7 days
   c. 1/13 (8%) developed endocarditis

4. Raad et al\textsuperscript{13} (1992)
   a. Retrospective chart review of 55 patients with catheter-related SAB
   b. Overall complication rate 22%
   c. Late complication rates according to duration of therapy
      i. < 10 days: 17% (3/18) patients
      ii. 10 – 14 days: 0% (0/18)
      iii. ≥ 10 days: 0% (0/10)

5. Jernigan et al\textsuperscript{14}
   a. Meta-analysis of 11 studies to determine effectiveness of short-course (≤ 2 weeks) for catheter-related SAB
   b. Late complication rates of 0-29%
   c. Pooled estimate of late complications 6.1% (95% CI, 2, 10.2)
   d. Authors believed risk too high to promote short-course therapy \(\rightarrow\) proposed randomized trials for optimal duration

6. Fowler et al\textsuperscript{15}
   a. Examined adherence to infectious diseases recommendations for treatment of SAB (see appendix A for full recommendations)
      i. Simple bacteremia \(\rightarrow\) 7 days
      ii. Uncomplicated bacteremia \(\rightarrow\) 14 days
      iii. Endocarditis/deep infection \(\rightarrow\) 4-8 weeks ± surgery
   b. 244 patients followed
   c. Patients whose therapy followed recommendations
      i. Higher cure rate (79.5% vs 64.4%; \(p = 0.01\))
      ii. Lower relapse rate (6.3% vs 18.2%; \(p < 0.01\))

   ii. Current recommendations
   1. Infectious Diseases Society of America (IDSA) Intravascular Catheter-Related Treatment Guidelines\textsuperscript{16}
      a. 4-6 weeks of therapy
      b. Shorter duration (at least 14 days) may be considered in specific patient populations
         i. Catheter removal PLUS
         ii. Absence of diabetes, immunosuppression, prosthetic intravascular device, endocarditis, thrombophlebitis, fever, prolonged bacteremia and evidence of metastatic complications
2. Mandell’s\textsuperscript{17}
   a. Removable focus: 10-14 days
      i. Removal of catheter
      ii. Exclusion of endocarditis
      iii. Follow-up cultures negative at 2-4 days
      iv. Afebrile within 72 hours
      v. Absence of metastatic foci
   b. Skin and soft tissue infection: 14 days
   c. Deep infections: 4-6 weeks
      i. Arthritis
      ii. Osteomyelitis
      iii. Endocarditis

3. UpToDate\textsuperscript{4}
   a. Removable focus: 7 days
      i. Negative TEE
      ii. No valvular abnormalities, afebrile within 72 hrs and no evidence of metastatic complications
      iii. Follow-up cultures are negative in 2-4 days
      iv. No indwelling devices
   b. Valvular abnormalities but no endocarditis: 14 days
      i. Negative surveillance cultures within 3 days
      ii. Lack signs of deep infections
   c. Suspected or proven deep tissue infection: 4-8 weeks
      i. Endocarditis
      ii. Deep tissue infection: osteomyelitis, mediastinitis, deep abscesses
      iii. Persistent bacteremia

II. Therapeutic Options
   a. MSSA
      i. Anti-Staphylococcal beta-lactams are the drug of choice for MSSA
         1. Chang et al\textsuperscript{18}
            a. Patients with SAB (excluding endocarditis)
            b. Bacteriologic failure decreased with nafcillin
               i. 0% (0/18) nafcillin vs 19% (13/70) vancomycin; \( p = 0.058 \)
               ii. Vancomycin associated with relapse; \( p = 0.048 \)
         2. Stryjewski et al\textsuperscript{19}
            a. Hemodialysis-dependent patients with SAB
            b. Treatment failure decreased with cefazolin vs vancomycin
               i. 13% (6/46) cefazolin vs 31.2% (24/77) vancomycin; \( p = 0.02 \)
               ii. Recurrence higher with vancomycin; \( p = 0.08 \)
               iii. Vancomycin associated with treatment failure; \( p = 0.02 \)
3. Kim et al\textsuperscript{20}
   a. Patients with SAB
   b. Higher SAB-related mortality with vancomycin
      i. 37% (10/27) vancomycin vs 18% beta-lactam (47/267); 
         \( p = 0.02 \)
   c. Higher 14-day mortality with vancomycin
      i. 33% (9/27) vancomycin vs 15% beta-lactam (40/267); \( p = 0.03 \)

b. MRSA
   i. Standard therapy
      1. Vancomycin
         a. Drug of choice for MRSA bacteremia
         b. Rates of treatment failure \( \sim 20-50\% \textsuperscript{18, 21} \)
   2. Question of treatment failures associated with increased MIC
      a. CLSI lowered vancomycin breakpoint in 2006\textsuperscript{17, 22}
      b. Studies by Hidayat et al\textsuperscript{23}, Soriano et al\textsuperscript{24}, and Lodise et al\textsuperscript{25} suggest 
         increased MIC associated with treatment failure
   ii. Newer Gram-Positive drugs
      1. Quinupristin/dalfopristin
      2. Linezolid
      3. Daptomycin
      4. Tigecycline
      5. Telavancin

III. Vancomycin vs Linezolid

Table 1: Comparison of Vancomycin and Linezolid\textsuperscript{26-28}

<table>
<thead>
<tr>
<th></th>
<th>Vancomycin</th>
<th>Linezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>Cell wall synthesis inhibitor</td>
<td>Protein synthesis inhibitor</td>
</tr>
<tr>
<td><strong>Cidal/Static</strong></td>
<td>Cidal</td>
<td>Static</td>
</tr>
<tr>
<td><strong>Dosage Form Availability</strong></td>
<td>Intravenous</td>
<td>Intravenous Oral</td>
</tr>
</tbody>
</table>
| **Adverse Events**    | Red man syndrome
                       Rash
                       Nephrotoxicity?
                       Ototoxicity? | Bone marrow suppression (> 14 days)
                       Mitochondrial toxicity: neuropathies and lactic 
                       acidosis (> 28 days)
                       Serotonin syndrome |
| **Routine Therapeutic Drugs Monitoring Performed** | Yes                                         | No                                        |
| **Resistance\textsuperscript{3}** | 0/14,635 (0%)                              | 3/14,635 (0.02%)                          |
| **Cost**              | VA: $5/gram                                 | VA: $98/day                                |
|                       | UH: $5/gram                                 | UH: $186/day                               |

\textsuperscript{*See appendix B for full comparison chart}
IV. Studies (See appendix C for complete charts summaries of studies)

a. Stevens et al
   i. Randomized comparator controlled, open-label trial comparing safety and efficacy of linezolid vs vancomycin for MRSA infections
   ii. Cure rates

<table>
<thead>
<tr>
<th>Table 2: Cure rate for linezolid vs vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>ITT</td>
</tr>
<tr>
<td>MRSA-ITT</td>
</tr>
<tr>
<td>Evaluable MRSA</td>
</tr>
</tbody>
</table>

   iii. Mean duration of therapy similar for linezolid and vancomycin (12.6 days vs 11.3 days)
   iv. Safety: substantially low platelet counts significantly higher in linezolid group vs vancomycin (10% vs 2.9%; p = 0.003)
   v. Critique
      1. Open label trial with small subgroup analysis of bacteremic patients
      2. No mention of vancomycin monitoring or adjustments
      3. Endocarditis patients excluded

b. Shorr et al
   i. Pooled analysis of five prospective, randomized, controlled studies comparing linezolid with vancomycin focusing on bacteremic subset
   ii. Baseline characteristics similar
      1. Mean duration of therapy 12.1 ± 6.5 days in linezolid group vs 11.7 ± 6.8 days in vancomycin group (p = 0.666)
      2. Shorter duration of IV treatment in linezolid group (8.6 days vs 11.5 days, p = 0.004)
   iii. Cure rates

<table>
<thead>
<tr>
<th>Table 3: Cure rates of linezolid vs vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>Clinical cure</td>
</tr>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>MRSA</td>
</tr>
<tr>
<td>Microbiological success</td>
</tr>
<tr>
<td>Survival</td>
</tr>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>MRSA</td>
</tr>
</tbody>
</table>

   iv. Safety: new-onset thrombocytopenia significantly higher in linezolid group vs vancomycin group (13% vs 0%; p = 0.02)
v. Critique
   1. Pooled analysis
   2. Vancomycin dosing adjustments per “local standard of care”
   3. Used cure/failure of primary infection for grouping patients without additional blood cultures (repeat cultures not obtained in 40% of patients)
   4. Missing or indeterminate outcomes were coded as failures
   5. High survival rate (74%) probably due to 1/3 of patients with SSTI and absence of endocarditis
   6. Not all studies monitored for late relapse

c. Jang et al
   i. Retrospective study of patients with persistent SAB using salvage therapy of linezolid ± carbapenem or vancomycin ± aminoglycoside or rifampin
   ii. Important baseline differences

Table 4: Significant baseline characteristics

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Linezolid</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocarditis</td>
<td>1/16 (6%)</td>
<td>4/19 (21%)</td>
</tr>
<tr>
<td>Complication in brain</td>
<td>1/16 (6%)</td>
<td>6/19 (32%)</td>
</tr>
<tr>
<td>Vancomycin trough ≥ 15</td>
<td>12/16 (75%)</td>
<td>8/19 (42%)</td>
</tr>
</tbody>
</table>

iii. Results

Table 5: Early microbiological responses and salvage success rates

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Substitution with Linezolid</th>
<th>Addition to Vancomycin</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Microbiological Response</td>
<td>12/16 (75%)</td>
<td>2/12 (17%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Salvage Success</td>
<td>14/16 (88%)</td>
<td>0/12 (0%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>S. aureus-Related Mortality</td>
<td>2/16 (13%)</td>
<td>10/19 (53%)</td>
<td>0.03</td>
</tr>
<tr>
<td>30-Day Mortality</td>
<td>4/16 (25%)</td>
<td>10/19 (53%)</td>
<td>0.166</td>
</tr>
</tbody>
</table>

iv. Safety: 7/12 (58%) had linezolid-associated thrombocytopenia (developing 7-21 days after initiation)

v. Critique
   1. Retrospective with very small number of patients
   2. Vancomycin group with more severe complications (selections bias)
   3. Does not address duration of vancomycin therapy prior to switch
   4. Address vancomycin troughs
   5. TEE performed on only 37% of patients so true incidence of complicating endocarditis unknown
   6. Results did not match study objective
d. Wilcox et al
i. Randomized, controlled, noninferiority phase III trial of linezolid vs control (vancomycin/β-lactams) for catheter-related bloodstream infections (CRBSI)
ii. Initial test for noninferiority in complicated skin and skin structure infections (cSSSI) and if met → followed with analysis of CRBSI
iii. Population

Table 6: Number of patients in each study group

<table>
<thead>
<tr>
<th>Population</th>
<th>Linezolid</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT (intent-to-treat)</td>
<td>363</td>
<td>363</td>
</tr>
<tr>
<td>MITT (modified intent-to-treat)</td>
<td>269</td>
<td>257</td>
</tr>
<tr>
<td>ME-1 (first microbiologically evaluable group)</td>
<td>193</td>
<td>189</td>
</tr>
<tr>
<td>MME-1 (first modified microbiologically evaluable group)</td>
<td>164</td>
<td>151</td>
</tr>
<tr>
<td>ME-2 (second microbiologically evaluable group)</td>
<td>95</td>
<td>74</td>
</tr>
</tbody>
</table>

iv. Mean duration of treatment similar for linezolid vs control (9.2 ± 5.2 days vs 8.7 ± 5.5 days)

v. Results

Table 7: Primary and secondary outcomes

<table>
<thead>
<tr>
<th>Success</th>
<th>Linezolid</th>
<th>Control</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiological Outcome</td>
<td>Linezolid</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>(Primary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ME-2 S. aureus MRSA</td>
<td>82/95 (86.3%)</td>
<td>67/74 (90.5%)</td>
<td>-13.8 – 5.4</td>
</tr>
<tr>
<td>ME-2 S. aureus MRSA</td>
<td>46/56 (82.1%)</td>
<td>35/42 (83.3%)</td>
<td>-16.3 – 13.9</td>
</tr>
<tr>
<td>ME-2 S. aureus MRSA</td>
<td>21/26 (80.8%)</td>
<td>18/21 (85.7%)</td>
<td>-26.2 – 16.4</td>
</tr>
<tr>
<td>Clinical Outcome (Secondary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ME-2 EOT S. aureus MRSA</td>
<td>73/89 (82%)</td>
<td>61/74 (82.4%)</td>
<td>-12.2 – 11.4</td>
</tr>
<tr>
<td>ME-2 EOT S. aureus MRSA</td>
<td>39/52 (75%)</td>
<td>29/42 (69%)</td>
<td>-12.3 – 24.2</td>
</tr>
<tr>
<td>ME-2 EOT S. aureus MRSA</td>
<td>22/25 (88%)</td>
<td>16/21 (76.2%)</td>
<td>-10.4 – 34.0</td>
</tr>
<tr>
<td>ME-2 TOC S. aureus MRSA</td>
<td>70/93 (75.3%)</td>
<td>59/73 (80.8%)</td>
<td>-18.1 – 7.0</td>
</tr>
<tr>
<td>ME-2 TOC S. aureus MRSA</td>
<td>36/54 (66.7%)</td>
<td>28/42 (66.7%)</td>
<td>-19.0 – 19.0</td>
</tr>
<tr>
<td>ME-2 TOC S. aureus MRSA</td>
<td>19/24 (79.2%)</td>
<td>16/21 (76.2%)</td>
<td>-21.4 – 27.4</td>
</tr>
</tbody>
</table>

vi. Safety: more patients in linezolid group had abnormal platelet values (< 75% of lower limit of normal or baselines value at EOT); 13.1% vs 7.4% (no p-value given)

vii. Critique
1. Open label but primary outcome was microbiologic outcome
2. Power determined for ME patients but MME-1 and ME-2 were used for primary outcome
3. Vancomycin monitoring not addressed
4. Stated similar adverse events but 48/363 (13%) in linezolid group vs 25/363 (7%) in control group discontinued secondary to adverse events (p = 0.006)
5. Very select subgroup of patients (not “typical” CRBSI patient)
e. Endocarditis
   i. Animal studies
      1. Dailey et al\textsuperscript{29}
         a. Rabbit model of aortic valve endocarditis with MRSA
         b. Group
            i. Control
            ii. Vancomycin 25 mg/kg BID
            iii. Linezolid 50 or 75 mg/kg TID
         c. Linezolid at 75 mg/kg with similar number of sterile valves to vancomycin (10/13 vs 11/11)
      2. Chiang et al\textsuperscript{30}
         a. Rabbit model of aortic valve endocarditis with MRSA
         b. Groups
            i. Control
            ii. Vancomycin 30 mg/kg BID
            iii. Linezolid 75 mg/kg TID X 1d then BID or 75 mg/kg TID
            iv. Vancomycin plus linezolid group
         c. Number of sterile valves significantly higher in vancomycin group (control 0/8, vancomycin 3/8, linezolid 0/8, vancomycin plus linezolid 0/8; p < 0.05)
         d. Mean bacterial count on valve significantly lower in vancomycin group (p < 0.05)
         e. In vivo antagonism?
   ii. Human data
      1. Munoz et al\textsuperscript{31}
         a. 42 patient case series
         b. Mostly salvage therapy but no definition of “therapeutic failure”
         c. Variety of organisms (63% \textit{S. aureus})
         d. Successful outcome in 79% patients but mean duration of therapy only 37 days (7-156 days)

V. Summary

Table 8: Pros/Cons with vancomycin and linezolid

<table>
<thead>
<tr>
<th>Pros/Cons</th>
<th>Vancomycin</th>
<th>Linezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>● Cidal</td>
<td>● Static</td>
</tr>
<tr>
<td></td>
<td>● IV only</td>
<td>● IV and PO available</td>
</tr>
<tr>
<td></td>
<td>● Nephrotoxicity?</td>
<td>● Long-term toxicities</td>
</tr>
<tr>
<td></td>
<td>● Routine TDM</td>
<td>● No routine TDM</td>
</tr>
<tr>
<td></td>
<td>● Questions of therapeutic failures</td>
<td>● Limited clinical data</td>
</tr>
<tr>
<td></td>
<td>● Lots of clinical data</td>
<td></td>
</tr>
</tbody>
</table>
VI. Conclusion
   a. Linezolid may be a viable alternative to vancomycin for the treatment of SAB in certain, limited populations
      i. CRBSI, clearance < 72 hrs, negative TEE, no evidence of metastatic complications → finish oral therapy
      ii. cSSSI with quick clearance with above criteria → finish with oral therapy
      iii. Not for serious infections (endocarditis, osteomyelitis, meningitis) as data extremely limited for these types of infections
   b. Must outweigh benefits and risk for long-term therapy with linezolid
References:


Appendix A: Recommendations for Treatment of SAB in Fowler et al study

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple bacteremia</td>
<td>All of the following:</td>
<td>7 days of IV antibiotics</td>
</tr>
<tr>
<td></td>
<td>• TEE negative on d 5-7 of therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Negative surveillance cultures after 2-4 days of therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Removable focus of infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Clinical resolution</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No indwelling prosthetic devices</td>
<td></td>
</tr>
<tr>
<td>Uncomplicated bacteremia</td>
<td>One or more of the following:</td>
<td>14 days of IV antibiotics</td>
</tr>
<tr>
<td></td>
<td>• Valvular abnormalities but no vegetations by TEE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Positive surveillance cultures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Superficial, non-removable focus of infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Persistent signs of infection &gt; 72 hrs of therapy</td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td>According to Duke criteria</td>
<td>4-8 wks IV antibiotics ± surgery</td>
</tr>
<tr>
<td>Extracardiac</td>
<td>All of the following:</td>
<td>4-8 wks IV antibiotics ± surgery</td>
</tr>
<tr>
<td></td>
<td>• TEE negative for vegetations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Deep-tissue infections</td>
<td></td>
</tr>
</tbody>
</table>

Appendix B: Comparison of Vancomycin vs Linezolid

<table>
<thead>
<tr>
<th></th>
<th>Vancomycin</th>
<th>Linezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action</td>
<td>Cell wall synthesis inhibitor</td>
<td>Protein synthesis inhibitor</td>
</tr>
<tr>
<td>Cidal/Static</td>
<td>Cidal</td>
<td>Static</td>
</tr>
<tr>
<td>Spectrum</td>
<td>Gram-positive organisms (MSSA, MRSA, Enterococci, Streptococcus)</td>
<td>Gram-positive organisms (MSSA, MRSA, Enterococci-including VRE, Streptococcus)</td>
</tr>
<tr>
<td>Dose</td>
<td>30 mg/kg load followed by 15 mg/kg Q12h</td>
<td>600 mg Q12h</td>
</tr>
<tr>
<td>Dosage Adjustment Necessary</td>
<td>Yes- renal adjustments</td>
<td>No</td>
</tr>
<tr>
<td>Pharmacokinetics/Pharmacodynamics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioavailability</td>
<td>Vd 0.7 L/kg</td>
<td>100% 0.7 L/kg</td>
</tr>
<tr>
<td></td>
<td>50% 5-11 hours</td>
<td>31% 4-6 hrs</td>
</tr>
<tr>
<td></td>
<td>Renally excreted unchanged AUC/MIC</td>
<td>Hepatically oxidized AUC/MIC</td>
</tr>
<tr>
<td>PD Predictor of Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosage Form Availability</td>
<td>Intravenous</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>Red man syndrome, Rash, Nephrotoxicity, Ototoxicity</td>
<td>Bone marrow suppression (&gt; 14 days), Mitochondrial toxicity: neuropathies and lactic acidosis (&gt; 28 days), Serotonin syndrome</td>
</tr>
<tr>
<td>Routine Therapeutic Drugs</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Monitoring Performed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resistance</td>
<td>0/14,635 (0%)</td>
<td>3/14,635 (0.02%)</td>
</tr>
<tr>
<td>Cost</td>
<td>VA: $5/gram</td>
<td>VA: $98/day</td>
</tr>
<tr>
<td></td>
<td>UH: $5/gram</td>
<td>UH: $186/day</td>
</tr>
</tbody>
</table>
Appendix C: Summary charts of studies

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>• Compare the safety and efficacy of linezolid vs vancomycin in patients with presumed MRSA infections</td>
</tr>
</tbody>
</table>
| **Design** | • **Randomized, comparator-controlled, open-label trial**  
• Conducted at 104 sites in North America, Europe, Latin America and Asia from July 1998 to July 1999  
• Inclusion: ≥ 13 yo with presumed MRSA infection  
• Exclusion: Left-sided endocarditis, osteomyelitis, infections of CNS, non-removable infected devices, ANC < 500, known liver disease, pregnancy, hypersensitivity, ≥ 24 hrs potentially effective antibiotics w/in 48 hrs of study entry  
• **Patients randomized to receive either linezolid (600 mg IV BID) or vancomycin (1 g IV BID) for at least 7 days**  
• Patients assessed at end of therapy (EOT) and at indication-specific test-of-cure (TOC) visit |
| **Statistics** | • Populations: Intent-to-treat (ITT), modified-intent-to-treat (MITT), MRSA-ITT  
• Assuming 90% treatment success, equivalence determination of 10% and a power of 80%, 284 evaluable patients required  
• 95% CI, Chi-squared, stepwise logistic regression and ORs |
| **Results** | • Demographic characteristics for ITT population were similar at baseline except mean age higher in linezolid group vs vancomycin group  
• **Bacteremia occurred in 45/240 (18.8%) in linezolid group and 40/220 (18.2%) in vancomycin group**  
  o **Source of bacteremia**  

<table>
<thead>
<tr>
<th>Source</th>
<th>Linezolid (n = 45)</th>
<th>Vancomycin (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSTI</td>
<td>8 (18%)</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8 (18%)</td>
<td>7 (18%)</td>
</tr>
<tr>
<td>UTI</td>
<td>1 (2%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Other*</td>
<td>11 (24%)</td>
<td>15 (38%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>26 (58%)</td>
<td>24 (60%)</td>
</tr>
</tbody>
</table>

*Includes catheter-associated infection, intra-abdominal or pelvic infection, laryngotracheobronchitis, mediastinitis, infected device, bacteremia secondary to parotitis, empyema, lumbar fistula, sinusitis, subgaleal empyema and right-sided endocarditis  
• **Cure rates for bacteremia**  

<table>
<thead>
<tr>
<th>Group</th>
<th>Linezolid</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>17/33 (51.5%)</td>
<td>15/32 (46.9%)</td>
</tr>
<tr>
<td>MRSA-ITT</td>
<td>13/23 (56.5%)</td>
<td>10/20 (50%)</td>
</tr>
<tr>
<td>Evaluable MRSA</td>
<td>9/15 (60%)</td>
<td>7/10 (70%)</td>
</tr>
</tbody>
</table>

• **Mean duration of therapy 12.6 days for linezolid group and 11.3 days for vancomycin group** (mean duration for bacteremic patients not reported)  
• **Safety**  
  o Adverse event leading to discontinuation in 10/240 (4.2%) in linezolid group vs 10/220 (4.5%) in vancomycin group  
  o Diarrhea and nausea were significantly higher in the linezolid group (10.8% vs 4.1%; p = 0.006 and 9.6% vs 4.5%; p = 0.037)  
  o **Substantially low platelet counts were significantly higher in linezolid group vs vancomycin group (10% vs 2.9%; p = 0.003)** |
| **Authors’ Conclusion** | Linezolid was safe, well tolerated and as effective as vancomycin for treatment of nosocomial MRSA infections |
| **Critique** | • Open-label trial with small subgroup analysis on bacteremic patients  
• No mention of vancomycin monitoring or adjustment  
• Endocarditis patients excluded  
• Majority of bacteremia from unknown source |
| **Take Home** | Linezolid as effective as vancomycin for treatment of nosocomial MRSA bacteremia  
• Small subgroup analysis |

**Objective**
- Compare clinical outcomes of linezolid therapy vs vancomycin therapy in patients with S. aureus bacteremia and to evaluate safety of these therapies

**Design**
- Pooled analysis of five prospective, randomized, controlled studies that comparing linezolid with vancomycin and focusing on the subset of patients with bacteremia
- Inclusion in pooled analysis: receive at least one dose of study drug and have blood cultures positive for S. aureus
- Treatment protocols similar: patients randomly assigned to linezolid 600 mg BID or vancomycin 1 g BID
- Primary outcome: clinical outcome of the primary infection after the end of therapy [or test of cure (TOC)] which ranged from 7 days for UTIs to 35 days for bacteremia of unknown origin

**Statistics**
- Student’s t-test, chi-squared test, OR with 95% CI, Mantel and Haenszel, and multivariate logistic regression

**Results**
- 3,228 patients enrolled in five studies: 144 had S. aureus bacteremia
  - 74 received linezolid (MRSA = 36; MSSA = 38)
  - 70 received vancomycin (MRSA = 28; MSSA = 42)
- Sources of bacteremia

<table>
<thead>
<tr>
<th>Primary Infection</th>
<th>Linezolid (n = 74)</th>
<th>Vancomycin (n = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>33 (44.6%)</td>
<td>27 (38.6%)</td>
</tr>
<tr>
<td>SSTI</td>
<td>22 (29.7%)</td>
<td>21 (30.0%)</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>8 (10.1%)</td>
<td>8 (11.4%)</td>
</tr>
<tr>
<td>UTI</td>
<td>1 (1.4%)</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (13.5%)</td>
<td>13 (18.6%)</td>
</tr>
</tbody>
</table>

- Baseline characteristics similar except shorter duration of IV treatment was seen in the linezolid group (8.6 days vs 11.7 days, p = 0.004)
- Mean duration of therapy 12.1 ± 6.5 days in linezolid group vs 11.7 ± 6.8 days in vancomycin group (p = 0.666)
- Clinical cure
  - Overall clinical cure in 28/51 (55%) of linezolid patients vs 25/48 (52%) of vancomycin patients (OR 1.12; 95% CI, 0.51-2.47)
  - MRSA clinical cure 14/25 (56%) of linezolid patients vs 13/28 (46%) of vancomycin patients (OR 1.47; 95% CI, 0.50-4.34)
  - No difference in cure between two groups in individual studies or in meta-analysis (OR 1.16; 95% CI, 0.50-2.65)
  - In multivariate analysis only significant predictors of clinical cure were absence of congestive heart failure (OR, 0.23; 95% CI, 0.06-0.84) and absence of renal insufficiency (OR, 0.32; 95% CI, 0.11-0.95)
- Microbiological success in 41/59 (69%) of linezolid patients vs 41/56 (73%) of vancomycin patients (OR 0.83; 95% CI, 0.37-1.87)
- Survival
  - Overall survival in 55/74 (74%) of linezolid patients vs 52/70 (74%) of vancomycin patients (OR 1.00; 95% CI, 0.47-2.12)
  - Survival in patients with MRSA in 24/36 (67%) of linezolid patients vs 24/37 (65%) of vancomycin patients (OR 1.08; 95% CI, 0.41-2.85)
  - In multivariate analysis the only variables significant for survival were any co-morbidity (OR, 5.82; 95% CI, 1.24-27.44), absence of malignancy (OR, 0.15; 95% CI, 0.03-0.70) and absence of congestive heart failure (OR, 0.10; 95% CI, 0.44; 95% CI, 0.02-0.43)
- Safety
  - No difference in any adverse event, serious adverse event or discontinuation from treatment (all p >0.1)
  - New-onset thrombocytopenia significantly higher in linezolid group vs vancomycin group (13.9% vs 0%, p = 0.02)

**Authors’ Conclusion**
- In this pooled retrospective meta-analysis from 5 prospective, randomized, controlled studies linezolid is associated with outcomes that are not inferior to those of vancomycin in patients with S. aureus bacteremia

**Critique**
- Vancomycin dosing adjustments per “local standard of care”
- Used cure/failure of primary infection for grouping patients without additional blood cultures (repeat cultures not obtained in 40% of patients)
- Missing or indeterminate outcomes were coded as failures
- High survival rate (74%) probably due to 1/3 of patients with SSTI and absence of endocarditis
- Not all studies monitored for late relapse

**Take Home**
- Linezolid was not inferior to vancomycin in patients with S. aureus bacteremia in this meta-analysis
- Small numbers (again)

Objective
- Examine incidence and clinical features of persistent S. aureus bacteremia
- Examine the efficacy of linezolid with or without a carbapenem for the salvage treatment of persistent S. aureus bacteremia

Design
- **Retrospective study identifying persistent SAB**
  - Inclusion: ≥ 16 yo with persistent S. aureus bacteremia from January 1, 2006 to March 31, 2008 at Seoul National University Hospital (Republic of Korea)
  - Vancomycin group: patients who were not switched to linezolid but may have addition of aminoglycoside or rifampin
  - Linezolid group: patients switched from vancomycin to linezolid with or without the addition of a carbapenem
  - Outcomes measured: early microbiological response and salvage success

Statistics
- Categorical variables compared with Fisher exact test or Pearson Chi-squared and continuous variables compared with Mann-Whitney U tests

Results
- 35/377 (9%) cases of S. aureus bacteremia were persistent MRSA infections
  - 34 were health care associated and 1 was community associated
  - Mean age in vancomycin group 59 years old vs 70 years old in salvage group (p = 0.01)
  - Duration of persistence of MRSA bacteremia was 7-168 days (median, 12 d; mean, 18.1 d)

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Linezolid</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocarditis</td>
<td>1/16 (6%)</td>
<td>4/19 (21%)</td>
</tr>
<tr>
<td>Complication in brain</td>
<td>1/16 (6%)</td>
<td>6/19 (32%)</td>
</tr>
<tr>
<td>Vancomycin trough ≥ 15</td>
<td>12/16 (75%)</td>
<td>8/19 (42%)</td>
</tr>
</tbody>
</table>

- Early microbiological responses and salvage success rates were significantly higher with linezolid based regimens than with comparator regimens

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Substitution with Linezolid</th>
<th>Addition to Vancomycin</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Microbiological Response</td>
<td>12/16 (75%)</td>
<td>2/12 (17%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Salvage Success</td>
<td>14/16 (88%)</td>
<td>0/12 (0%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Substitution with Linezolid</th>
<th>Addition to Vancomycin</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus-Related Mortality</td>
<td>2/16 (13%)</td>
<td>10/19 (53%)</td>
<td>0.03</td>
</tr>
<tr>
<td>30-Day Mortality</td>
<td>4/16 (25%)</td>
<td>10/19 (53%)</td>
<td>NR</td>
</tr>
</tbody>
</table>

- Adverse events
  - 7/12 (58%) had linezolid-associated thrombocytopenia (developing 7-21 days after initiation)
  - Five of these 7 patients switched to vancomycin and were successfully treated

Authors’ Conclusion
- When treating persistent MRSA bacteremia, the substitution of linezolid for vancomycin appeared superior to addition of rifampin or aminoglycoside to vancomycin

Critique
- Retrospective with very small number of patients
- Vancomycin group with more severe complications
- Does not address how long were patients on vancomycin before switching
- Address vancomycin troughs saying most had vancomycin troughs > 10 mcg/mL and 56% of patients had vancomycin troughs > 15 mcg/mL
- TEE performed on only 37% of patients so true incidence of complicating endocarditis unknown
- Results did not match study objective

Take Home
- Linezolid salvage therapy appeared to be superior to vancomycin for persistent MRSA bacteremia
- Very small numbers with extremely different baseline characteristics

**Objective**
- To test the non-inferiority of linezolid to vancomycin for catheter-related infections

**Design**
- Randomized, controlled, prospective study in 100 centers from May 2002 to May 2005 (Europe, US, Latin America, Asia)
- Inclusion: adults (≥ 13 yo; ≥40 kg) with central venous, pulmonary artery, or arterial catheter in place for > 3 d and suspicion of catheter-related infection (CRI)
- Exclusion: intravascular catheter that could not be removed for culturing, endovascular or other infection likely to result in bacteremia, permanent intravascular device infection, treatment contraindication, treatment with active antibiotic w/in 72h before study entry, underlying condition that would interfere with assessment
- Patients randomly assigned to receive linezolid 600 mg IV Q12 or vancomycin 1 g IV Q12 for 7-28 days
- ALL catheters were removed
- Primary end point was microbiologic outcome in the first modified microbiologically evaluable (MME-1) and second microbiologically evaluable (ME-2) group at test of cure (TOC)
- Study groups
  - ITT (intent-to-treat)- all randomized patients receiving at least one dose
  - MITT (modified intent-to-treat)- ITT patients with baseline gram-positive (GP) organisms
  - ME-1 (first microbiologically evaluable group)- pts w/baseline GP organism except CoNS or CoNS isolated in > 1 culture and catheter tip
  - MME-1 (first modified microbiologically evaluable group)- patients w/ cSSSI due to GP pathogens associated with indwelling catheter
  - ME-2 (second microbiologically evaluable group)- patients with catheter-related bloodstream infections

**Statistics**
- Assuming a 70% microbiologic success rate, a power of 80% would be achieved with 147 patients in each group
- Initial test for noninferiority in complicated skin and skin structure infections (cSSSI) and if met follow analysis to CRBSI
- Both analyses exclude missing or indeterminate outcomes (sensitivity analyses performed counting as failures)
- Pearson chi-squared and Kaplan-Meier curves used

**Results**
- Total of 739 patients enrolled

<table>
<thead>
<tr>
<th>Population</th>
<th>Linezolid</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT (intent-to-treat)</td>
<td>363</td>
<td>363</td>
</tr>
<tr>
<td>MITT (modified intent-to-treat)</td>
<td>269</td>
<td>257</td>
</tr>
<tr>
<td>ME-1 (first microbiologically evaluable group)</td>
<td>193</td>
<td>189</td>
</tr>
<tr>
<td>MME-1 (first modified microbiologically evaluable group)</td>
<td>164</td>
<td>151</td>
</tr>
<tr>
<td>ME-2 (second microbiologically evaluable group)</td>
<td>95</td>
<td>74</td>
</tr>
</tbody>
</table>

- Baseline characteristics similar between groups
  - Median duration of catheter placement was 10 days
  - Mean duration of treatment 9.2 ± 5.2 day for linezolid group vs 8.7 ± 5.5 days in control group
  - Mean duration of IV treatment 6.4 ± 3.9 days for linezolid group vs 8.3 ± 5.3 days for control group (95% CI, 1.22 – 2.58)
- Primary and secondary outcomes

<table>
<thead>
<tr>
<th>Microbiological Outcome (Primary)</th>
<th>Linezolid</th>
<th>Control</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ME-2</td>
<td>82/95 (86.3%)</td>
<td>67/74 (90.5%)</td>
<td>-13.8 – 5.4</td>
</tr>
<tr>
<td>S. aureus MRSA</td>
<td>46/56 (82.1%)</td>
<td>35/42 (83.3%)</td>
<td>-16.3 – 13.9</td>
</tr>
<tr>
<td>MRSA</td>
<td>21/26 (80.8%)</td>
<td>18/21 (85.7%)</td>
<td>-26.2 – 16.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Outcome (Secondary)</th>
<th>Linezolid</th>
<th>Control</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ME-2 EOT S. aureus MRSA TOC</td>
<td>73/89 (82%)</td>
<td>61/74 (82.4%)</td>
<td>-12.2 – 11.4</td>
</tr>
<tr>
<td>MRSA</td>
<td>39/52 (75%)</td>
<td>29/42 (69%)</td>
<td>-12.3 – 24.2</td>
</tr>
<tr>
<td>MRSA</td>
<td>22/25 (88%)</td>
<td>16/21 (76.2%)</td>
<td>-10.4 – 34.0</td>
</tr>
<tr>
<td>MRSA</td>
<td>70/93 (75.3%)</td>
<td>59/73 (80.8%)</td>
<td>-18.1 – 7.0</td>
</tr>
<tr>
<td>MRSA</td>
<td>36/54 (66.7%)</td>
<td>28/42 (66.7%)</td>
<td>-19.0 – 19.0</td>
</tr>
<tr>
<td>MRSA</td>
<td>19/24 (79.2%)</td>
<td>16/21 (76.2%)</td>
<td>-21.4 – 27.4</td>
</tr>
<tr>
<td>Safety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Frequency and severity of adverse events similar between groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Only reports of treatment related myelosuppression occurred in linezolid group (5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o More patients in linezolid group had abnormal platelet values (&lt; 75% of lower limit of normal or baseline value at EOT); linezolid group, 13.1% vs control group, 7.4% (p-value not given)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Authors’ Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid was non-inferior to vancomycin in patients with cSSSI or catheter related BSI due to gram-positive organisms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Critique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open label but primary outcome was microbiologic outcome</td>
</tr>
<tr>
<td>Power determined for ME patients but MME-1 and ME-2 were used for primary outcome</td>
</tr>
<tr>
<td>Vancomycin monitoring not addressed but dose could be adjusted based on local practices</td>
</tr>
<tr>
<td>Stated similar adverse events but 48/363 (13%) in linezolid group vs 25/363 (7%) in control group discontinued secondary to adverse events (p = 0.006)</td>
</tr>
<tr>
<td>Very select subgroup of patients</td>
</tr>
<tr>
<td>Sensitivity analysis counting missing data as failure did not change outcomes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Take Home</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid was non-inferior to vancomycin</td>
</tr>
<tr>
<td>Small population when subgroup analysis of bacteremia</td>
</tr>
</tbody>
</table>