Treatment of serious infections due to MDR Acinetobacter baumannii:

Presentation of a multicenter randomised clinical trial

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R. Utili - Disclosures

Speaker activity for Novartis, MSD, Pfizer

Research support: Novartis, MSD, Pfizer
Fig. 1. Number of citations found in PubMed from 1999 to the end of 2010 using either ‘Acinetobacter baumannii’ or ‘Acinetobacter baumannii and antibiotic resistance’.
A. baumannii infections (especially VAP) usually occurs late in the course of a severe disease (multiple comorbidities) in the ICUs. Thus, patients may die for the Acinetobacter or with the Acinetobacter.

Crude mortality rate is high (40-60%). Attributable mortality is a clinical judgment (risk of assessment bias) and can only be estimated in a case control study.

Need of strong outcomes to get reliable results, i.e.,
- 30 day mortality (including later f-u or out of hospital events)
- microbiological data collected at predetermined times
- length of hospitalisation
A. baumannii: a ‘successful pathogen’

- Porins
- Efflux Pumps
- Aminoglycoside modifying enzymes (AMEs)
- Imipenem - Meropenem (not Aztreonam)
- PBP2 alteration
- Loss of OMP (outer membrane proteins) – USA & Europe
- Integrons for MDR
- MexAB-OprM
- Fq, B-lactams, CAF, macrolides, sulfamides, trimetoprim, tetraciclins
- Aminoglycosides
- (Oxa; Imp; VIM)
- Plasmides - Europe
- AmpC B-lactamase
- Ampicillin
- Cefalosp 1-2-3 gen
- Aztreonam
- (hyperproduction in 50% of isolates)

Adapted from Limanski JCM 2002; Urban CID 2003
COLISTIN

- It acts by altering membrane permeability
- Poor lung diffusion
- Nephrotoxic
- Overall low efficacy when used as monotherapy
- Treatment is largely empiric
Antibiotic combinations
as an alternative approach to colistin monotherapy

Log10 (viable cells) CFU/mL

Time (h)

CT
RIF
COL
COL + RIF

Co.R.A.b. study

Colistin vs Colistin+Rifampicin in A.baumannii infections

Open label, parallel, randomized

5 clinical sites,

210 pts enrolled (2008-2011)

(Funded by the Italian Medicines Agency, AIFA; ClinicalTrials.gov number, NCT01577862).

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Co.R.A.b. study
Colisitin vs Colistin+Rifampicin in A.baumannii infections

**INCLUSION CRITERIA**
- Age >18 y
- ICU admission
- Life-threatening infection (HAP, VAP, BSI, cIAI)
- Positive A.baumannii cultures
- XDR antibiotype
- Strain susceptible to colistin

**EXCLUSION CRITERIA**
- Previous treatment with colistin or rifampicin
- Hypersensitivity to either study drug
- Significant liver dysfunction (serum conjugated bilirubin >3 mg/dl).

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Typical antibiogram

<table>
<thead>
<tr>
<th>Microorganismo #1: Acinetobacter baumannii (acibau)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td></td>
</tr>
<tr>
<td>Amikacina</td>
<td>&gt;=64 R</td>
</tr>
<tr>
<td>+Amoxicillina/A.CLAVAL</td>
<td>R</td>
</tr>
<tr>
<td>+Ampicillina</td>
<td>R</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>&gt;=64 R</td>
</tr>
<tr>
<td>Cefepime</td>
<td>&gt;=64 R</td>
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<tr>
<td>+Cefotaxime</td>
<td>R</td>
</tr>
<tr>
<td>Cefpirome</td>
<td>&gt;=64 R</td>
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<tr>
<td>Ceftazidime</td>
<td>&gt;=64 R</td>
</tr>
<tr>
<td>+Ceftiraxone</td>
<td>R</td>
</tr>
<tr>
<td>Ciprofloxacina</td>
<td>&gt;=4 R</td>
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<tr>
<td>Gentamicina</td>
<td>&gt;=16 R</td>
</tr>
<tr>
<td>Imipenem</td>
<td>&gt;=16 R</td>
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<tr>
<td>Meropenem</td>
<td>&gt;=16 R</td>
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<tr>
<td>+Mezlocillina</td>
<td>R</td>
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<tr>
<td>Netilmicina</td>
<td>&gt;=32 R</td>
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<tr>
<td>Pefloxacina</td>
<td>&gt;=16 R</td>
</tr>
<tr>
<td>Piperacillina</td>
<td>&gt;=128 R</td>
</tr>
<tr>
<td>Piperacillina/tazobal</td>
<td>&gt;=128 R</td>
</tr>
<tr>
<td>Ticarcillina</td>
<td>&gt;=128 R</td>
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<tr>
<td>Ticarcillina/A.CLAVAL</td>
<td>&gt;=128 R</td>
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<tr>
<td>Tobramicina</td>
<td>&gt;=16 R</td>
</tr>
<tr>
<td>Trimetoprim/Sulfam.</td>
<td>&gt;=320 R</td>
</tr>
<tr>
<td>+Amoxicillina</td>
<td>R</td>
</tr>
<tr>
<td>Colistina</td>
<td>&lt;=0,5 S</td>
</tr>
<tr>
<td>Isepamicina</td>
<td>&gt;=64 R</td>
</tr>
</tbody>
</table>
Co.R.A.b. study

Treatment arms

**Colistin monotherapy**
- Colistimethate sodium
- 2 MU (=160 mg), q8h, i.v.
- Treatment duration: 10-21 d.

**Colistin + Rifampicin combination**
- Colistimethate sodium, same dose
- Rifampicin, 600 mg q12h, i.v.
- Treatment duration: 10-26 d.

Randomization

- Centre site
- Simplified Acute Physiology Score (SAPS) II <40 or ≥40

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Acinetobacter baumannii infection

COLISTIN AND RIFAMPICIN FOR XDR-ACINETOBACTER

COLISTIN, 2MU TID

CENTRAL RANDOMIZATION
- CENTRE
- SEVERITY OF ILLNESS

COLISTIN, 2MU TID RIFAMPIN, 600 MG BID

t0: baseline; EoT: end of treatment; EoS: end of study;
The study was designed to identify an absolute mortality reduction of 20%.

Assuming a raw 30-day mortality rate of 60% in the control group, a two-tailed significance level of 0.05, a power of 0.8, an allocation ratio of 1:1 and a drop-out rate of 10%,

207 patients had to be enrolled (East software v. 4).
Co.R.A.b. study

Primary end point
30-day crude mortality
(death for any cause within 30 days from randomization)

Secondary end points

• disease-specific death
• microbiological eradication
• hospitalization length
• emergence of resistance to colistin during treatment

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Safety evaluation

- renal dysfunction possibly related to colistin
- neurotoxicity, possibly related to colistin
- hepatic dysfunction, possibly related to rifampicin

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The end