Issues In The Diagnosis of VAP: Definitions for Use In a Prevention Measure

Michael S. Niederman, M.D., FCCP
Chairman, Department of Medicine
Winthrop-University Hospital
Mineola, NY

Professor of Medicine
Vice-Chairman, Department of Medicine
SUNY at Stony Brook
Issues for Discussion

- Diagnosis of VAP: Clinical vs. microbiologic
  - The value of clinical diagnosis
- Problems with quantitative cultures/ microbiologic diagnosis
- Management of VAP with clinical methods
- VAP diagnosis and quality of care
  - Do VAP rates reflect quality of care?
  - If not, what can we measure?
    - Rates vs. patient relevant outcomes and processes of care
Diagnosis of VAP: Clinical vs. microbiologic

The value of clinical diagnosis
Clinical Definition HAP and VAP

- Hospitalized for at least 48 hours
  - Intubated and mechanically ventilated for at least 48 hours at onset: VAP
  - Not intubated and mechanically ventilated for at least 48 hours at onset: HAP
  - Both HAP and VAP can be in ICU

- New, progressive or persistent pulmonary infiltrate on x-ray

  AND

- At least 2 of the following:
  - Temperature: <36 °C or ≥38.3 °C
  - WBC <5000 cells/mm³ or >10,000 cells/mm³
  - Purulent sputum or endotracheal aspirate (VAP)

  AND

- Microbiologic Confirmation (qualitative vs. quantitative cultures)
What About Antibiotic Use?

- Should the therapeutic decision to use antibiotics be part of the clinical diagnostic criteria for VAP?
  - The goal is to reduce antibiotic use, not just the rate of VAP
  - What if antibiotics are used empirically without getting cultures?
- Would this be considered NO VAP?
Quantitative Bacteriologic Definition of VAP

- Clinical signs of pneumonia PLUS
- Microbiologic confirmation by quantitative cultures
  - > $10^3$ cfu/ml on PSB
  - > $10^4$ or $10^5$ cfu/ml in BAL
  - > $10^6$ cfu/ml in endotracheal aspirate
- Maybe accept lower threshold if already on antibiotics for < 48-72 hours.
A “weighted” clinical diagnosis of VAP, giving 0-2 points each for:
- Fever, leukocytosis, purulence of secretions, oxygenation, type of infiltrate, growth of tracheal aspirate

28 patients, studied with BAL and with Bacterial Index
- 15 no infection, 13 with infection

Correlation of BI from bronch BAL and CPIS of 0.84
- If CPIS > 6, 93% with BI ≥ 5
- If CPIS ≤ 6, all BI < 5
- CPIS > 6 has sensitivity of 93%, specificity and PPV 100%

## Calculating the CPIS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Scoring Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>- 0 point: 36.5–38.4 C'&lt;br&gt;- 1 point: 38.5–38.9 C&lt;br&gt;- 2 points: &lt;36 or &gt;39 C</td>
</tr>
<tr>
<td>Oxygenation (PaO2/FiO2)</td>
<td>- 0 point: PaO2/FiO2 &gt; 240 or ARDS&lt;br&gt;- 2 points: PaO2/FiO2 &lt; 240 and no evidence of ARDS</td>
</tr>
<tr>
<td>Tracheal secretions (score)</td>
<td>- 0 point: &lt; 14&lt;br&gt;- 1 point: &gt; 14&lt;br&gt;- 2 points: purulent sputum&lt;br&gt;- 3 points: culture of tracheal aspirate</td>
</tr>
<tr>
<td>Blood leukocytes (cells/μL)</td>
<td>- 0 point: 4000–11000&lt;br&gt;- 1 point: &lt; 4000 or &gt; 11000&lt;br&gt;- 2 points: &gt; 500 band forms</td>
</tr>
<tr>
<td>Pulmonary radiography</td>
<td>- 0 point: no infiltrate&lt;br&gt;- 1 point: diffuse or patchy infiltrates&lt;br&gt;- 2 points: localized infiltrate</td>
</tr>
</tbody>
</table>

Total score of > 6 points suggests ventilator-associated pneumonia

ARDs = acute respiratory distress syndrome
Other Studies of The CPIS: Better Done Prospectively Than Retrospectively

• Compare CPIS to non-bronchoscopic BAL in 145 patients
  – 34 with VAP with CPIS 7.6 vs 4.1 without (p < 0.001)
  – Prospective, no bacteriologic data

• Most negative studies use a “modified” score
  – No tracheal aspirate cultures on initial dx
  – No recording of sputum volume by nurses
  – No measurement of band forms
  – Often calculated RETROSPECTIVELY

• Not as valuable if measured retrospectively
  – Applied to 201 patients in the French multicenter study of invasive methods
  – Values on day 1 similar with and without bacteriologic confirmation; not on day 3 with bacteriologic data and radiographic progression (89% sensitivity, 47% specificity, 84% NPV)
Adding Gram Stain of LRT Secretions Improves the Accuracy of CPIS

- Prospective study of 79 episodes suspected VAP
- 3 steps: inclusion (CPIS); Gram stain of blind PTC and BAL and CPIS; Culture of PTC and qualitative EA and CPIS
- 40 confirmed VAP by BAL as gold standard
- Sensitivity and specificity of CPIS >6 increased if add Gram stain of PTC (78%, 56%).
Problems with quantitative cultures/ microbiologic diagnosis

- False positives and negatives with quantitation
- Methodologic problems with quantitative cultures
- Qualitative tracheal aspirates are just as effective
Accuracy of Invasive Bacteriologic Methods

- The autopsy as gold standard
  - 28 MV patients with bronch within 3 days of death
  - Autopsy with full lung dissection: Central and peripheral, 2 samples/segment
  - PSB, BAL, quantitative EA in all patients. 53% off antibiotics. > 48 hours
  - 67% with histologic pn: bilateral, dependent; could be central without peripheral
  - Non-infectious Dx commonly coexist: DAD, fibrosis, infarction; also bronchiolitis, purulent mucus plugs

Sampling Error: Uneven Distribution of the Histologic Stages of VAP

- Pneumonia is in multiple stages of evolution, in multiple sites
  - Potential for sampling error: uninfected site, site of early infection while other sites with advanced infection
- In a piglet model of VAP, found
  - No bacteriologic cutoff could define the presence of histologic pn
  - Histologic lesions unevenly distributed
  - Single organisms unevenly distributed
  - EA more sensitive and discriminating for the organisms causing pneumonia than PSB or BAL

Problems with using quantitative microbiology to guide therapy decisions

- Patients with **false positive** results will receive therapy when colonized
  - 54 quantitative cultures (PSB, BAL) from 32 without suspected pneumonia. 6/23 with positive cults at > threshold. Rodriguez de Castro, et al. AJRCCM 1994; 149: 320

- Patients with **false negative** diagnostic testing will not receive timely therapy
  - Methodologic (processing) errors may lead to inaccurate results
  - 246 surgical/trauma patients with BAL.
    - 100 with organisms > threshold (10⁵ cfu/ml), 333 at subthreshold concentrations
    - 16% at threshold, 11% at subthreshold had bacteremia (False negative BAL??)
How Is Quantitation Done? Is it Accurate?
Repeatability of BAL and PSB

- 44 patients, BAL x 2 same site, within 30 min, 3 aliquots (40 mL)
  - 28: both samples sterile; 16 positive: 14 both positive, 2 mixed results
  - Same log in only 5 of 16 with positive samples
- Similar data for repeated PSB
  - 22 patients, 5 PSB’s at same site. 100% qualitative reproducibility
  - 59% of patients with samples> 1 log difference. 3/22 on either side of dx threshold.

(Using $10^4$ threshold)
Tracheal Aspirates May Give More True Positives than Quantitative PSB

- Excellent correlation with invasive methods
  - 60 episodes VAP with TBAS, PSB, BAL
    - 90% positive with BAL ($10^4$), TBAS ($10^5$)
    - 83% positive PSB ($10^3$)
      - Woske et al. Critical Care 2001; 5: 167
  - 15 surgical patients with paired TBAS and PSB
    - Often organisms at $>10^4$ in TBAS, and not $>10^3$ on PSB
    - Same species in TBAS: sens 82%, specificity 79%
  - 48 patients with non-responding VAP on therapy for at least 72 h: TBAS, PSB and BAL on antibiotics
    - TBAS at $10^5$ with sensitivity of 93%, specificity of 80%. Some invasive results may have been false negatives since these cults often +, but below dx threshold
      - Wu et al. Chest 2002; 122: 662
Management of VAP with clinical methods
Canadian Clinical Trial

- 740 patients with suspected VAP after 4 days MV.
- Omit known colonization / infection with MRSA or P. aeruginosa
  - BUT 5.1% had MDR pathogens, 14.2% high risk organisms
- Randomized to BAL + quantitative cults or endotracheal aspirate + no quantitation
  - Mono vs. combination rx.
  - No initial withhold of therapy in either group
- No difference in mortality or use of targeted therapy (de-escalation)

Heyland D, et al. NEJM 2006; 355: 2619-2630
Diagnostic Methods and Focused Antibiotic Therapy

- 740 patients, suspected VAP after 4 days ICU
- BAL (quantitative cultures) or EA (non-quantitative cult)
  - Initial rx with meropenem and cipro vs. meropenem
  - Try to exclude if Pseudomonas or MRSA (14% high risk organisms)
- 74% targeted therapy in both groups (discontinuation or modification based on cultures)
  - Positive cults: 76% EA; 79% BAL
  - Negative cults: 73% EA; 67% BAL
RCT Data

- 5 RCT’s comparing invasive vs. non-invasive methods.
  - 3 quantitative vs. qualitative samples, 2 used quantitative methods in both arms
  - No difference in mortality, time in ICU, time on mechanical ventilation, rate of antibiotic change.

**MORTALITY DATA**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Invasive Events</th>
<th>Invasive Total</th>
<th>Non-Invasive Events</th>
<th>Non-Invasive Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCCTG 2006</td>
<td>68</td>
<td>365</td>
<td>69</td>
<td>374</td>
<td>37.6%</td>
<td>1.02 [0.76, 1.38]</td>
</tr>
<tr>
<td>Fagor 2000</td>
<td>63</td>
<td>204</td>
<td>81</td>
<td>209</td>
<td>44.1%</td>
<td>0.80 [0.61, 1.04]</td>
</tr>
<tr>
<td>Ruiz 2000</td>
<td>14</td>
<td>37</td>
<td>18</td>
<td>39</td>
<td>9.7%</td>
<td>0.82 [0.48, 1.40]</td>
</tr>
<tr>
<td>Sanchez-Nieto 1998</td>
<td>11</td>
<td>24</td>
<td>7</td>
<td>27</td>
<td>3.6%</td>
<td>1.77 [0.82, 3.83]</td>
</tr>
<tr>
<td>Solé Violán 2000</td>
<td>10</td>
<td>45</td>
<td>9</td>
<td>43</td>
<td>5.1%</td>
<td>1.06 [0.48, 2.36]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>675</strong></td>
<td><strong>692</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.93 [0.78, 1.11]</strong></td>
</tr>
</tbody>
</table>

Total events 167, 184

Heterogeneity: Ch² = 4.68, df = 4 (P = 0.32); P = 14%
Test for overall effect: Z = 0.76 (P = 0.45)
Management of VAP WITHOUT Quantitative Cultures

- In clinical practice can use a clinical diagnosis (CPIS ≥ 6) supplemented by non-quantitative cultures.

- All patients need a lower respiratory tract culture prior to antibiotic therapy (tracheal aspirate) but quantitative cultures (non-bronchoscopic or bronchoscopic LRT sample) not necessary.
  - Clinical approach: Culture semi-quantitatively or qualitatively
    - Surveillance cultures may supplement other data to guide accurate empiric therapy
  - Quantitative cultures done with bronchoscopic or non-bronchoscopic samples, are NOT NEEDED.
    - Quantitative cultures may increase specificity for pneumonia dx
    - Are NOT necessary to improve outcome, assure appropriate therapy or de-escalation
    - Their use assures defining only a SUBSET of people with VAP (there are many false negatives)

- A negative LRT culture can be used to de-escalate antibiotics if done in absence of an antibiotic change within 72 hours.
VAP diagnosis and quality of care

---Do VAP rates reflect quality of care?
---If not, what can we measure?
The Argument That VAP Rates Reflect Quality of Care Is Not Logical UNLESS

- VAP is ALWAYS preventable and thus constitutes a Medical Error
  - Then infection rates are a reflection of the quality of care
- Prevention strategies are available, and evidence –based to show efficacy for the diagnosis that is used
- Infection is easily and reproducibly defined
  - Certainly not the case for VAP
- All hospitals have a similar case mix of severity and indigent patients, or else there is an adjustment for these factors
- The hospital is able to REFUSE to give futile care
  - Aggressive and futile care is often complicated by nosocomial infection and in this setting, withholding payment penalizes other non-futile patients
Limitations of The Never Event Concept

- Aiming for zero can have adverse clinical consequences
  - Treating colonization present on admission, and not infection
  - Treating VAT: Is this useful or is it overuse of antibiotics?

- Cost to hospitals can spiral out of control.
  - **Diminishing returns** after a certain point, and will spend a lot of money for a small (or no) incremental benefit, when resources should be used elsewhere

- Data base research may be flawed by the entry of inaccurate data from public reporting. **Low VAP rates do not always lead to better outcomes** such as: reduced mortality, reduced antibiotic use, reduced LOS.

- Recommend process measures and population based outcomes
  - Provide positive and negative incentives, not just negative

What Other Approaches Are Possible?

- Adjust for preventability
- Our current model
  - May provide little motivation to improve care
  - High performers are satisfied with status quo
  - Low performers discredit the adjustment model
- Link care actually received to outcomes
  - How many patients with an adverse outcome had an appropriate prevention efforts?
    - Those without prevention effort are defined as avoidable harm
- Pronovost P and Colantuoni E. JAMA 2009; 301: 1273-5
Getting To Zero : A “Sound Bite” and Marketing Idea

• An unhealthy convergence of infection control and quality improvement: 2 different cultures

• Edmond MB. ICHE 2009; 30: 74-76

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hospital epidemiology</th>
<th>Quality improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focus</td>
<td>Exploration and analysis</td>
<td>Modification</td>
</tr>
<tr>
<td>Primary task</td>
<td>Defining problems and elucidating risk factors</td>
<td>Designing and implementing interventions</td>
</tr>
<tr>
<td>Analytic orientation</td>
<td>Population based</td>
<td>Often case based</td>
</tr>
<tr>
<td>Primary influences</td>
<td>Science and medicine</td>
<td>Business</td>
</tr>
<tr>
<td>Strength</td>
<td>Rigorous methodology and validity</td>
<td>Process design</td>
</tr>
<tr>
<td>Approach</td>
<td>Structured, relatively uniform</td>
<td>Encourages innovation</td>
</tr>
<tr>
<td>Delivery style</td>
<td>Instructive</td>
<td>Collaborative</td>
</tr>
<tr>
<td>Solutions</td>
<td>Targeted: solutions evolve from understanding the problem</td>
<td>Empiric: attempt various solutions and keep what works, discard the rest</td>
</tr>
<tr>
<td></td>
<td>Data oriented, relatively dull</td>
<td>Flashy campaigns, catchy slogans</td>
</tr>
<tr>
<td>Perspective</td>
<td>Long term</td>
<td>Short term, evolving</td>
</tr>
<tr>
<td>Tempo</td>
<td>Relatively slow</td>
<td>Relatively fast</td>
</tr>
</tbody>
</table>