Treatment of Infections due to Pan-Drug Resistant Pathogens

Difficulties in conducting clinical trials

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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

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

Bouza E, et al CID 2007;44:382

Which antimicrobial drug to use?

Mostly these pathogens are XDR, ie. 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** can not be used as monotherapy because of development of resistance.

Examples of PK/PDs

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**

Dosage Regimen Reevaluation:

Loading with 9 x 10^6 iu followed by 3 x 10^6 iu q8h ?

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.

Daikos GL, et al. J Chemother 2010;22:175

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?

An Example of Co-operation

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2009, p. 1868–1873 Vol. 53, No. 5
0066-4804/09/$08.00+0 doi:10.1128/AAC.00782-08
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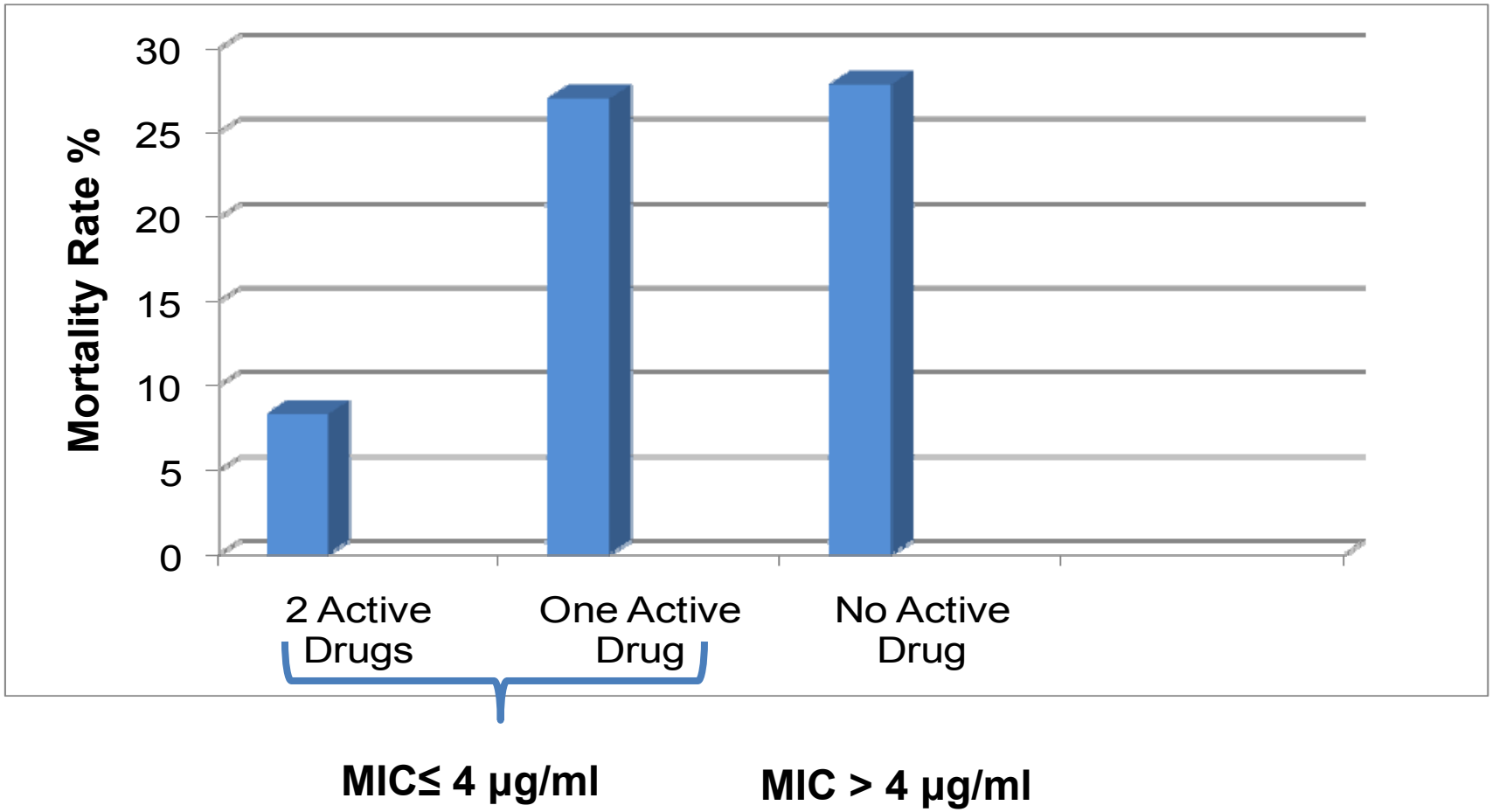
Prospective Observational Study of the Impact of VIM-1 Metallo-β-Lactamase on the Outcome of Patients with *Klebsiella pneumoniae* Bloodstream Infections▽

- **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 ≤ 4μg/ml

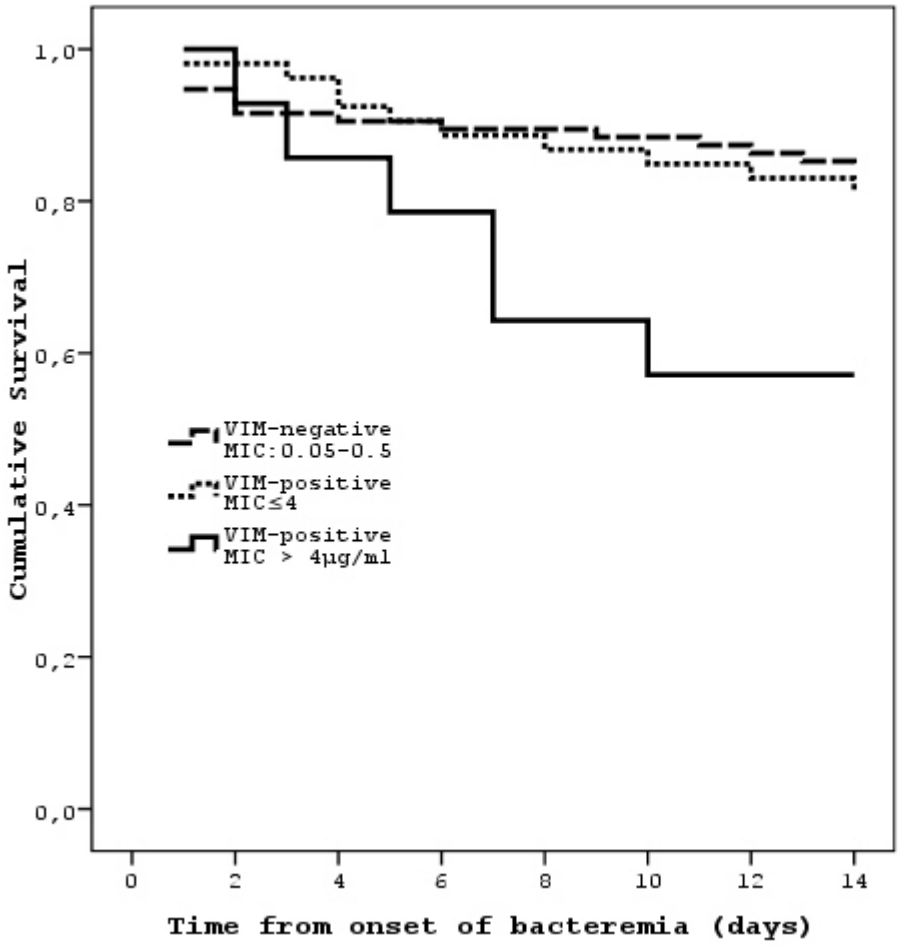
GL Daikos et al
Antimicrob Agents Chemother 2009;53:1868

Mortality Rates According to Treatment Regimens

GL Daikos et al. Antimicrob Agents Chemother 2009;53:1868



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



p=0.03

GL Daikos et al . Antimicrob Agents Chemother 2009;53:1868

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

<u>From the Presented Preliminary Data it Seems that:</u>

- ***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).***

GL Daikos et al. Antimicrob Agents Chemother 2009;53:1868

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.