Vancomycin & New Agents for MRSA Infections

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Objectives
- Using vancomycin MIC values define what is meant by vancomycin sensitive, h-VISA, intermediate (VISA/GISA), & resistant MRSA.
- Define how tolerance affects vancomycin performance.
- Identify how the vancomycin MIC affects the eradication of MRSA from blood, overall cure, and risk of mortality.
- Define vancomycin performance from a pharmacodynamic perspective (rapid vs slow bacterial killing, cidal vs static, appropriate PD outcome parameter and targeted value).
- Identify the value and risks of current clinical strategies to use higher trough serum concentrations.
- Identify appropriate antibiotic alternative to vancomycin and their potential limitations.

MRSA Treatment Options

Currently Available Options
- Vancomycin
- Clindamycin
- TMP/SMX
- Doxycycline/Minocycline
- Quinupristin/Dalfopristin
- Linezolid
- Daptomycin
- Tigecycline
- Telavancin (Approvable Letter from FDA)
- Delbavancin (Approvable Letter from FDA)

Vancomycin Susceptibility S. aureus CLSI 2006
- Sensitive (VSSA)
  - Vancomycin MIC < 2 mg/L
- Heteroresistant strain (h-VISA)
  - h-VISA likely when vancomycin MIC = 1 or 2 mg/L (Surrogate Marker)
  - Most labs will not do definitive testing
- Intermediate (VISA or GISA)
  - Vancomycin MIC = 4-8 mg/L
- Resistant (VRSA)
  - Vancomycin MIC ≥ 16 mg/L
  - Lab needs to backup primary testing with 6mg/L vancomycin overnight plate
- Tolerance ( MBC / MIC > 16-32 )

Vancomycin Treatment Guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Organ</th>
<th>Dose</th>
<th>Trough (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAP/VAP</td>
<td>ATS/IDSA</td>
<td>15 mg/KgQ12H</td>
<td>15-20</td>
</tr>
<tr>
<td>Meningitis</td>
<td>IDSA</td>
<td>15 mg/Kg Q8 or 12H</td>
<td>15-20*</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>BSAC</td>
<td>1GmQ12H</td>
<td>10-15</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>AHA</td>
<td>15 mg/KgQ12H</td>
<td>10-15*</td>
</tr>
</tbody>
</table>

• No evidence offered that:
  - Initial dose will produce desired troughs
  - That higher troughs are more effective
  - That higher troughs are safe

Factors Affecting Vancomycin Clinical Performance
- Poor tissue penetration
- Bactericidal but a slow killer of gram positive pathogens
- Level of glycocalyx production
- Limited to no affect on toxin production
- Lysis of cell wall could aid toxin release
- High bacterial inoculum
- Anaerobic conditions
Vancomycin Pharmacokinetics

Vancomycin Pharmacodynamics:
Which Parameter? & What Quantitative Value?

Susceptible S. aureus vs. GISA
Intensive Care Med 2007

Target Attainment for Dalbavancin & Vancomycin for S. aureus.

Clinical Laboratory Support for Vancomycin Susceptibility Reporting
- Many hospitals still report (S) – susceptible, (I) - intermediate, or (R) - resistant
- Automated systems in the past would report an MIC ≤ 1 mg/L (Vitek II) or ≤ 2 mg/L (Microscan)
  - Vitek II Fall 2008 will change to ≤ 0.5 mg/L
  - 5.01 software update required
  - Microscan Dec 2007 changed to ≤ 0.25 mg/L
  - Need 3.0 software upgrade or 2.0 & Pos 29 or Pos 26 panel
- Limited evidence of Vancomycin MIC creep over the years
**Relationship of MIC & Bactericidal Activity to Efficacy of Vancomycin for the Treatment of MRSA Bacteremia**

Sakoulas, G et al J Clin Micro 42:2398-2402, 2004

- If MRSA MIC < 0.5 mg/L
  - 55.6% successful outcome
- If MIC 1 or 2 mg/L
  - 9.5% successful outcome
- High vancomycin MIC’s may increase risk of resistance to newer agents (i.e. Daptomycin)

**Median Duration of Bacteremia & Fever in MRSA Endocarditis**


<table>
<thead>
<tr>
<th>N</th>
<th>Median Duration of Bacteremia (Days)</th>
<th>Median Duration of Fever (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>42</td>
<td>9 (6-11)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>22</td>
<td>7 (5-11)</td>
</tr>
<tr>
<td>Vanc/Rifampin</td>
<td>20</td>
<td>9 (6-13)</td>
</tr>
<tr>
<td>Left Sided</td>
<td>8</td>
<td>9 (3-10)</td>
</tr>
<tr>
<td>Right Sided</td>
<td>34</td>
<td>7 (5-11)</td>
</tr>
</tbody>
</table>

**Vancomycin MIC versus eradication rates**

<table>
<thead>
<tr>
<th>Vancomycin (µg/ml)</th>
<th>No. of Isolates</th>
<th>Median DTE*</th>
<th>Median Duration of Vancomycin Therapy (days)</th>
<th>Eradication Rate by EOT#</th>
<th>Median Reduction in log_{10} CFU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>13</td>
<td>6.0</td>
<td>15.0</td>
<td>16/13 (77)</td>
<td>3.06</td>
</tr>
<tr>
<td>1.0</td>
<td>7</td>
<td>9.5</td>
<td>17.0</td>
<td>5/7 (71)</td>
<td>2.09</td>
</tr>
<tr>
<td>2.0</td>
<td>14</td>
<td>&gt; 15.5</td>
<td>15.5</td>
<td>3/14 (21)</td>
<td>2.75</td>
</tr>
</tbody>
</table>

*DTE, day to eradication.
*EOT, end of treatment.
#The median time to eradication is >15 days, as only 21% of patients showed clearance of bacteremia.

Moise, PA et al AAC 51(7): 2582-2586, 2007

**Vancomycin Trough Concentrations (mcg/ml) vs Hospital Mortality**

Jeffres, MN et al Chest 130:947-955, 2006

**Clinical Response Based on Targeted Trough (Goal = Unbound Trough Concentration ≥ 4 X MIC)**

Hidayat, LK et al Arch Intern Med 166:2138-2144, 2006
Vancomycin Nephrotoxicity

<table>
<thead>
<tr>
<th>Study</th>
<th>Cpmin &lt; 15 mg/L</th>
<th>Cpmin ≥ 15 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeffres K789 ICAAC 2006</td>
<td>30.2%</td>
<td>58.8%</td>
</tr>
<tr>
<td>Such L1299 ICAAC 2006</td>
<td>0.0%</td>
<td>15.0%</td>
</tr>
<tr>
<td>Hidayat Arch Intern Med 2006</td>
<td>0.0%</td>
<td>12.0%</td>
</tr>
<tr>
<td>Nguyen K1096 ICAAC 2007</td>
<td>6.2%</td>
<td>18.2%</td>
</tr>
</tbody>
</table>

Therapeutic monitoring of vancomycin in adult patients: A consensus review of the ASHP, IDSA, and SIDP

- Troughs are the most accurate & practical method for monitoring efficacy
- Troughs should be maintained > 10 mg/L
- 15-20 mg/L for complicated infections (AUC/MIC > 400)
- Monitoring trough serum concentrations to reduce nephrotoxicity
- Best suited for aggressive dosing (troughs 15-20 mg/L)
- Recommended for patients with unstable renal function
- All patients receiving prolonged therapy should have at least one steady state trough concentration (> 4th dose)

Suggested First Line Agents for CA-MRSA S/STI

- Clindamycin (D-test to screen for inducible resistance)
  - 300-450 mg 3 times per day oral
- TMP/SMX (Does not cover Group A Streptococcus)
  - DS tab (160mg/800mg) Q12H X 10-14 days oral
- Minocycline or Doxycycline (21% failure rates reported)
  - 100mg Q12H X 10-14 days oral
- Adjunct Therapy
  - 4% Chlorhexidine gluconate wash Q24H X 5 days
  - 2% Calcium Mupirocin 1Gm single use tube Q12H X 10 days

Therapeutic monitoring of vancomycin in adult patients: A consensus review of the ASHP, IDSA, and SIDP

- For rapid target attainment in seriously ill patients a 25-30 mg/Kg loading dose should be considered
  - 15-20 mg/Kg Q8-12H required if S. aureus MIC ≤ 1 mg/L
  - If S. aureus MIC ≥ 2 mg/L dynamic target will not be achieved
- Frequent monitoring for short course therapy or for troughs < 15 mg/L not recommended
- Limited data to support safety of troughs 15-20 mg/L

Community Acquired MRSA (CA-MRSA)

- Background
  - Influenza common preceding CA-MRSA or concomitant
  - Gram positive cocci in groups on gram stain
  - X-ray has cavitary infiltrates ± multiple lobes
  - CA-MRSA prolific toxin producer & can kill quickly
- Treatment (No preference)
  - Vancomycin
    - Possible issues with lung penetration, slow kill rate, failure to shut down toxin production, & cell lysis upon death
  - Linezolid
    - Note:
      - Recommendations for pneumonia different than S/STI
      - Daptomycin cannot be used for pneumonia
Superior results for linezolid vs vancomycin in ventilator-associated pneumonia (VAP)

MRSA Treatment Options

- Investigational agents when approved will likely have complicated skin infection as only FDA approved indication
  - Oritavancin (Targenta)
  - Ceftobiprole
  - Ceftaroline
  - Iclaprim (Arpida)

New Agents

- Where should these new drugs be used
  - VRE
  - When MRSA Vancomycin MIC ≥ 1 mg/L
    - Automated testing may under estimate MIC value
    - Difficult to call if MIC < 1-2 mg/L or S,L, or R
  - Empiric therapy for HAP / VAP
    - Exception Daptomycin which binds to surfactant
- Where not to use the drug
  - First line agent MSSA or VSE
  - First line therapy for CA-MRSA
    - Possible exception pneumonia

Conclusions

- Tremendous diversity in what we call staphylococci today
- Decision to use vancomycin is complicated & at minimum probably requires a MIC
- Concerns about the future utility of vancomycin as a first line agent
- Been difficult to establish new agents as superior to vancomycin
- Pharmacoeconomic arguments favor new agents