Hospital Acquired Pneumonia:  
2012 Literature Update  
Daniel H. Kett, M.D.  
Professor of Clinical Medicine  
University of Miami School of Medicine  
Department of Veterans Affairs Medical Center
Potential Conflicts of Interests

- Research Grants
  - Agency for Healthcare Research and Quality
  - Akers Bioscience, Inc.
  - Pfizer, Inc.
- Scientific Advisory Boards
  - Pfizer, Inc.
  - Cadence Pharmaceuticals
  - Kimberly Clark
- Consult
  - Pfizer, Inc.
Potential Topics: 25 minutes

- Prevention
- Diagnosis
- Treatment
  - Gram-positive (MRSA)
  - Gram-negative (multi-drug resistant pathogens)
  - Duration of therapy
- Outcomes
ATS-IDSA Guidelines: Lower Airway Cultures

- Endotracheal aspirate
  - threshold of $10^6$ cfu/mL
    - sensitivity mean of $76 \pm 9\%$
    - specificity a mean of $75 \pm 28\%$

- Bronchoscopic BAL
  - threshold of $10^4$ cfu/mL
    - sensitivity mean of $73 \pm 18\%$
    - specificity mean of $82 \pm 19\%$

- Bronchoscopic PSB
  - threshold of $10^3$ cfu/mL
    - sensitivity mean of $66 \pm 19\%$
    - specificity mean of $90 \pm 15\%$

- Blind mini-BAL
  - threshold of $10^4$ cfu/mL
    - sensitivity of between 63 to 100%
    - specificity of between 66 to 96%

Campbell GD. Chest. 2000; 117:207S–211S
Quantitative versus Qualitative Cultures: Clinical Outcomes in Patients with VAP

- Meta-analysis of randomized controlled trials (RCTs) comparing respiratory samples processed quantitatively or qualitatively, obtained by invasive or non-invasive methods from immunocompetent patients with VAP.

\[ \text{Difference in Mortality} \]

\[ \text{Difference in Duration of MV} \]

\[ \text{Difference in ICU LOS} \]
A BALANCING ACT

ADEQUATE INITIAL ANTIMICROBIAL TREATMENT

AVOID UNNECESSARY ANTIBIOTICS
**Staphylococcus aureus**

Scanning electron micrograph of *S. aureus*

Gram stain of *S. aureus*

Day 28 Mortality Stratified by Vancomycin MIC:

- 158 cases of MRSA HAP/VAP were evaluated
- Vancomycin MICs were determined using the standard Etest method

Panton-Valentine Leukocidin and Outcome in Staph. aureus Hospital-Acquired Pneumonia

- S. aureus isolates from patients with (HAP) enrolled in two registrational multinational clinical trials
  - 127 centers in 34 countries
- Genotyped for the genetic elements carrying pvl and 30 other virulence genes.
- pvl was detected by PCR 23 isolates
  - 18/173 (8.0%) MRSA, isolates
  - 5/114 (4.4%) MSSA isolates
- The presence of pvl was not associated with clinical failure (4/23) [17.4%] vs. 48/264 [18.2%] or mortality.

Cure rates among patients with MRSA or MSSA HAP according to presence or absence of PVL.
IMPACT-HAP: Characteristics of MRSA strains causing HAP/VAP by PVL status

- 109 cases of MRSA HAP/VAP were evaluated
- The incidence of PVL(+) MRSA was 27%
- No difference in baseline characteristics or severity of illness scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>PVL+ n=29 (%)</th>
<th>PVL- n=80 (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCCmec Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>II</td>
<td>0 (0.0)</td>
<td>58 (72.5)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>0 (0.0)</td>
<td>2 (2.5)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>27 (100.0)</td>
<td>20 (25.0)</td>
<td></td>
</tr>
<tr>
<td>USA-300</td>
<td>29 (100)</td>
<td>7 (8.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clindamycin Resistant</td>
<td>2 (6.9)</td>
<td>63 (78.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Erythromycin Resistant</td>
<td>27 (93.1)</td>
<td>74 (92.5)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Clinical outcomes of patients with MRSA HAP/VAP by PVL status

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PVL+ n=29 (%)</th>
<th>PVL- n=80 (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>3/29 (10.3)</td>
<td>8/80 (10)</td>
<td>1.00</td>
</tr>
<tr>
<td>28-day mortality</td>
<td>8/25 (32)</td>
<td>24/63 (38.1)</td>
<td>0.59</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>20.4 ± 8.1</td>
<td>21.0 ± 7.6</td>
<td>0.74</td>
</tr>
<tr>
<td>Length of stay in the ICU</td>
<td>17.7 ± 9.6</td>
<td>17.1 ± 9.7</td>
<td>0.68</td>
</tr>
<tr>
<td>Time on mechanical ventilation</td>
<td>16.1 ± 11.2</td>
<td>15.5 ± 10.5</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Vancomycin Trough and Nephrotoxicity: IMPACT-HAP Study

• A retrospective study of 188 adult pneumonia patients.

• Patients were excluded if they had a baseline serum creatinine level ≥2 mg/dL or known history of ESRD.

• Nephrotoxicity was defined as an increase in serum creatinine ≥0.5 mg/dL or 50% above baseline, whichever was greater, in at least 2 consecutive measurements.

  • During the period from initiation of vancomycin therapy to 72 hours after completion of therapy.

Study Design

Linezolid IV 600 mg q12h
7-14 days

Vancomycin IV 15 mg/kg q12h
Within 5 days of EOT

EOT Visit

EOS Visit
7-30 days after EOT

1:1 Randomization

- Vancomycin dose adjusted by unblinded pharmacist based on renal function and trough concentration
- Initial Cefepime or other Gram-negative coverage (not MRSA active) required

Analysis Sets

**Intent-to-treat (ITT)**
- All subjects who received at least 1 dose of study drug
- Included non-MRSA patients
- Safety analysis only

**Modified intent-to-treat (mITT)**
- ITT subjects who received at least 1 dose of study drug and had a **positive baseline MRSA culture**

**Per protocol (PP)**
- Key inclusion/exclusion criteria
- Adequate compliance
- No prohibited concomitant meds
- EOT/EOS visits within windows

Clinical Efficacy

Proportion of patients with successful response (%)

- **Linezolid**
- **Vancomycin**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Linezolid</th>
<th>Vancomycin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP at EOS</td>
<td>57.6%</td>
<td>46.6%</td>
<td>0.042</td>
</tr>
<tr>
<td>MITT at EOS</td>
<td>54.8%</td>
<td>44.9%</td>
<td>0.049</td>
</tr>
<tr>
<td>PP at EOT</td>
<td>83.3%</td>
<td>69.9%</td>
<td>0.002</td>
</tr>
<tr>
<td>MITT at EOT</td>
<td>80.1%</td>
<td>67.8%</td>
<td>0.004</td>
</tr>
</tbody>
</table>

**Clinical Efficacy**

<table>
<thead>
<tr>
<th></th>
<th>Linezolid</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proportion of patients with successful response (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP at EOS</td>
<td>57.6</td>
<td>46.6</td>
</tr>
<tr>
<td>MITT at EOS</td>
<td>54.8</td>
<td>44.9</td>
</tr>
<tr>
<td><strong>PP at EOT</strong></td>
<td>83.3</td>
<td>69.9</td>
</tr>
<tr>
<td><strong>MITT at EOT</strong></td>
<td>80.1</td>
<td>67.8</td>
</tr>
</tbody>
</table>

* n=7, n=2, n=38, n=19, n=3, n=2, n=23, n=10

Microbiologic response rates

## Vancomycin Trough Plasma Concentrations: PP

<table>
<thead>
<tr>
<th>Treatment Day</th>
<th>n</th>
<th>Mean concentration (µg/mL)</th>
<th>Median concentration (µg/mL)</th>
<th>Concentration range (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>140</td>
<td>14.1</td>
<td>12.3</td>
<td>2.8 – 50.8</td>
</tr>
<tr>
<td>6</td>
<td>90</td>
<td>16.9</td>
<td>14.7</td>
<td>2.7 – 45.0</td>
</tr>
<tr>
<td>9</td>
<td>33</td>
<td>17.4</td>
<td>16.1</td>
<td>2.0 – 46.9</td>
</tr>
</tbody>
</table>

As a double-blind study, only the research pharmacist and unblinded monitor were aware of the levels.
Clinical Response by Maximum Vancomycin Trough Concentrations at Either Day 3, 6, or 9 (mITT at EOS)

<table>
<thead>
<tr>
<th></th>
<th>0-11.35 (μg/mL)</th>
<th>&gt;11.35-15 (μg/mL)</th>
<th>&gt;15-22.2 (μg/mL)</th>
<th>&gt;22.2 (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=41</td>
<td>n=42</td>
<td>n=36</td>
<td>n=38</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Success</td>
<td>20 (48.8)</td>
<td>20 (47.6)</td>
<td>17 (47.2)</td>
<td>17 (44.7)</td>
</tr>
<tr>
<td>Failure</td>
<td>21 (51.2)</td>
<td>22 (52.4)</td>
<td>19 (52.8)</td>
<td>21 (55.3)</td>
</tr>
</tbody>
</table>

As a double-blind study, only the research pharmacist and unblinded monitor were aware of the assignment.
60 Days Kaplan-Meier Survival Plot: mITT Population

94 subject deaths (15.7%) in linezolid arm
100 subject deaths (17.0%) in vancomycin arm

- Patients has pneumonia
  - Clinical signs and symptoms
  - CPIS > 6
- High likelihood of MRSA
  - Prior colonization
  - Prior infection
  - Positive gram stain
- Three days of either Linezolid or vamcomycin
  - Re-evaluate need for anti-MRSA therapy

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>Response (circle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient has the following:</td>
<td></td>
</tr>
<tr>
<td>a) Chest X-Ray with new or worsening infiltrate</td>
<td>Yes No</td>
</tr>
<tr>
<td>b) Two of the following clinical criteria</td>
<td></td>
</tr>
<tr>
<td>i) purulent sputum</td>
<td>Yes No</td>
</tr>
<tr>
<td>ii) &gt; or equal to 38.5 and &lt; or equal to 38.9</td>
<td>Yes No</td>
</tr>
<tr>
<td>iii) 4,000/mm³ &lt; WBC ≥ 11,000/mm³ or &gt;10% immature neutrophils</td>
<td>Yes No</td>
</tr>
<tr>
<td>f) Modified CPIS score greater than or equal to 8</td>
<td>Yes No</td>
</tr>
<tr>
<td>g) Evidence suggesting a gram positive source if infection</td>
<td></td>
</tr>
<tr>
<td>i) gram stain with gram positive cocci</td>
<td>Yes No</td>
</tr>
<tr>
<td>ii) recent lower airway culture with MRSA</td>
<td>Yes No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modified Clinical Pulmonary Pneumonia Score (CPIS) Score</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°C)</td>
<td></td>
</tr>
<tr>
<td>&gt; or equal to 36.5 and &lt; or equal to 38.4</td>
<td>0</td>
</tr>
<tr>
<td>&gt; or equal to 38.5 and &lt; or equal to 38.9</td>
<td>1</td>
</tr>
<tr>
<td>&gt; or equal to 39 and &lt; or equal to 36</td>
<td>2</td>
</tr>
</tbody>
</table>

| Blood leukocytes (mm³)                                    |        |
| > or equal to 4,000 and < or equal to 11,000             | 0      |
| < 4,000 or > 11,000                                      | 1      |

| Tracheal secretions                                      |        |
| Absence of tracheal secretions                           | 0      |
| Presence of nonpurulent tracheal secretions              | 1      |
| Presence of purulent tracheal secretions                 | 2      |

| Oxygenation: (PaO2/FiO2 mm Hg)                           |        |
| > 240 or ARDS (ARDS defined as PaO2/FiO2 or equal to 200, pulmonary arterial wedge pressure < or equal to 18 mm Hg and acute bilateral infiltrates) | 0 |
| < or equal to 240 and no ARDS                           | 1      |

| Pulmonary radiography                                    |        |
| No infiltrate                                            | 0      |
| Diffuse (or patchy) infiltrate                           | 1      |
| Localized infiltrate                                     | 2      |

| Progression of pulmonary infiltrate                      |        |
| No radiographic progression                              | 0      |
| Radiographic progression (after CHF and ARDS excluded)   | 2      |

| Culture of tracheal aspirate                             |        |
| Pathogenic bacteria cultured in rare or light quantity or no growth | 0 |
| Pathogenic bacteria cultured in moderate or heavy quantity | 1 |
| Same pathogenic bacteria seen on Gram stain              | 1      |

| Total CPIS points                                        |        |

<table>
<thead>
<tr>
<th>DATE:</th>
<th>TIME:</th>
<th>Keyplate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Physician signature
Physician number
Pharmacist signature
Pseudomonas and Acinetobacter

Gram stain of *Pseudomonas aeruginosa*

Gram stain of *Acinetobacter baumannii*

7-days of Doripenem vs. 10-days Imipenem

- Doripenem vs. Imipenem arms:
  - Clinical cure rate: 45.6% vs. 56.8% (95% CI, -26.3% to 3.8%)
    - VAP due to Pseudomonas: 41.2% vs. 60.0% (95% CI, -57.2 to 19.5)
  - 28-day mortality: 21.5% vs. 14.8% (95% CI, -5.0 to 18.5)
  - Consideration should be given to treating patients with VAP for more than seven days to optimize clinical outcome.

Kollef MH et al. Critical Care. 2012. 16:R218
Duration of Antibiotic Therapy: 8 vs. 15 Days

- 401 patients with VAP
  - BAL
  - Initial appropriate therapy
- Interventions
  - 197 patients received 8 days of antibiotics
  - 204 patients received 15 days of antibiotics
- Results 8 vs. 15 days
  - No difference in mortality, LOS or MV days
  - Less multi-drug resistant recurrent infections in the 8 day group (42.1 vs. 62.3%, p=0.038)
  - VAP with non-fermenting gram negative bacilli (Pseudomonas) had a higher recurrence rate in the 8 day group

Survival in the ITT Population.

- 227 adult VAP patients in the ITT population
- ITT population
  - Received at least 1 dose of study drug
  - Not from the excluded sites
- \( P = 0.118 \)
- Data from additional files

Kollef MH et al. Critical Care 2012, 16:R218
Survival in the ITT Population.

Kollef MH et al. Critical Care 2012, 16:R218
Doripenem vs. Imipenem for VAP

- Prospective, randomized trial
- 531 adult VAP ICU patients
- 7-14 days of IV antibiotics:
  - Doripenem 500 mg q8h over 4 hours
  - Imipenem 500 mg q6h/1000 mg q8h
  - The duration of therapy: 8.6 vs. 9.0 days, respectively.
- Day 28 mortality
  - 10.8% with Doripenem
  - 9.5% with Imipenem
  - Difference: 1.3% (95% CI -4.4% to 7.0%).


— METHODS: Patients (n = 4,479)
  • In the intensive care unit (ICU) for at least 2 days
  • Received mechanical ventilation (MV) within 48 hours after ICU admission.

— RESULTS: 685 (15.3%) patients acquired at least one episode of VAP.
  • ICU mortality attributable to VAP of about 1% on Day 30 and 1.5% on Day 60.

— CONCLUSIONS: In contrast to the majority of previous reports, found a relatively limited attributable ICU mortality of VAP.

The attributable ICU mortality of VAP as a function of time

My Conclusions for 2012

- The attributable mortality from VAP is controversial.

- Gram-positive (MRSA)
  - MRSA may be changing (importance of \( pvl \)).
  - Higher MICs to vancomycin are associated with worse outcomes.
  - Higher vancomycin trough levels are associated with renal injury.
  - In patients with MRSA pneumonia, linezolid demonstrated improved clinical efficacy compared to vancomycin.

- Gram-negative (multi-drug resistant pathogens)
  - Determine the duration of therapy based on your patient, the pathogen and clinical response.
  - A shorter duration of therapy has increased 28-day antibiotic-free days, less reduced recurrence of VAP due to multi-resistant organisms and similar outcomes.
  - For cases of VAP due to NF-GNB recurrence was greater after short-course therapy, but other outcomes did not significantly differ.