Endpoints in HAP/VAP trials: Mortality, Clinical Endpoints, Biomarkers

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Populations and Pathogens
Etiology of non-ICU HAP

Unknown: 16
Pseudo: 7
Acinetobacter: 2
A. fumigatus: 8
Staph: 4
Enterbacter: 7
H. influenzae: 5
Legionella: 7
S. pneumoniae: 3
Other: 105

Mortality 26%

Sopena, Chest, 2005
Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study


Summary

Background The American Thoracic Society and Infectious Diseases Society of America provide management of hospital-acquired, ventilator-associated, and health-care-associated pneumonias, respectively. In this observational study, we sought to augment these guidelines with the most recent evidence.

Discussion

In our cohort study, compliance with the ATS–IDSA guidelines was associated with increased mortality.
413 patients in IMPACT-HAP database

110 patients excluded
- 41 no risk of multidrug-resistant organism
- 54 received pathogen-directed therapy
- 13 no outcomes data
- 2 no follow-up at day 14

303 assessable for primary analyses

171 HCAP or HAP but not VAP
- 38 not mechanically ventilated
- 133 mechanically ventilated

132 VAP
- 36 ventilation started 0–2 days before diagnosis of pneumonia
- 97 ventilation started after diagnosis of pneumonia

Etiology of ICU HAP

Kett, Lancet ID, 2011
Mortality Endpoint
# Mortality in ICU HAP/VAP

<table>
<thead>
<tr>
<th></th>
<th>Compliant treatment (n=129)</th>
<th></th>
<th>Non-compliant treatment (n=174)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Treatment active</td>
<td>Deaths</td>
</tr>
<tr>
<td>MRSA</td>
<td>27 (21%)</td>
<td>25 (93%)</td>
<td>11 (42%)</td>
</tr>
<tr>
<td>Pseudomonas spp</td>
<td>33 (26%)</td>
<td>29 (88%)</td>
<td>15 (45%)</td>
</tr>
<tr>
<td>Klebsiella spp</td>
<td>11 (9%)</td>
<td>9 (82%)</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>MSSA</td>
<td>7 (5%)</td>
<td>7 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Acinetobacter spp</td>
<td>11 (9%)</td>
<td>5 (46%)</td>
<td>0</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>3 (2%)</td>
<td>2 (67%)</td>
<td>2 (67%)</td>
</tr>
<tr>
<td>Enterobacter spp</td>
<td>2 (2%)</td>
<td>2 (100%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Polymicrobial*</td>
<td>25 (19%)</td>
<td>17 (68%)</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>Culture negative</td>
<td>30 (23%)</td>
<td>...</td>
<td>10 (33%)</td>
</tr>
</tbody>
</table>
Lethal Bacterial HAP/VAP

- *Pseudomonas aeruginosa*
- Methicillin-resistant *S. aureus*
- *Acinetobacter* sp.
- MDR Enterbacteriaceae
  - ESBL
  - KPC
- *Stenotrophomonas maltophilia*
# Attributable Mortality of Ventilator-Associated Pneumonia

A Reappraisal Using Causal Analysis

Maarten Bekaert¹, Jean-François Timsit², Stijn Vansteelandt¹,⁴, Pieter Depuydt⁵,⁶, Aurélien Vésin³, Maïté Garrouste-Orgeas⁷, Johan Decruyenaere⁵, Christophe Clec’h⁸, Elie Azoulay⁹, and Dominique Benoit⁵ on behalf of the Outcomerea Study Group

## TABLE 3. HAZARD RATIOS OF INTENSIVE CARE UNIT DEATH PER ADDITIONAL DAY SINCE INFECTION CALCULATED FOR PATIENTS WITH DIFFERENT SAPS II SCORES ON ADMISSION (DIFFERENT PERCENTILES)

<table>
<thead>
<tr>
<th>SAPS II on Admission</th>
<th>Hazard Ratio of ICU Death per Additional Day Since Infection (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 (5%)</td>
<td>1.023 (0.980–1.068)</td>
<td>0.31</td>
</tr>
<tr>
<td>20 (10%)</td>
<td>1.033 (1.007–1.061)</td>
<td>0.07</td>
</tr>
<tr>
<td>28 (25%)</td>
<td>1.037 (1.018–1.056)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>40 (50%)</td>
<td>1.038 (1.025–1.052)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>53 (75%)</td>
<td>1.027 (1.013–1.041)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>65 (95%)</td>
<td>1.08 (1.050–1.113)</td>
<td>0.49</td>
</tr>
<tr>
<td>73 (95%)</td>
<td>0.990 (0.960–1.010)</td>
<td>0.28</td>
</tr>
<tr>
<td>Overall</td>
<td>1.023 (1.011–1.034)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

![Graph showing observed ICU mortality and ICU mortality without VAP over days since ICU admission]

- 4.4%
- 5.9%
Hospital-acquired MRSA Pneumonia

$p = 0.025$

Wunderink, Chest, 2003
Mortality of MRSA HAP/VAP

![Graph showing mortality rates for different studies with Vancomycin and Linezolid.]

- Kolleff* (Intens Care Med 2004): 38.3%, N=47, p<0.05
- Wunderink+ (Chest 2008): 30%, N=20
- Couch# (abstract, IDSA, 2007): 13.3%, N=30
- Wunderink& (Clin Infect Dis, 2012): 26.3%, N=224
- Linezolid: 28.1%, N=224

*p<0.05
Clinical Failures (~15%) and Mortality Rates

Clinical Failures in Non-Inferiority Studies

- T = Test
- C = Comparator

Mortality Rate
Rescue Rate*

* Patient who received alternative therapy for rescue

Laessig, FDA, 2009
Effect of Linezolid by Baseline APACHE II Score

ITT Population

Wunderink, Clin Therap, 2003

Survival (%) by APACHE II Score:
- 0-11: 96.6 (Linezolid), 96.7 (Vancomycin)
- 12-15: 83 (Linezolid), 55 (Vancomycin)
- 16-19: 28 (Linezolid), 29 (Vancomycin)
- 20-39: 17 (Linezolid), 22 (Vancomycin)

*p = 0.01
Mortality as an endpoint for HAP/VAP Studies

- Probably is an attributable mortality
  - Significantly less in sophisticated, high-tech North American/Western European systems
  - Requires focus on recruiting populations at risk
Clinical and Biomarker Endpoints
Effect of Microorganism and Initially Appropriate Antibiotics on VAP Resolution

Vidaur, Chest, 2008
CPIS Score in Response to VAP Treatment

Luna, Crit Care Med, 2003
Short Course Empiric Strategy

Antibiotics Continued

Singh, Am J Respir Crit Care Med, 2000

- Short course Cipro: 97% for All, 96% for CPIS<6
  - Significance: \( p = 0.0001 \) for All, \( p < 0.02 \) for CPIS<6

- Standard: 28% for All, 14% for Res/Super, 13% for Mortality
  - Significance: \( p = 0.06 \) for Mortality
Procalcitonin Response in VAP

Luyt, AJRCCM, 2005

D3

PCT > 1.5 ng/ml

D7

PCT > 0.5 ng/ml
Procalcitonin to Guide Duration of Antibiotic Therapy in Sepsis
Nobre, AJRCCM, 2008

Majority were pulmonary infections, both CAP and HAP. *Pseudomonas, Acinetobacter, Legionella* were *a priori* excluded because of perceived need for prolonged antibiotics.
PRORATA Study
Bouadama, Lancet, 2010
Biomarkers: Procalcitonin

- “a better WBC”
- Value in clinical trials
  - More objectively define success
  - Trigger for further evaluations
- At some point, reverts to marker of uncontrolled inflammatory state
Why do patients with HAP/VAP Die?
Why do patients with HAP/VAP Die?

- Septic shock
  - More of an issue with CAP
  - Marker for inadequate antibiotics
- Respiratory failure
- Multiple organ dysfunction
- Recurrent Infections

Withdrawal of Care
Mortality as an endpoint for HAP/VAP Studies

- Probably is an attributable mortality
  - Significantly less in sophisticated, high-tech North American/Western European systems
  - Requires focus on recruiting populations at risk
- Unsophisticated understand of the role of antibiotic treatment in mortality
  - “Treatment as prevention”
Recurrent *Pseudomonas* VAP

Silver, Chest, 1992
Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study

Daniel H Kett, Ennie Cano, Andrew A Quartin, Julie E Mangino, Marcus J Zervos, Paula Peyrani, Cynthia M Cely, Kimbal D Ford, En Cao, Julio A Ramirez, and the Improving Medicine through Pathway Assessment of Critical Therapy of Hospital-Acquired Pneumonia Investigators

Summary
Background The American Thoracic Society and Infectious Diseases Society of America provide management of hospital-acquired, ventilator-associated, and health-care-associated pneumonias, respectively. The American Thoracic Society has recommended that patients with pneumonia be treated with a specific antibiotic treatment based on the site of infection and the patient's clinical response.

Discussion In our cohort study, compliance with the ATS–IDSA guidelines\(^ {13} \) was associated with increased mortality.
ATS/IDSA Guideline-based Therapy

Kett et al, Lancet ID, 2011
Inadequacies of Study

- **Lacks face validity**
  - empirical coverage for MRSA is associated 2.4 OR excess mortality in culture-positive MRSA patients?

- **Inadequacy of propensity score adjustment**
  - Higher shock, higher # Pseudomonas in “compliant”

- **Non-compliance with de-escalation**
  - 52% of vanco/LZD in MRSA negative
  - <50% of second GN agent in Pseudo/Acineto negative
  - ? Culture negative (OR 1.8 for “compliant’)
  - More nephrotoxicity in “compliant” group

If compliant with de-escalation (not analyzed), study may actually validate ATS/IDSA guidelines
Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*
Conclusions

- Mortality is an appropriate endpoint but a blunt instrument to measure outcome in HAP/VAP trials
- Clinical scores and biomarkers objectify clinical outcomes but regress to the mean
- More sophisticated endpoints paralleling ARDS/ALI may need to be developed
  - “Days alive and infection/organ failure free”