Use of Colistin

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CUB-Erasme, Université Libre de Bruxelles
NVMM/VIZ/BVIKM/SBIMC Fall Meeting
17/11/2017
<table>
<thead>
<tr>
<th>(potential) conflict of interest</th>
<th>None</th>
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<tr>
<td>For this meeting possibly relevant relationships with companies</td>
<td>Company names: None</td>
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<tr>
<td>• Sponsoring or research funding</td>
<td>•None</td>
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<td>• Fee or other (financial) compensation</td>
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<td>• Shareholder</td>
<td>•None</td>
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<td>• Other relationship, namely ...</td>
<td>•None</td>
</tr>
</tbody>
</table>
Introduction

• Discovered in 1949

• Obtained from the *Bacillus polymyxa* subspecies *colistinus* by fermentation

• Was abandoned in the 1970s because:
  – Toxic+++++
  – Development of more effective antimicrobial agents
Introduction

- And in the 1990s,

Colistin was once again used!

<table>
<thead>
<tr>
<th>03/10/2008 11:10 - Lavage broncho-alvéolaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examen direct</td>
</tr>
<tr>
<td>Type</td>
</tr>
<tr>
<td>Polynucléaires (3+)</td>
</tr>
<tr>
<td>Hématies Rares</td>
</tr>
<tr>
<td>Macrophages (3+)</td>
</tr>
<tr>
<td>Lymphocytes Rares</td>
</tr>
<tr>
<td>Cel. bronchiques Rares</td>
</tr>
<tr>
<td>Flure Présence de</td>
</tr>
<tr>
<td>Bacilles gram négatif (3+)</td>
</tr>
<tr>
<td>Culture aérobie</td>
</tr>
<tr>
<td>&gt;100,000 CFU/ml</td>
</tr>
<tr>
<td>Culture aérobie</td>
</tr>
<tr>
<td>1. Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>Présence de carbapénémase</td>
</tr>
<tr>
<td>Pipéra +Tazobactam</td>
</tr>
<tr>
<td>Cefazidime</td>
</tr>
<tr>
<td>Céfepime</td>
</tr>
<tr>
<td>Aztreonam</td>
</tr>
<tr>
<td>Impéronem</td>
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<tr>
<td>Méropénem</td>
</tr>
<tr>
<td>Gentamicine</td>
</tr>
<tr>
<td>Amikacine</td>
</tr>
<tr>
<td>Tobramycine</td>
</tr>
<tr>
<td>Ciprofloxacine</td>
</tr>
<tr>
<td>Colistine S</td>
</tr>
</tbody>
</table>

β-lactams

Aminoglycosides

Quinolones
Bacteria resistant to carbapenems in Europe

Indication for use of Colistin!

Antimicrobial Surveillance in Europe 2015
Plan

- Structure and Mechanism of action
- Spectrum of activity
- PK of Colistin
- Adverse events: nephrotoxicity
- Optimized treatment regimens
  - Loading dose
  - Intrathecal therapy
  - Aerosol therapy
  - Therapeutic drug monitoring
- Conclusions
  - Resistance to Colistin and clinical implications
Structure and mechanism of action

Displaces Ca\(^{2+}\) and Mg\(^{2+}\) from outer cell of Gram-negative bacteria

Binds with anionic LPS molecules

Δ permeability of cell envelope

Cell leakage → CELL DEATH!

Acts as a detergent by disrupting cell membranes!

Spectrum of activity

Only Gram-negative aerobic bacteria (GNB)!

- **Active against:**
  - *E. coli*
  - *Pseudomonas sp*
  - *Klebsiella sp*
  - *Enterobacter sp*
  - *Salmonella sp*
  - *Shigella sp*

- **Not active against (due to intrinsic R):**
  - *Proteus sp*
  - *Serratia sp*
  - *Burkholderia sp*
  - *Providencia sp*
  - *Morganella morganii*
  - *Edwardisella sp*
# Current susceptibility breakpoints

MIC testing: ISO-20776 standard broth microdilution (BMD) method

<table>
<thead>
<tr>
<th>Species</th>
<th>EUCAST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>2</td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>2</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>2</td>
</tr>
</tbody>
</table>

Target Colistin$_{SS}$ concentrations: $\geq 2$ mg/L

2. EUCAST. 2016. Recommendations for MIC determination of Colistin as recommended by the joint CLSI-EUCAST Polymyxin Breakpoints W group.
PK/PD properties

**Colistimethate (CMS)**
- Must be hydrolyzed to be active
- Conversion is spontaneous in aqueous solutions → complicates PK studies
- Half-life: short (~ 2.3h)
- Less toxic than colistin

**Colistin**
- Rapid bactericidal effect
- Protein binding: ~50%
- PK/PD index for efficacy: $fAUC/MIC$
  - Ratio of 12 =2 log bacterial kill for $C_{SS}$ of 1 mg/L
- VD: small (~ 0.5 ± 0.06 L/kg)
- Half-life: long (~ 14.4 h)
- Elimination rate depends on renal function
- Considerable inter and intra-individual variability
  - Loading dose 9 MIU: 0.95 to 5.1 mg/L
  - Steady state: 0.68 to 8.72 mg/L

PK of Colistin

CMS = product of fermentation → each batch of the drug contains a mixture of CMS derivatives

Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

Mix of > 30 polymyxin compounds, mainly Colistin A + B

Li et al, Lancet Infect. Dis. 2006; 6:589-601
PK of Colistin: Impact of renal function on elimination

If renal clearance is augmented

- Renal clearance
- Colistimethate
- Non-renal clearance (Hydrolysis)
- Colistin
- Non-renal clearance

If renal function is impaired

- Renal clearance
- Colistimethate
- Non-renal clearance (Hydrolysis)
- Colistin
- Non-renal clearance

Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium.

↓ dose of CMS!

Li et al, Lancet Infect. Dis. 2006; 6:589-601
Colistin dose needs to be adjusted to renal function

Physicians selected daily dose of colistin base activity (CBS)

Resultant average steady-state plasma colistin concentrations in function of CrCL

PK of CMS: need for a loading dose?

FIG. 1. Observed individual concentrations of CMS (A) and colistin (B) in plasma after the administration of the first dose of CMS. Data for patients 14, 15, 17, and 18 (Table 1) were not available after the first dose.

FIG. 2. Observed individual concentrations of CMS (A) and colistin (B) in plasma after the administration of the fourth dose of CMS. Data for patients 4, 14, 15, 16, 17, and 18 (Table 1) were not available after the fourth dose.

Dosage regimens

- 1 MIU CMS = 30 mg of colistin base activity (CBA)

**Table 2. European Medicines Agency— and US Food and Drug Administration—Approved Daily Maintenance Dose Suggestions Evaluated**

<table>
<thead>
<tr>
<th>EMA (MIU)</th>
<th>Creatinine Clearance (mL/min)</th>
<th>European Medicines Agency Daily Dose Evaluated</th>
<th>Patient Body Weight Approach</th>
<th>Uniform Weight of 80 kg Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 MIU</td>
<td>≥80</td>
<td>360 mg CBA</td>
<td>5 mg/kg CBA</td>
<td>360 mg CBA</td>
</tr>
<tr>
<td>9 MIU</td>
<td>50 to &lt;80</td>
<td>300 mg CBA</td>
<td>3.8 mg/kg CBA</td>
<td>304 mg CBA</td>
</tr>
<tr>
<td>7.5 MIU</td>
<td>30 to &lt;50</td>
<td>250 mg CBA</td>
<td>2.5 mg/kg CBA</td>
<td>200 mg CBA</td>
</tr>
<tr>
<td>5.5 MIU</td>
<td>10 to &lt;30</td>
<td>183 mg CBA</td>
<td>1 mg/kg CBA</td>
<td>80 mg CBA</td>
</tr>
<tr>
<td>3.5 MIU</td>
<td>&lt;10</td>
<td>117 mg CBA</td>
<td>1 mg/kg CBA</td>
<td>80 mg CBA</td>
</tr>
</tbody>
</table>

**Physicians’choice**

- ≤ 0.5
- ≤ 1.0
- ≤ 1.5
- ≤ 2.0

**EMA dosing**

- ≤ 0.5
- ≤ 1.0
- ≤ 1.5
- ≤ 2.0

**FDA dosing IBW**

- 20 mg
- 40 mg
- 60 mg
- 80 mg

**FDA dosing 80 Kg**

- 10 mg
- 20 mg
- 30 mg
- 40 mg

Adverse effects: Nephrotoxicity

• Mechanism:
  – accumulation of colistin in renal tubular cells
  – Δ morphology of mitochondria, loss of cytoplasmic membrane potential → apoptosis

• Rates: 6-55%
  – Limited number of patients included in studies
  – Variability in severity of the underlying illness
  – Dose of Colistin administered
  – Definition of nephrotoxicity (AKIN, RIFLE,..)

• Mild-to-moderate

• Reversible in most cases

Risk factors for nephrotoxicity

- Other concomitant nephrotoxic agents
- Age
- Weight and/or BMI
- Co-morbidities: Charlson Index
- Severity of baseline illness
- Dose of Colistin
- Duration of treatment
- Colistin $C_{SS,avg} > 2.5 \text{ mg/L}$
- Minimum colistin plasma concentration $\geq 2.2 \text{ mg/L}$
  (odds ratio= 4.6 on day 7)

3. Forrest A et al. 54th ICAAC 2014; Washington DC.
Optimized administration of Colistin

When treating infections due to XDR/MDR GNB, using Colistin:
• Mortality rates: 8-62%
• Treatment failure: 15-75%

Loading dose of Colistin

**In favor of loading dose:**
- Almost no ICU patient achieved Colistin concentrations > 1 mg/L within 1st 8h treatment
- CMS loading doses of 6-9 MIU improved target attainment (Greek studies)
- CMS loading doses based on patient’s weight should improve PD target attainment (based on Monte Carlo simulations)

**Not in favor:**
- PK studies in France (73 pts)/India (15 pts): PD targets attained in > 3h without loading dose
- Mortality is no different in observational studies. How about RCT?
  - 1 Malaysian RCT with 31 pts: 42.1% vs. 23.1%; p = 0.2
  - 2 other RCT under way (NCT02162966 (Saudi Arabia, and NCT02117986 Chile)

Loading dose of Colistin

• What dose?
  – EMA « standard dose »:
    9 MIU CMS
  – Adjustable to body weight?
    • But max dose of 9 MIU → inadequate for obese patients!

Patients with actual body weight of 60 kg: loading dose of 9 MIU!!

– FDA: no loading dose

When to administer next dose?

- EMA does not specify when maintenance doses should be started\(^1\)

- 24h after loading dose, for safety concerns\(^2\)?

But, colistin concentrations after the first 8-12h may be insufficient to facilitate bacterial killing!

- At next dosing interval (i.e. 8h or 12h later)?

Bacterial killing is increased in a PK/PD model\(^3\)

---

1. EMA completes review of polymyxin-based medicines. 2014
Intrathecal therapy: clinical context

- Hospital related ventriculitis/meningitis due to GNB:
  - Head trauma
  - Post neurosurgery
  - External ventricular deviation (EVD)
PK of Colistin in CSF

• Penetration of CMS and colistin into CSF is poor:
  – ratio CSF/serum concentration of colistin: 0.051-0.057

Systemic Colistin results in inadequate CSF concentrations to treat infections due to MDR GNB!

• Intrathecal colistin?

PK of Intrathecal Colistin

Hydrolysis of CMS is not lineaire

Significant correlation between drained CSF and CL of Colistin

Colistin CL: 10%/H

Clinical data concerning the intrathecal/ventricular administration of colistin

**Dose?**

- > 60,000 IU/day → CSF concentrations of colistin ≥ 2 mg/L
- 125,000 IU/day + IV(3 MIU TID) → CSF concentration < 2 mg/L

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Number of infections treated</th>
<th>Median dose of Colistin IT/ventricular</th>
<th>Clinical success</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Acinetobacter spp.</em></td>
<td>107</td>
<td>125.000 IU</td>
<td>90%</td>
</tr>
<tr>
<td><em>Pseudomonas spp.</em></td>
<td>12</td>
<td>125.000 IU</td>
<td>83%</td>
</tr>
<tr>
<td><em>Klebsiella spp.</em></td>
<td>15</td>
<td>62.500- 250.000 IU</td>
<td>79%</td>
</tr>
</tbody>
</table>

Clinical data concerning intrathecal/ventricular administration of colistin

- Colistin intrathecal/intraventricular ± IV vs. Colistin IV:
  - Better survival
  - Shorter hospital stays
  - Higher CSF concentrations of Colistin

- Adverse effects: rare
  - Chemical ventriculitis/meningitis
  - Seizures
  - Cauda equina syndrome

EMA Recommendations: 125,000 IU/day in IT (dilution in 3-4 mL NaCl) + 1h clamping of the EVD

4. EMA. 2014
Aerosols of Colistin

• Rationale:
  – Colistin penetrates poorly into pulmonary parenchyma
  – Aerosolized Colistin:
    • Achieves high drug concentrations in the respiratory tract
    • Avoids systemic effects
    • Has successfully prevented pulmonary exacerbation and lung deterioration in patients with CF colonized with *Ps. aeruginosa*

Aerosols of Colistin

• Parameters that may affect effectiveness of inhaled Colistin:
  – Generators/ delivery circuit of colistin aerosol
    • droplet size
    • Extent of particle disposition
    • Residual volume
  – Patient’s clinical status
    • Level of consciousness
    • Mechanically ventilated
    • Not mechanically ventilated: Inhalation techniques

Important variations in delivered dose of AB in function of the nebulizer used!!!!
Aerosols of Colistin: clinical data?

Great variations in the mean dose of aerosols of Colistin

\[ \Rightarrow \text{optimal dose still to be established!} \]

Aerosol Colistin Monotherapy: systematic review and meta-analysis:

- Mortality: 33.8% (95% CI: 24.6%-43.6%)
- Clinical success: 65.9% (53.3-77.5%)
- Microbiological success: 71.3% (57.6-83.2%)

<table>
<thead>
<tr>
<th>Variable</th>
<th>IV group</th>
<th>Nebulizer group</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotoxicity</td>
<td>26/43 (60.5%)</td>
<td>8/51 (15.7%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Risk</td>
<td>10/43 (22.7%)</td>
<td>4/51 (7.8%)</td>
<td></td>
</tr>
<tr>
<td>Injury</td>
<td>8/43 (18.2%)</td>
<td>3/51 (5.9%)</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>8/43 (18.2%)</td>
<td>1/51 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>17/43 (39.5%)</td>
<td>43/51 (84.3%)</td>
<td></td>
</tr>
<tr>
<td>Microbiological outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eradication</td>
<td>26/40 (65.0%)</td>
<td>33/50 (66.0%)</td>
<td>0.921</td>
</tr>
<tr>
<td>Persistence</td>
<td>8/40 (20.0%)</td>
<td>1/50 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>6/40 (15.0%)</td>
<td>16/50 (32.0%)</td>
<td></td>
</tr>
<tr>
<td>Clinical outcomes</td>
<td></td>
<td></td>
<td>0.719</td>
</tr>
<tr>
<td>Cure</td>
<td>4 (9.1%)</td>
<td>5 (9.8%)</td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>31 (70.5%)</td>
<td>34 (66.7%)</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>9 (20.5%)</td>
<td>12 (23.5%)</td>
<td></td>
</tr>
<tr>
<td>Infectious mortality</td>
<td>6 (13.6%)</td>
<td>10 (19.6%)</td>
<td>0.438</td>
</tr>
</tbody>
</table>

Table 2: Nephrotoxicity and outcomes in the IV and nebulizer groups.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intervention Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kofferidis 2010 [18]</td>
<td>10</td>
<td>43</td>
<td>18</td>
<td>18.5%</td>
<td>0.42 [0.17, 1.07]</td>
</tr>
<tr>
<td>Korbila 2010 [19]</td>
<td>28</td>
<td>78</td>
<td>43</td>
<td>27.7%</td>
<td>0.78 [0.36, 1.67]</td>
</tr>
<tr>
<td>Tumbarello 2013 [20]</td>
<td>45</td>
<td>104</td>
<td>48</td>
<td>53.8%</td>
<td>0.89 [0.51, 1.54]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>225</td>
<td>190</td>
<td>100.0%</td>
<td>0.75 [0.50, 1.11]</td>
<td></td>
</tr>
</tbody>
</table>

Mortality

Combination or Monotherapy?

- Observational studies:
  - Mortality for polymyxins vs. β-lactams (carbapenems)
- Strong in-vitro proof showing synergy between Carbapenems + Polymyxins
- More rapid killing
- Killing at lower drug concentrations:
  - Toxicity and
  - Risk of R selection

- In-vitro proof does not always translate into clinical reality (i.e. aminoglycosides + β-lactams for sepsis)
- Less resistance selection due to less widespread carbapenem usage
- Less toxicity/antagonistic interactions between AB

2 RCT ongoing (AIDA/ NIH): Meropenem + Colistin vs. Colistin

**Primary endpoint:** to show superiority of Colistin–Meropenem to Colistin monotherapy in treatment of patients infected with CR GN

**Secondary endpoint:** to obtain improved Pop-PK models for Colistin

Multicentre, open-label, 1:1 superiority randomised controlled trial:
- Greece
- Israel
- Italy

Proven infections due to carbapenem non-susceptible and colistin susceptible GNB:
- HAP
- VAP
- Urosepsis
- Bloodstream (any source)
360 patients

Colistin: 9 MUI loading dose, then 4.5 MIU x 2/d (10 days)

Colistin + Meropenem 2g x 3/d (10 days)

Endpoint (Day 14): treatment success
1. Patient alive
2. TA systolique > 90 mmHg without vasopressor treatment
3. SOFA: stable or improved
4. If HAP/VAP: PaO2/FiO2 stable or improved
5. If bloodstream infection: fever, and negative blood cultures

+ 2 TDM during study
NIH-funded RCT

• Blood stream infections and/or pneumonia due to XDR Gram-negative bacteria

• Multicentric, randomized, controlled, double blinded study:
  – USA
  – Thailand
  – Taiwan
  – Israel

  **Meropenem + Colistin 14 days**

  vs.

  **Colistin 14 days**

• Number of patients to include: 444

• Endpoint: mortality
Therapeutic drug monitoring

Narrow therapeutic index

Target concentration: 2-2.5 mg/L

Nephro-toxicity

Difficulties to attain adequate serum concentrations of Colistin

Trough blood sampling

Conclusions

We begin to see the light at the end of the tunnel!

- We know a lot more today on Polymyxin E than when we began to revive this old AB in the ‘90s
- However, administering an optimal dosage regimen remains difficult
  - < very narrow therapeutic index of colistin!
- Current clinical data has many limitations!
But, RCT are ongoing............maybe we will have answers to some of our questions............ unless we have no more use of Colistin!!!!
Colistin resistance

• Mechanisms for colistin resistance: chromosomal mutations or adaptive mechanisms
  – modification of genes involved in lipopolysaccharide biosynthesis → changes in the outer membrane of the bacteria → reduced affinity for polymyxins.
  – Presence of an efflux pump

• These resistance genes: not transmissible between bacteria → not so widely disseminated

• Risk factors for Colistin resistance 1-4
  – Neutropenia
  – Lengthy hospitalisation
  – Previous treatment with colistin

Colistin R strains in Europe

Currently, 25% of *Klebsiella pneumoniae* KPC are Colistin R!

• The **plasmid** bearing the colistin resistance mechanism was readily passed between *Escherichia coli* strains, including strains with known epidemic potential, such as ST131.

• The plasmid also passed to strains of:
  – *Klebsiella pneumoniae*
  – *Pseudomonas aeruginosa*

• The plasmids are quite stable → even in the absence of selection pressure by colistin, the plasmids persist
Figure 4

Countries (n = 32)* reporting presence of *mcr-1* in samples of animal, environmental or human origin (data collected till 27 June 2016)
Clinical implications of infections due to pathogens resistant to Colistin

Blood stream infections due to *Kl. pneumoniae* KPC

↑ mortality

Giacobbe et al. Clin Microb Infect. 2015
New treatment strategies/
New classes of antibiotics!
3rd International Conference on Polymyxins

Wednesday - Thursday, April 25-26, 2018
7:30 am - 1:00 pm

Hospital Universitario 12 de Octubre
Avenida de Córdoba s/n, 28041
Madrid, Spain
Phone: 91-390-80-00

Course Overview

The University of Michigan and the University of Buffalo are excited to announce the 3rd International Conference on Polymyxins, April 25-26, 2018, at the Hospital Universitario 12 de Octubre in beautiful Madrid, Spain.

This opinion-leader conference will feature cutting-edge presentations by world leaders in research and clinical use of polymyxins, and regulatory and funding agency representatives. Each symposium session will provide opportunity for discussion and input from the audience.

Topics will include:

- Setting the Scence: Polymyxins in an Age of New Antibiotics
- Walking the Tightrope between Efficiency and Toxicity
- Young Investigator Session: Oral Presentations for Polymyxin New and Upcoming Research
- Polymyxin Combinations: Thinking out of the Box and Clinical Use of Combinations
- The Road Ahead: Optimizing Clinical Use, Advances and Challenges