Vancomycin & New Agents for the Treatment of MRSA

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MRSA Treatment Options

• Currently Available Options
  – Vancomycin
  – Quinupristin/Dalfopristin
  – Linezolid
  – Daptomycin
  – Tigecycline
• Investigational Agents
  – Delbavancin
  – Telavancin
  – Oritavancin
  – Ceftobiprole
  – Ceftaroline

MRSA: Drug of Choice?

Vancomycin
Factors Affecting Clinical Performance

• Apparently vancomycin has been broken
  – Under dosing
    • Higher troughs recommended in treatment guidelines
    • Change in CLSI breakpoints
  – Environmental factors
• MIC creep with Vancomycin over the years?
• Micro-colony variants
• MSSA vs. MRSA
• Heteroresistance
• Tolerance
• GiSA/VISA or VRSA

Vancomycin Susceptibility S. aureus
CLSI 2006

• Sensitive (VSSA)
  – Vancomycin MIC ≤ 2 mg/L
• Heteroresistant strain (h-VISA)
  – Vancomycin MIC = 1-2 mg/L (Still CLSI Sensitive)
• 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 )

Tolerance to Vancomycin at MD Anderson Cancer Center

<table>
<thead>
<tr>
<th></th>
<th>MRSA</th>
<th>MRSE</th>
<th>Staph. hemolyticus</th>
<th>Strep. viridans</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC (mg/L)</td>
<td>0.25</td>
<td>0.25</td>
<td>1.0</td>
<td>0.12</td>
</tr>
<tr>
<td>MIC (mg/L)</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>1.0</td>
</tr>
<tr>
<td>MIC (mg/L)</td>
<td>2.0</td>
<td>4.0</td>
<td>8.0</td>
<td>1.0</td>
</tr>
<tr>
<td>MIC (mg/L)</td>
<td>32</td>
<td>64</td>
<td>64</td>
<td>32</td>
</tr>
</tbody>
</table>

Ref: JID 2000; 183.
Microbiology of Vancomycin in the 21st Century: MIC Creep, Bactericidal/Static Activity & Applied Breakpoints to Predict Clinical Outcomes or Detect Resistant Strains

Jones, RN Clin Infect Dis 2006

ENTRY Antimicrobial Surveillance Program

data 1997-2003 N = 75,168 gram positive isolates
- S. aureus (35,458), CNS (5,902), S. pneumoniae (22,103), E. faecium (3,315), E. faecalis (8,390)

LSU (NCCLS) methods used

Relationship of MIC & Bactericidal Activity to Efficacy of Vancomycin for the Treatment of MRSA Bacteremia

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

- If MRSA MIC $\leq$ 0.5 mg/L
  - 55.6% successful outcome
- If MIC 1 or 2 mg/L
  - 9.5% successful outcome
- Problem if lab only reports S, I, or R & Vitek that reports $<$ 1 mg/L, 2 mg/L etc.
- High vancomycin MIC’s may increase risk of resistance to newer agents

Antibiotics Suggested for CA-MRSA Infections

IDSA Guidelines 41:1373-1830, 2005

- Clindamycin (D-test to screen for inducible resistance)
  - 300-450 mg 3 times per day oral
- TMP/SMX
  - DS tab (160mg/800mg) Q12H X 10-14 days oral
- Minocycline or Doxycycline (21% failure rates reported)
  - 100mg Q12H X 10-14 days oral
- Vancomycin (30 mg/Kg/day in 2 divided doses)
- Linezolid (600mg Q12H)
- Daptomycin (4mg/Kg Q24)
- + Adjunct Therapy
  - 4% Chlorhexidine gluconate wash Q24H X 5 days
  - 2% Calcium Mupirocin 1Gm single use tube Q12H X 10 days

D Test for Clindamycin

How Good an Antibiotic is Vancomycin?

- Vancomycin kills bacteria at a slower rate than beta-lactam
- Higher mortality with vancomycin treated patients vs beta-lactam
  - Gonzalez: CID 29:1171, 1999
### Median Duration of Bacteremia & Fever in MRSA Endocarditis


<table>
<thead>
<tr>
<th>N</th>
<th>Median Duration of Bacteremia</th>
<th>Median Duration of Fever</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>

### How Good an Antibiotic is Vancomycin?

- 40% of S. aureus lower respiratory infections failed on vancomycin therapy
- Cloxacillin/gentamicin significantly better than Vancomycin or Teicoplanin/gentamicin in short course therapy of right side endocarditis
  - Fortun: CID 33:120-125, 2001

### Vancomycin Dosing Methods


<table>
<thead>
<tr>
<th>Cpmax (mg/L)</th>
<th>Matzke</th>
<th>Neilsen</th>
<th>Moellering</th>
<th>Lake-Peterson</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 40</td>
<td>30(100%)</td>
<td>2(7%)</td>
<td>3(10%)</td>
<td>6(20%)</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>0(0%)</td>
<td>24(80%)</td>
<td>24(80%)</td>
<td>11(36%)</td>
</tr>
<tr>
<td>Cpmin(mg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10</td>
<td>6(20%)</td>
<td>4(13%)</td>
<td>2(6%)</td>
<td>7(23%)</td>
</tr>
<tr>
<td>&lt; 5</td>
<td>19(64%)</td>
<td>19(64%)</td>
<td>15(50%)</td>
<td>11(36%)</td>
</tr>
<tr>
<td>Cpmax and Cpmin (mg/L)</td>
<td>30-40 &amp;</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>1(3%)</td>
</tr>
<tr>
<td>5-10</td>
<td></td>
<td></td>
<td></td>
<td>7(23%)</td>
</tr>
</tbody>
</table>

### Vancomycin Treatment Guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Organization</th>
<th>Dose (mg/Kg)</th>
<th>Trough (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAP/VAP</td>
<td>ATS</td>
<td>15</td>
<td>15-20</td>
</tr>
<tr>
<td>Meningitis</td>
<td>IDSA</td>
<td></td>
<td>15-20*</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>BSAC</td>
<td>1Gm</td>
<td>10-15</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>AHA</td>
<td>15 mg/Kg</td>
<td>10-15*</td>
</tr>
</tbody>
</table>

* Graded Recommendation

### Vancomycin Trough Recommendations from Treatment Guidelines

- Guidelines recommending vancomycin trough concentration of 10-20 mg/L based on expert opinion not clinical trial data
- No data that empiric doses will produce desired vancomycin trough concentrations
- No data that higher vancomycin trough concentrations are safe &/or more effective
- Would FDA allow a change in the vancomycin product insert?
Appropriate Vancomycin Trough Concentrations

Standard Dose Q12H infused over 1 hr

<table>
<thead>
<tr>
<th>Cp-min</th>
<th>MIC</th>
<th>XCP-n</th>
<th>MIC</th>
<th>Cp-x/MIC*</th>
<th>AUC/MIC**</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5/4.5</td>
<td>0.5</td>
<td>9.00</td>
<td>32</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>4.50</td>
<td>16</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>2.25</td>
<td>8</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

*Values likely higher as model assumes 1 compartment model
*Assume half-life of 6 hrs & 40% protein binding
*Assume linear pharmacokinetics

Pneumonia caused by oxacillin-resistant S. aureus treated with glycopeptides

- 75 ORSA VAP patients vs 75 matched controls
- Retrospective cohort study in 4 ICU’s
- Vancomycin used intermittently or continuously with Cp_{min} = 20 mg/L or teicoplanin 6 mg/Kg Q12h X 3 then QD
- 37/76 (48%) VAP ORSA patients died VS 19/48 (25%) controls p<0.01
- Despite appropriate antibiotic therapy there is an increased attributable mortality that cannot be explained


Predictors of Mortality for MRSA HCAP: Specific Evaluation of Vancomycin PK Indices

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

- Retrospective study N=102 over 6.5 years
  - BAL confirmed MRSA HCAP
  - Extrapolated Cp_{min} & estimated AUC
  - No MIC done (S, I, R)

<table>
<thead>
<tr>
<th>Survivors</th>
<th>NonSurvivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>70</td>
</tr>
<tr>
<td>Cp_{min}</td>
<td>13.6 mg/L</td>
</tr>
<tr>
<td>AUC</td>
<td>351±143</td>
</tr>
<tr>
<td></td>
<td>354±109</td>
</tr>
</tbody>
</table>

- No evidence that greater vancomycin Cp_{min}'s or AUC values correlated with hospital outcome
- Aggressive dosing strategies for vancomycin may not offer any advantage over traditional dose targets.

High Dose Vancomycin Therapy for MRSA Infections

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

- Prospective cohort study
  - 95 patients
    - 51/95 (54%) MRSA with elevated vancomycin MIC (2 mg/L)
    - 77% had HAP &/or bacteremia
    - Goal to obtain unbound troughs 4X MIC
    - 74% had initial response if targeted trough was obtained
      - High MIC group 24/39 (62%) responded
      - Low MIC group 35/46 (75%) responded (p=0.02)
    - Mortality 24% vs 10% in high vs low MIC group
    - High vancomycin MIC and APACHE score independent predictors of poor response
    - MRSA with vancomycin MIC of 2 mg/L require aggressive empiric vancomycin therapy to achieve troughs > 15 mg/L
    - Patients in which target obtainment was achieved within 72 hrs had 20% higher response rate

Increased Incidence of Nephrotoxicity with Higher Vancomycin Serum Trough Concentrations.

M. N. JEFFRES K789 (ICAAC 2006)

- 94 patients (N=43 < 15 mg/L, N=51 ≥ 15 mg/L)
- Nephrotoxicity was defined as a 25% decrease in estimated CrCl
- Trough concentrations ≥15 mg/L & length of therapy are associated with increased risk of renal toxicity
- Nephrotoxicity occurred in 13 patients (30.2%) with troughs < 15 mg/L and 30 patients (58.8%) with troughs ≥ 15 mg/L (p=0.006)

Nephrotoxicity Associated with Aggressive Vancomycin Therapy.


- Retrospective review Jan 2004 – Jan 2006
- Nephrotoxicity defined on % change in creatinine
- Patient > 18 yrs receiving vancomycin 14 days
- 59/120 qualified for study
  - Group 1 vancomycin trough < 15 mg/L N=19
  - Group 2 vancomycin trough >15 mg/L N=40
- No Nephrotoxicity in group 1 vs 15% group 2
**Superior results for linezolid vs vancomycin in ventilator-associated pneumonia (VAP)**

- **Clinical cure (%):**
  - Linezolid: 45.4%
  - Vancomycin: 46.9%

- **TOC (42 days):**
  - Linezolid: 53/120 (44.2%)
  - Vancomycin: 48/115 (41.7%)

**Daptomycin vs. Standard Therapy for S. aureus Bacteremia & Infective Endocarditis**


- Daptomycin dosed at 6 mg/Kg/day vs semisynthetic penicillin or vancomycin with low dose gentamicin X 4 days
- TOC (42 days) 53/120 (44.2%) DAP vs. 48/115 (41.7%) COMP
- CPK elevation 25.0% DAP vs. 12.5% COMP (p= 0.038)
  - Drug D/C’d due to CPK elevation in 3/120 (2.5%) DAP
- Worsening renal function 19.8% DAP vs. 46.8% COMP (p < 0.001)
  - Vancomycin troughs averaged just under 15 mg/L
- MIC elevations in 7 daptomycin patients (6/7 microbiologic failures)
- No difference between drugs in time to sterilize blood

**New Agents**

- **Where should these new drugs be used**
  - VRE
  - MRSA
  - When *S. aureus* Vancomycin MIC > 2 mg/L
    - Possibly MIC ≥ 1mg/L with automated testing
    - Very difficult to call if lab reports out MIC ≤ 1 mg/L
  - 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

**Summary**

- **Optimizing Therapy:**
  - Future value of vancomycin vs newer agents will likely become more clear with time
  - Appropriate therapy for CA-MRSA will continue to be defined
  - Variety of new antibiotics to manage MRSA
  - Thusfar, linezolid only drug to offer any data of possible superiority over vancomycin