Reviving old antibiotics: the AIDA experience
Preserving old antibiotics for the future

U. Theuretzbacher
Center for Anti-Infective Agents, Vienna, Austria
Re-developing process

- Identify the knowledge gaps, assess quality of information
- Use cutting-edge methods to close the knowledge gaps
- Share knowledge with regulatory agencies and policy makers
- Disseminate and communicate to the medical community and all stakeholders
AIDA: “Re-developing” of old antibiotics

14 partners from 11 different countries, complimentary expertise
“Re-developing” of old antibiotics: Principles

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Non-clinical
Single drugs, combinations

PK/PD index magnitude exposure-res

population PK exposure relationships
• exposure-clinical outcome
• exposure-safety
• exposure-res
MCS, PTA

Aims:
- Dosing recommendations
- Efficacy (superiority, non-inferiority)
- PK
- Safety
- Combination therapy
- Emergence of resistance
- Breakpoints
- Valid comparators for new antibiotics

RCT

PK
• sparse sampling

endpoints
• microbiol
• clinical
  ➢ efficacy
  ➢ safety
  ➢ res

microbiol
• res mechan
• colonisation
“Re-developing” of old antibiotics: Colistin

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Prior knowledge <2004

Prior knowledge >2004

2010

Non-clinical studies

Optimised usage

Randomised controlled clinical trial in critically ill patients

PK microbiology outcome

Production Regulation Nomenclature

Current evolving knowledge

Grant Health-F3-2011-278348
“Re-developing” of old antibiotics: Colistin

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Non-clinical studies
- kill dynamics
- single drug, combination, synergy, res. analysis
- protein binding
- population PK
- PK/PD modeling + simulation

RCT
carbapenem resistant Gram-negative inf.
colistin alone vs. colistin + carbapenem

superiority
- Microbiology:
  - MIC, synergy, colonisation, res. mech.

safety
- Exposure:
  - efficacy, toxicity, resistance relationship

emergence of resistance
- PK
- Sparse sampling

PK/PD
“Re-developing” of colistin: Challenges

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Analytical issues
- Measurement of concentrations

Clinical trial in severely sick patients, superiority RCT
- Informed consent
- Diagnostics, pre-treatment
- Lack of evidence and preconceptions

Translating results to clinical practice
- Regulatory, guidelines, training
"Re-developing" of colistin: Policy actions in Europe

http://www.aida-project.eu

- SPC updated and harmonised
- Quality and production standards updated
- Animal farming/veterinary
“Re-developing” of colistin: Policy actions in Europe

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Introduced dose content conversion table between CMS expressed in IU, CMS expressed in mg and CBA expressed in mg

<table>
<thead>
<tr>
<th>Colistimethate sodium (IU)</th>
<th>Colistimethate sodium (mg)</th>
<th>Colistin-base activity (CBA) (mg)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 500</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>150 000</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>1 000 000</td>
<td>80</td>
<td>34</td>
</tr>
<tr>
<td>4 500 000</td>
<td>360</td>
<td>150</td>
</tr>
<tr>
<td>9 000 000</td>
<td>720</td>
<td>300</td>
</tr>
</tbody>
</table>

ⁱ Colistimethate sodium (IU) / Colistimethate sodium (mg) × 0.4 = Colistin-base activity (CBA) (mg)

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Adults: 9 M IU daily in 2 or 3 divided doses as a slow iv infusion; in critically ill patients a loading dose of 9 M IU should be given. The most appropriate time interval to the first maintenance dose has not been established.

Doses should be reduced according to creatinine clearance in patients with renal impairment.

Modelling suggests that loading and maintenance doses of up to 12 M IU may be required in patients with good renal function in some cases. Clinical experience with such doses is however extremely limited, and safety has not been established.

The loading dose applies to patients with normal and impaired renal functions including those on renal replacement therapy

Children <40kg: 75,000 to 150,000 IU/kg daily, in 3 divided doses. The use of doses >150,000 IU/kg/day has been reported in children with cystic fibrosis. There are no data regarding the use or magnitude of a loading dose in critically ill children. No dose recommendations have been established in children with impaired renal function.

Consideration should be given to co-administration with another antibacterial agent whenever this is possible.
Indicated for the treatment of serious infections due to selected aerobic Gram-negative pathogens in patients with limited treatment options.
**EUCAST Breakpoints**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Susceptible (S)</th>
<th>Resistant (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Acinetobacter</em></td>
<td>S ≤ 2</td>
<td>R &gt; 2 mg/L</td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>S ≤ 2</td>
<td>R &gt; 2 mg/L</td>
</tr>
<tr>
<td><em>Pseudomonas spp</em></td>
<td>S ≤ 4</td>
<td>R &gt; 4 mg/L</td>
</tr>
</tbody>
</table>

* Breakpoints apply to dosage of 2-3 MIU x 3. A loading dose (9 MIU) may be needed.
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Filling knowledge gaps

- Critically sick patients with infections caused by extensively drug-resistant Gram-negative bacteria
- Outpatient treatment of patients with acute IUTI and high risk of multi drug-resistant Gram-negative bacteria
- Outpatient treatment of patients with acute skin- and soft tissue infections caused by MRSA

Policy, regulatory, funding issues
Communication, education