Treatment of Infections due to Pan-Drug Resistant Pathogens

Difficulties in conducting clinical trials

Prof. Helen Giamarellou MD, PhD
London, 7 February 2011
The Greek View of the Appropriate Definitions Based on the Chaos of Resistance Mechanisms

1. “Pandrug Resistant (PDR):
   To all classes of antibiotics
   (in the Greek language the prefix “pan-” means “all” or “whole”)

1. Extensive Drug Resistant:
   To all classes of antibiotics except 1 or 2 (colistin-tygecycline)

2. Multidrug Resistant:
   Resistance to ≥3 major classes of antibiotics

Falagas ME, Karageorgopoulos DE. CID 2008;46:1121
Dilemmas during the design of the clinical trial
Which setting or patient population?

• Usually critically ill patients (in the ICUs) harbor such pathogens and develop infections due to them.

• This is a patient population with many confounding factors when evaluating:
  - response,
  - mortality
  - drug toxicity
Which infections to focus to?

• Various types of infections of varying severity.
• Not big enough numbers of cases if aimed at a certain type of infection. Only in multicenter trials such studies could be conducted, however sharing the well-known drawbacks.
• VAP which is common and popular is difficult to define.
• Bacteremia (primary) is another choice.
Isolation of Pathogen(s)

• Prompt and rapid identification of pathogens

• **Direct susceptibility** testing is required.

• Surveillance cultures
Target Antimicrobial Therapy

Direct E-Test (AB Biodisk) of Respiratory Samples Improves Antimicrobial Use in Ventilator-Associated Pneumonia

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CID 2007;44:382
## Direct E-Test in 250 Episodes of VAP

<table>
<thead>
<tr>
<th>Outcome</th>
<th>E-test group (n=167)</th>
<th>Control group (n=83)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever, mean days±SD</td>
<td>4.61 ± 5.06</td>
<td>7.84 ± 6.24</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Antibiotic therapy, mean days ±SD</td>
<td>15.72 ± 9.47</td>
<td>18.92 ± 10.92</td>
<td>.02</td>
</tr>
<tr>
<td>Clostridium difficile-associated diarrhea, no. of patients(%)</td>
<td>3 (1.8)</td>
<td>8 (9.6)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Median no. of days on mechanical ventilation from VAP diagnosis (IQR)</td>
<td>8 (3-19)</td>
<td>12 (6-21)</td>
<td>.04</td>
</tr>
</tbody>
</table>

*Bouza E, et al CID 2007;44:382*
Which antimicrobial drug to use?

Mostly these pathogens are XDR, i.e. sensitive to one (colistin) or 2 drugs (tigecycline, colistin or genta)

Tigecycline:

• Unresolved questions about effectiveness, especially in VAP and severe sepsis, as well as in case of bacteremia.

• In the latter case, and when the approved dosage schedule of 50mg Q 12h is followed, the obtained peak levels in the blood are as a rule lower than the expected MIC of pathogens such as *Acinetobacter baumannii* and *Klebsiella pneumoniae*. 
Which antimicrobial drug to use? Monotherapy or combination therapy?

- **Colistin** with no clear dosage regimen and lack of PK/PDs.

- **Colistin plus genta**: ↑ Nephrotoxicity?

- **Fosfomycin** cannot be used as monotherapy because of development of resistance.
Dosage Regimen Reevaluation:

Loading with $9 \times 10^6$ iu followed by $3 \times 10^6$ iu q8h?

PKs of Colistin in Critically ill Patients: a Greek Study

How to Improve Therapeutic Results?

- Longer colistin half-life (14.4h) than previously described
- **Sub-therapeutic** concentrations (0.6μg/ml) during the first days that may lead to:
  - Treatment failures
  - Emergence of resistance

*Plachouras D et al. AAC 2009;53:3430*
Serum Bactericidal Activity in humans of Three Different Dosing Regimens of Colistin with Impact on Optimum Clinical Use

• All serum samples containing colistin > 4μg/ml (serum concentration/MIC: > 4) eliminated *P. aeruginosa*

• Only 40% of samples containing colistin < 4μg/ml resulted in complete bacterial killing.

Problems in the design of the study

• Can we reliably identify patients at risk of infections due to XDR pathogens?

• In settings with low incidence of XDR bacteria this would result in initial overtreatment of a high number of patients rising questions about ecological damage. On the other hand, physicians do not like to change a successful therapy!
Problems in the design of the study

• Impossible to have a control or a comparator treatment arm and to perform a randomized study because it is also unethical.

• Treatment should start as initial empiric antimicrobial therapy [based on local resistance patterns and risk factors] and cases will be finally enrolled after documentation of infection and identification of the responsible pathogen and its sensitivity.

• The “Golden hour” of therapy should be considered.

• De-escalation should be obligatory.
International registry?

Would a prospective international registry of these infections be able to provide some answers initially helping to collect more information in order to design more effectively a clinical trial?
Participants: Three tertiary hospitals located in Athens

Consecutive patients with K. pneumoniae BSIs

A total of 162 patients were included in the analysis

- 95 VIM-negative:
- 67 VIM-positive: 14 with MIC > 4 μg/ml for both carbapenems and 53 with MICs ≤ 4 μg/ml

GL Daikos et al
Mortality Rates According to Treatment Regimens

Kaplan-Meier Survival Curves of 162 Patients with *K. pneumoniae* BSIs According to Susceptibilities to Imipenem

Which is the Correct Carbapenem Clinical Sensitivity Break Point for *Klebsiella-pneumoniae* VIM (+) or KPC (+) that Guides to the most Appropriate Therapeutic Decision?

From the Presented Preliminary Data it Seems that:

- **An MIC ≤ 4μg/ml is predictive of combination of high-dose meropenem (2g every 6 or 8 hrs) with colistin (or with an aminoglycoside or with tigecycline).**

An Example of a Multicenter Prospective Study or of a European Registry for Evaluation of Fosfomycin

- Patients in the ICU with VAP and bacteremia.
- Appropriate cultures are obtained.
- The patient is given 2 or 3 antibiotics to cover any possibility of XDR (i.e. fosfomycin plus meropenem plus colistin).
- On the 3rd day and according to culture results de-escalation to two antibiotics, i.e. fosfomycin plus colistin or meropenem.