Challenges in developing drugs for critical illness

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Disclosure

Conflicts of interest:
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– Bayer, Medimmune/AstraZeneca,
Pfizer, Arsanis, Cubist/Merck,
Basilea, Aridis, Astellas
How to prove the efficacy of a new drug in patients with VAP/HAP?
How to prove the **efficacy** of a new **drug** in patients with HAP/VAP?

**Randomization with double blinding** is the only methodology that permits a non-biased evaluation.

**Two key issues:**
- Selection of the study population
- Selection of the comparator

**Group 1:** Study drug

**Group 2:** Comparator
Selection of dosing

Randomization with **double blinding** is the only methodology that permits a non-biased evaluation.
Defining Antibiotic Levels in ICU Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients?


<table>
<thead>
<tr>
<th>Dosing and PK/PD Data</th>
<th>Cefepime (n = 14)</th>
<th>Doripenem (n = 19)</th>
<th>Piperacillin (n = 109)</th>
<th>Meropenem (n = 89)</th>
<th>Total (N = 361)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage per 24 h, g</td>
<td>6.0 (5.0–6.0)</td>
<td>1.75 (1.50–3.0)</td>
<td>12.0 (12.0–16.0)</td>
<td>3.0 (3.0–4.0)</td>
<td></td>
</tr>
<tr>
<td>50% fT &gt; MIC achieved</td>
<td>78.6%</td>
<td>100.0%</td>
<td>80.6%</td>
<td>95.0%</td>
<td>78.9%</td>
</tr>
<tr>
<td>50% fT &gt; 4×MIC achieved</td>
<td>50.0%</td>
<td>69.2%</td>
<td>48.9%</td>
<td>68.8%</td>
<td>48.9%</td>
</tr>
<tr>
<td>100% fT &gt; MIC achieved</td>
<td>78.6%</td>
<td>76.9%</td>
<td>67.0%</td>
<td>69.7%</td>
<td>60.4%</td>
</tr>
<tr>
<td>100% fT &gt; 4×MIC achieved</td>
<td>71.4%</td>
<td>30.8%</td>
<td>30.3%</td>
<td>41.6%</td>
<td>35.0%</td>
</tr>
</tbody>
</table>
Penetration of Meropenem into Epithelial Lining Fluid of 39 Patients with VAP

Lodise TP, et al. AAC 2011;55:1606–10

Median $\text{AUC}_{\text{ELF}}/\text{AUC}_{\text{plasma}}$ penetration ratio $=25.4\%$

[Graph showing concentration over time for plasma and ELF]
Vancomycin trough plasma concentrations obtained in the control group

<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

Selection of the Study Population

1. Age >18 yrs, non pregnant
   Patient on MV
   HAP/VAP suspicion: **New infiltrate** and at least 2 of the following:
   - fever
   - high leukocyte/immature neutrophil count
   - new onset of purulent sputum
   - PaO₂/FIO₂ decrease

Randomization 1/1

Group 1: Study drug

Group 2: Comparator
Potential limitations of clinical approaches to VAP recognition

- Such features are subject to different interpretations and can be easily manipulated.
- In a context where healthcare-associated infection are stigmatized, they have led to a zero-VAP rate in many ICUs worldwide, replacing VAP by VAT, and rendering extremely difficult the conduct of RCTs.
Mean VAP Rates Reported to the National Healthcare Safety Network, Data Summary for 2009


<table>
<thead>
<tr>
<th>Type of location</th>
<th>No. of Locations†</th>
<th>No. of VAPs</th>
<th>Ventilator days</th>
<th>Pooled mean</th>
<th>Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>Critical care units</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burn</td>
<td>21</td>
<td>109</td>
<td>14,703</td>
<td>7.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Medical, major teaching</td>
<td>25 (74)</td>
<td>263</td>
<td>140,784</td>
<td>1.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Medical, all other</td>
<td>97 (122)</td>
<td>178</td>
<td>31,185</td>
<td>1.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Medical cardiac</td>
<td>125 (116)</td>
<td>149</td>
<td>100,768</td>
<td>1.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Medical/surgical, major teaching</td>
<td>118 (115)</td>
<td>338</td>
<td>194,776</td>
<td>2.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Medical/surgical, all others</td>
<td>359 (305)</td>
<td>284</td>
<td>209,206</td>
<td>1.4</td>
<td>0.0</td>
</tr>
<tr>
<td>≤15 beds</td>
<td>154 (152)</td>
<td>348</td>
<td>295,884</td>
<td>1.2</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Note: VAP rate is calculated as VAP cases per 1000 ventilator days.*
The Zero-VAP Infection Rate is a Fallacy

If prevention of VAP was effective, use of antibiotics in the ICU should have decreased dramatically.

The disturbing issue is that very low rates of infection have NOT been associated with corresponding reports of decreased antibiotic use or mortality.

One explanation for the discrepancy is that the reporting system is being gamed by avoiding the diagnosis of infection while continuing to treat patients using antibiotics.

Undefined “severe sepsis” and VAT are the diagnoses used for justifying antibiotics.

Klompas M. Current Opin Infect Dis 2012;25:176-82
Bonten MJM Clin Infect Dis 2011;52:115-21
Selection of the *Study Population*

1. Age >18 yrs, non pregnant
   Patient on MV
   HAP/VAP suspicion: **New infiltrate** and at least 2 of the following:
   - fever
   - high leukocyte/immature neutrophil count
   - new onset of purulent sputum
   - PaO₂/FIO₂ decrease

Randomization 1/1

Group 1: **Study drug**

Group 2: **Comparator**
Potential limitations of clinical approaches to VAP recognition

- A contrario, such features permit to include patients with only proximal airways colonization or even no infection, diluting any effect of the study drug, and potentially confounding the interpretation of the treatment effect in a non-inferiority trial.
Determining the pathogen(s) responsible for the infection

Selection of the Study Population

- Trial population should only include patients who have developed a true pneumonia, i.e., NOT patients with only proximal airways colonization or a fortiori no infection at all.
- They also should be sufficiently ill to respect the initial hypotheses sustaining the NI margin.
Two criteria are thus required for establishing the diagnosis of VAP:

1. an intense infiltration of the intraalveolar spaces by neutrophils, fibrinous exudates and cellular debris, particularly around terminal bronchioles,
2. an infectious agent not present or incubating at MV onset
Does this patient have VAP?

- Histopathological findings are out of reach most of the time.
- Thus, in clinical practice, it is extremely difficult to confirm or exclude lung parenchyma invasion by bacterial pathogens — i.e., to distinguish between patients with a true pneumonia and those merely colonized or with only some form of tracheobronchitis.
Serial chest radiographs allows VAP diagnosis when a new or progressive infiltrate is **clearly documented**

9 June 2015
\[\text{PaO}_2/\text{FIO}_2 = 256 \text{ mmHg}\]

11 June 2015
\[\text{PaO}_2/\text{FIO}_2 = 138 \text{ mmHg}\]
A new or progressive radiographic infiltrate CANNOT be documented in many patients with VAP.

**June 10, 2015**

**BAL quantitative culture results:** *Serratia marcescens* 10^6 cfu/mL

**June 10, 2015**

Blind Bronchial Sampling ROC Curves for Diagnosing VAP

Papazian et al. Am J Respir Crit Care Med 1995

Area under the curve=0.83

Area under the curve=0.94
Determining which pathogen(s) is(are) responsible for the infection

1. Age >18 yrs, non pregnant
   Patient on MV
   HAP/VAP suspicion: **New infiltrate** and at least 2 of the following:
   - fever
   - high leukocyte/immature neutrophil count
   - new onset of purulent sputum
   - PaO₂/FIO₂ decrease

2. Respiratory secretions sampling

Randomization 1/1

Group 1: **Study drug**

Group 2: **Comparator**
Obtaining microbiological specimens after antibiotic introduction considerably decreases their yield.

New fever, High leukocytosis, Deterioration of gas exchange and pulmonary mechanics, Deterioration of hemodynamics.

New ABs Getting pulmonary secretions

Never do that
Evolution of Microbial Isolates Grown During the First 72 h of Antibiotic Treatment in 35 Patients with VAP


No. of isolates recovered in significant concentrations

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>66</td>
</tr>
<tr>
<td>12</td>
<td>34</td>
</tr>
<tr>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>48</td>
<td>9</td>
</tr>
<tr>
<td>72</td>
<td>2</td>
</tr>
</tbody>
</table>
Microscopic examination of distal respiratory secretions permits to only randomize patients with a high probability of VAP

Targeting a specific pathogen

1. Age >18 yrs, non pregnant
   Patient on MV
   HAP/VAP suspicion: **New infiltrate** and at least 2 of the following:
   - fever
   - high leukocyte/immature neutrophil count
   - new onset of purulent sputum
   - PaO₂/FI₂ decrease

2. Respiratory secretions sampling

Randomization 1:1

Group 1: Study drug

Group 2: Comparator
The Zephyr Trial: Study Design


- **Linezolid IV**: 600 mg q12h
- **Vancomycin IV**: 15 mg/kg q12h

7-14 days

Within 5 days of EOT

EOT Visit

EOS Visit

7-30 days after EOT

- Vancomycin dose adjusted by unblinded pharmacist based on renal function and trough concentrations
- Initial Cefepime or other Gram-negative coverage (not MRSA active) required
1225 Patients randomized
At 154 centers

No study drug (n = 41)

Linezolid 600mg IV q 12 h
N=597 (ITT population)

Have MRSA proven on culture
N=224 (mITT population)

Have MRSA proven on culture
And meet other criteria
N=172 (PP population)

Vancomycin 15 mg/kg IV q 12 h
N=587 (ITT population)

Have MRSA proven on culture
N=224 (mITT population)

Have MRSA proven on culture
And meet other criteria
N=176 (PP population)

New advances in microbiological approaches
Determining the pathogen(s) responsible for the infection ASAP

Day 0
Direct microscopic examination of LRT specimens

Day 1
Conventional microbiological cultures

Day 2
Pathogen identification

Day 3
Pathogen antibiogram
Rapid point-of-care diagnostic tests for bacterial respiratory tract infections


<table>
<thead>
<tr>
<th>Time to result</th>
<th>Type of technology</th>
<th>Targets</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 h</td>
<td>Automated sample preparation of respiratory specimen, real-time PCR and detection using molecular beacon technology</td>
<td>MSSA and MRSA</td>
<td>99.0% compared with quantitative culture of endotracheal aspirates</td>
<td>72.2% compared with quantitative culture of endotracheal aspirates</td>
</tr>
<tr>
<td>4 h</td>
<td>Multiplex endpoint PCR and amplicon detection by hybridization to oligo probes spotted on membrane arrays, direct from respiratory samples</td>
<td>Detection of 17 bacterial and fungal pathogens in addition to 22 antibiotic resistance genes</td>
<td>80-9% overall; target specific values 50-100%</td>
<td>99.0% overall; target specific values 72-3-100%</td>
</tr>
<tr>
<td>1 h</td>
<td>Pouch format comprising nucleic acid extraction, and nested PCR from nasopharyngeal swabs</td>
<td>20 targets including respiratory viruses, Bordetella pertussis, Mycoplasma pneumoniae and Chlamydia pneumoniae</td>
<td>84-100%</td>
<td>98-100%</td>
</tr>
</tbody>
</table>

MSSA = methicillin-sensitive Staphylococcus aureus. MRSA = methicillin-resistant S. aureus. SSTI = skin and soft tissue infection.

Table 3: Rapid molecular platforms and tests available for the diagnosis of bacterial respiratory tract infections.
Matrix-Assisted Laser Desorption Ionization - Time Of Flight Spectrometry (MALDI-TOF)
Determining the pathogen(s) responsible for the infection: “A light at the end of the tunnel”
But still a long way to go...
Prestudy effective antibacterial agents can obscure the treatment effect of the investigational drug

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   Patient on MV
   HAP/VAP suspicion: New infiltrate and at least 2 of the following:
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   - new onset of purulent sputum
   - PaO₂/FIO₂ decrease

2. Respiratory secretions sampling

3. Immediate AB therapy (ATS/IDSA)

4. Informed consent

Group 1: Study drug

Group 2: Comparator
Making the **time interval** between onset of therapy and randomization as short as possible

1. Age >18 yrs, non pregnant
   Patient on MV
   HAP/VAP suspicion: New infiltrate and at least 2 of the following:
   - fever
   - high leukocyte/immature neutrophil count
   - new onset of purulent sputum
   - PaO₂/FIO₂ decrease

2. Respiratory secretions sampling

3. Immediate AB therapy (ATS/IDSA)

4. Informed consent

<24 hours

Randomization 1/1

Group 1: Study drug

Group 2: Comparator
Challenges in developing drugs for critical illness: the informed consent issue

- Voluntary IC to participate in a clinical trial is the foundation upon which all ethical research is conducted.
- However, most patients with HAP/VAP are not capable of making decision on their own behalf.
- Legally authorized representative (LAR) – most of the time, a family member – are often reluctant to sign a lengthy and complex document.
- Approaching patients at risk and/or LAR before HAP/VAP onset to discuss their views on participating in research is difficult.
Making the **time interval** between onset of therapy and randomization **as short as possible**

1. Age >18 yrs, non pregnant
   Patient on MV
   HAP/VAP suspicion: **New infiltrate** and at least 2 of the following:
   - fever
   - high leukocyte/immature neutrophil count
   - new onset of purulent sputum
   - PaO₂/FIO₂ decrease

2. Respiratory secretions sampling

3. Immediate AB therapy (ATS/IDSA)

4. Waiver of consent

Randomization 1/1

Group 1: Study drug

Group 2: Comparator
Defining efficacy endpoints

1. Age >18 yrs, non pregnant
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   HAP/VAP suspicion: **New infiltrate** and at least 2 of the following:
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   - high leukocyte/immature neutrophil count
   - new onset of purulent sputum
   - PaO₂/FIO₂ decrease

2. Respiratory secretions sampling

3. Immediate AB therapy (ATS/IDSA)

4. Waiver of consent

Randomization 1/1

Group 1:
Study drug

Group 2:
 Comparator

Assessing endpoints at EOT, TOC and LFU
What should be the primary efficacy variable for HAP/VAP?

- Overall mortality
- Infection-related mortality
- Clinical cure rate
- Duration of MV
- Days to pathogen eradication
- Length of stay in the ICU and the hospital
- Other patient centered outcomes
Appropriateness of initial antimicrobial therapy and survival in 5715 patients with septic shock

Using clinical success (failure) at Test-of-Cure (TOC)

- Definition of clinical cure was frequently investigator-based and rather loose and subjective, based on the following:
  - Complete resolution of all signs and symptoms
  - Improvement or lack of progression of all abnormalities on chest radiographies at TOC visit (Days 7 to 10 after EOT).
How to better define clinical success at TOC in HAP/VAP trials?

- “Clinical Success”: all 5 criteria should be fulfilled at TOC (7 to 10 days after EOT):
  1. The patient was extubated before TOC visit or improved his/her oxygenation, as assessed by PaO$_2$/FiO$_2$ values
  2. Antibiotics for pneumonia were stopped as specified in the protocol (±2 days) and not restarted until TOC visit
  3. Antibiotics for pneumonia were not restarted after TOC until LFU visit
  4. The patient has not developed a pneumonia-related complication through LFU (such as lung abscess)
  5. The patient survived through LFU visit (Day 28)
Challenges in developing drugs for critical illness are enormous:

- How to identify patients having developed the disease?
- How to get the number of patients needed?
- How to identify the pathogens responsible for the infection ASAP?
- How to target specific MDR/XDR/PDR pathogens?
- How to get informed consent without delaying randomization?
- Which efficacy endpoints should be selected?
- How to decrease the workload and costs associated with data collection and conduct of trials?
Trials in HAP/VAP patients with Infection caused by XDR/PDR pathogens

- Two types of active-controlled trial designed to show superiority are considered in this setting, using clinical response at TOC as primary endpoint:
  - Patients are randomized to receive either the investigational drug or the best comparator available
  - Patients are randomized to receive adjunctive therapy with experimental drug or placebo, plus the best comparator available