Educational Workshop

EW12: Colistin use in clinical practice

Arranged with AIDA (FP7 project: „Preserving old antibiotics for the future“)

Convenors: Mical Paul (Petah-Tiqva, IL)  
Johan W. Mouton (Nijmegen, NL)

Faculty: Johan W. Mouton (Nijmegen, NL)  
William Couet (Poitiers, FR)  
Mical Paul (Petah-Tiqva, IL)  
Yehuda Carmeli (Tel Aviv, IL) – no presentation submitted
Optimizing Use of Old Antibiotics
The PK/PD perspective

Johan W. Mouton MD PhD FIDSA

Discovery void

Steady decline in the No. of FDA approvals
Drugs developed 30 or more years ago have not undergone the rigorous development and regulatory scrutiny to which are new agents subject. Often the "label" is not updated as new information becomes available. The prescriber, as an occasional user, may be relying on obsolete information to make treatment or dosing decisions.
Dosing should be such that the level of antimicrobial activity is associated with a high likelihood of therapeutic success.

Potency of a drug (MIC)  Exposure to the bug
In vivo (PK)

Dose Finding and Breakpoints- The Past

Efficacy of the drug
Mouton - Optimizing Use of Old Antibiotics: The PK/PD perspective

Potency of a drug in vitro (MIC) Exposure to the bug in vivo (PK) Dosing Regimen

Antimicrobial Efficacy of the Drug (Microbiological Cure)

Effect on Host (Clinical Cure)

Potency of a drug in vitro (MIC) Exposure to the bug in vivo (PK) Dosing Regimen

Antimicrobial Efficacy of the Drug (Microbiological Cure)

Effect on Host (Clinical Cure)

Probability of cure after treatment with fluconazole

Oropharyngeal Candidiasis n=132

• Prob cure correlates with AUC/MIC
• POSITIVE correlation with EXPOSURE
• INVERSE correlation with MIC

Each data point represents the proportion of patients cured within a group representing a certain AUC/MIC value

Rodriguez-Tudela et al, AAC 2007

The role of pharmacokinetics/pharmacodynamics in setting clinical MIC breakpoints: the EUCAST approach

Mouton et al, CMI 2012
What do we know of colistin?

Colistin

In vitro pharmacodynamics

– Killing pattern: concentration-dependent
– Post-antibiotic effect: modest at best
– PRODRUG!
Colistin
In vitro pharmacodynamics - IVIM

• 2 pseudomonas strains
• Dosing q8, q12 and q24

Colistin
In vitro pharmacodynamics - IVIM

• 3 pseudomonas strains
• Dosing CI, q8, q12 and q24

Colistin pharmacodynamics

P. aeruginosa ATCC 27853 and PA01

R² = 81%

R² = 93%

R² = 70%
Colistin
In vitro pharmacodynamics - IVIM

• 3 pseudomonas strains
• Dosing CI, q8, q12 and q24

In vivo pharmacodynamics – thigh mice

• Dose fractionation study
• AUC/MIC correlates best with outcome

TABLE 2. Median target values from 1,000 bootstrapping replicates of,colistin MIC for 1- and 2-log{sub}reduction in the area
under the concentration time curves relative to growth control and for
90% (P90) of retention effect

<table>
<thead>
<tr>
<th>Killing effect</th>
<th>AUC/MIC</th>
<th>P90</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-log{sub}reduction</td>
<td>2.4 (19.9-25.7)</td>
<td>17.4 (23.4-29.8)</td>
<td>5.0 (3.5-5.3)</td>
</tr>
<tr>
<td>2-log{sub}reduction</td>
<td>10.4 (17.3-31.0)</td>
<td>15.7 (26.1-31.5)</td>
<td>6.0 (5.7-8.0)</td>
</tr>
<tr>
<td>P90</td>
<td>4.0 (15.8-52.1)</td>
<td>46.4 (43.6-65.5)</td>
<td>2.4 (4.7-20.5)</td>
</tr>
</tbody>
</table>
• Dose fractionation study
• AUC/MIC correlates best with outcome
**Colistin**

**Protein binding in Mice**

![Graph showing protein binding of colistin](image)

**Colistin**

**Animal model toxicodynamics**

Toxicity is dose-related and also regimen related

- Doses mimicking once-daily dosing give more severe lesions more frequent dosing

**The role of pharmacokinetics/pharmacodynamics in setting clinical MIC breakpoints: the EUCAST approach**

![Diagram showing the role of pharmacokinetics/pharmacodynamics in setting MIC breakpoints](image)
Acknowledgements:

This work was financially supported by:

the EU-project AIDA
(grant Health-F3-2011-278348)
Colistin PK/PD: lessons from recent studies

William Couet, PharmD, PhD

Colistin: an old antibiotic

CMS: prodrug

Colistin: active moiety

Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections.
Couet - Colistin PK/PD: lessons from recent studies

**CMS and colistin pharmacokinetics**
(from Li et al., Lancet Inf Dis, 2006)

Colistin assay

From bioassay…

… to HPLC and LC-MS/MS assay

Pharmacokinetics of Colistin and Colistimethate Sodium After a Single 80-mg Intravenous Dose of CMS in Young Healthy Volunteers
Couet - Colistin PK/PD: lessons from recent studies

![Diagram showing the pharmacokinetic and pharmacodynamic properties of colistin.]

- **Vss = 14.0(7) L**
- **t1/2,β = 2.0 h**
- **t1/2 = 3.0 h**
- **CL = 148(5) mL/min**

**fm = ?**

Post-excretion hydrolysis in urine

**CL = 148(5) mL/min**

**Vss = 14.0(7) L**

**CLNR = 48 mL/min**

**fm = 30%**

Renal clearance

**CLR = 1.9(19) mL/min**

**Ae12-24**

**CLR = Ae12-24 / AUC12-24**

**Aecoli**

**AeCMS = Ae12-24 - Aecoli**

**Urine 12h – 24h**

**Urine 0 – 12 h**

**Conc. (mg/L)**

**Time (h)**

0, 0.1, 1, 10, 24, 6, 8, 12, 16, 18, 24

**CMS**

**Colistin**

**CLR = 103(8) mL/min**

**CLNR = 46 mL/min**

**fe = 70%**

Non-renal clearance (hydrolysis)

**CL = 148(5) mL/min**

Non-renal clearance
Couet - Colistin PK/PD: lessons from recent studies

- Loading dose of CMS Colistin C_{ss} close to 2 µg/mL with limited fluctuations

- ... including patients under hemodialysis

(Marchand S., et al., J Antimicrob Chemother. 2010)
Couet - Colistin PK/PD: lessons from recent studies

CL_{coli} was the major PK factor in the maintenance dosing algorithm

<table>
<thead>
<tr>
<th>TABLE 3: Suggested loading dose and daily maintenance doses of CMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>CMT</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

But 3 parameters govern colistinCss

\[ \frac{fm}{\tau} \cdot \frac{Dose}{CL_{coli}} = C_{SS} \]

\[ C_{SS} = \frac{CL_{NR}}{CL_{NR} + CL_{NR} \cdot \frac{Dose}{\tau \cdot CL_{coli}}} \]

Colistin concentrations at steady-state

Rate of formation = Rate of elimination

Limited impact on Css

Uncontrolled
Effect of CMS renal clearance on colistin C\textsubscript{ss}

\( \text{CL}_{\text{CMS,R}} = 0.85 \text{ CL}_{\text{Creat}} \)

9 MIU loading dose + 4.5 MIU / 12h

\text{CL}_{\text{Creat}} (\text{mL/min})

- 30
- 60
- 90
- 120

\text{CL}_{\text{CMS,R}}: \text{ Real impact but easy to predict }

\text{How to reduce maintenance dose when GFR decreases?}

\text{CL}_{\text{CMS,R}} = 24 \text{ mL/min} \quad \text{CL}_{\text{coli}} = 35 \text{ mL/min}

Effect of CMS non-renal clearance on colistin C\textsubscript{ss}

9 MIU loading dose + 4.5 MIU / 12h

\text{CL}_{\text{CMS,NR}} (\text{mL/min})

- 48
- 24
- 12
- 6

\text{CL}_{\text{CMS,NR}}: \text{ Probably of moderate impact }

\text{CL}_{\text{CMS,NR}} = 90 \text{ mL/min} \quad \text{CL}_{\text{coli}} = 35 \text{ mL/min}

Effect of Colistin clearance on colistin C\textsubscript{ss}

9 MIU loading dose + 4.5 MIU / 12h

\text{CL}_{\text{coli}} (\text{mL/min})

- 8.75
- 17.5
- 35
- 70

\text{CL}_{\text{coli}}: \text{ Important impact and difficult to predict }

\text{CL}_{\text{ CMS,R}} = 90 \text{ mL/min} \quad \text{CL}_{\text{CMS,NR}} = 35 \text{ mL/min}
**Time for individualized dosing regimen?**

\[
C_{\text{SN}} = \frac{\text{CL}_{\text{NR}}}{\text{CL}_{\text{R}} + \text{CL}_{\text{NR}}} \cdot \text{Dose} / \tau \cdot \text{CL}_{\text{coli}}
\]

Expected: 3.4 µg/mL

Initial guess: 35 mL/min

Revised: 15 mL/min

**What would be the best sampling time?**

At « trough » when CMS concentrations are the lowest

**What would be the best strategy?**

And after loading dose...

... when bayesian procedures become available

CL_{coli} (mL/min)

9 MIU loading dose

8.75
17.5
35
70

CL\text{CMS,R} = 90 mL/min
CL\text{CMS,NR} = 35 mL/min
What would be the optimal concentrations?

fAUC/MIC is the most predictive pharmacokinetic/pharmacodynamic

Acknowledgements:

- Nicolas Grégory
- Patrice Gobin
- Sandrine Marchand
- Olivier Mimoz

This work was financially supported by:

the EU-project AIDA (grant Health-F3-2011-278348)
Handouts

Efficacy, use and dosing of colistin: what have contemporary studies taught us?

Mical Paul
Rabin Medical Center, Beilinson Hospital
Tel-Aviv University
Israel

IV colistin vs. comparator antibiotics for sepsis
All-cause mortality

Colistin vs. inappropriate antibiotics
All-cause mortality
Paul - Efficacy, use and dosing of colistin: what have contemporary studies taught us?

Dosing and clinical outcomes univariate

- Retrospective cohort study, 2000-2007, Henry Dunant Hospital, Athens, Greece
- Overall 258 patients, 222 (86%) hospitalised in the ICU

<table>
<thead>
<tr>
<th>In-hospital mortality (%)</th>
<th>3 MIU</th>
<th>6 MIU</th>
<th>9 MIU</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>38.6%</td>
<td>27.8%</td>
<td>21.7%</td>
</tr>
<tr>
<td>Normal RF</td>
<td>34.3%</td>
<td>27.6%</td>
<td>19.5%</td>
</tr>
</tbody>
</table>

Falagas et al. Int J Antimicrob Agents 2010

Dosing and clinical outcomes multivariate

- Retrospective cohort study, 2000-2007, Henry Dunant Hospital, Athens, Greece
- Overall 258 patients, 222 (86%) hospitalised in the ICU

<table>
<thead>
<tr>
<th>Multivariable analysis, in-hospital mortality</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher daily colistin dose</td>
<td>1.22 (1.05–1.42)</td>
</tr>
<tr>
<td>Cure of infection</td>
<td>9 (3.6–23.1)</td>
</tr>
<tr>
<td>Higher APACHE II score</td>
<td>0.89 (0.84–0.95)</td>
</tr>
<tr>
<td>Rise in creatinine</td>
<td>0.21 (0.1–0.45)</td>
</tr>
<tr>
<td>Haematological disease</td>
<td>0.23 (0.08–0.66)</td>
</tr>
</tbody>
</table>

Falagas et al. Int J Antimicrob Agents 2010

Hieronymus Bosch. Allegory of Gluttony and Lust. 1490-1500
Colistin-carbapenem combination therapy

- Data from two retrospective cohorts
- Carbapenem-resistant bacteria

<table>
<thead>
<tr>
<th>Location, Bacteria</th>
<th>Outcome</th>
<th>Colistin monotherapy</th>
<th>Combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falagas 2010 1</td>
<td>Failure</td>
<td>2/20 (10%)</td>
<td>14/84 (16.7%)</td>
</tr>
<tr>
<td>mostly A. baumannii</td>
<td>Mortality</td>
<td>Not significant</td>
<td></td>
</tr>
<tr>
<td>Qureshi 2012 2</td>
<td>Failure</td>
<td>4/7 (57%)</td>
<td>1/5 (20%)</td>
</tr>
<tr>
<td>US, KPC-producing K. pneumoniae</td>
<td>Mortality</td>
<td>Not significant</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>27</td>
<td>89</td>
</tr>
</tbody>
</table>


Colistin-related nephrotoxicity

Mechanism

- Increased membrane permeability, cell swelling and lysis (bladder)
- Oxidative stress

Nephrotoxicity for colistin vs. comparators in sepsis
“Interesting” risk factors for nephrotoxicity

- Obesity (BMI ≥31.5 kg/m²) ¹
- Dosing of ≥5.0 mg/kg CBA per day of ideal body weight (adjusted OR 15-23) and dosing ≥3.0 mg/kg (adjusted OR 3) ²
- Duration of therapy/ total cumulative dose ³
- Male sex ⁴

Protection from colistin-induced nephrotoxicity

- Avoidance of concomitant nephrotoxic agents (including IV contrast material) ¹

In-vivo studies:
- Ascorbic acid ²
- N-acetylcysteine ³
- Melatonin ⁴

Colistin inhalation vs. IV colistin all-cause mortality


Paul - Efficacy, use and dosing of colistin: what have contemporary studies taught us?

**IV + inhalation colistin vs. IV colistin all-cause mortality**

<table>
<thead>
<tr>
<th>Infections</th>
<th>IV + inhalation</th>
<th>IV only</th>
<th>All-cause</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenic CF</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>0.05</td>
</tr>
<tr>
<td>Meningitis &amp; BRC infection</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>0.01</td>
</tr>
<tr>
<td>Penetration dose</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>0.001</td>
</tr>
<tr>
<td>Total output</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>0.001</td>
</tr>
<tr>
<td>Meningitis &amp; BRC infection</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Intrathecal/ventricular colistin**
- Main indication: post neurosurgical A. baumannii meningitis with/without shunt
- Q1: Penetration of intravenous colistin
- Q2: Comparative effectiveness of IV and IT treatment
- Q3: Safety/efficacy of intrathecal/ventricular colistin

**Colistin penetration to CSF**

Paul - Efficacy, use and dosing of colistin: what have contemporary studies taught us?

<table>
<thead>
<tr>
<th>Study</th>
<th>CMS dose (mg/kg)</th>
<th>Serum</th>
<th>CSF</th>
<th>CSF/serum</th>
<th>Serum</th>
<th>CSF</th>
<th>CSF/serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>30-60 min. after IV dose</td>
<td>Before next IV dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 *</td>
<td>8.3 (0.1)</td>
<td>1.55</td>
<td>0.083</td>
<td>5.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 *</td>
<td>10.1 (0.13)</td>
<td>1.92</td>
<td>0.099</td>
<td>5.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 *</td>
<td>4.4 (0.05)</td>
<td>0.82</td>
<td>0.043</td>
<td>5.3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>8.3 (0.1)</td>
<td>1.95</td>
<td>0.083</td>
<td>5.4%</td>
<td>0.82</td>
<td>0.042</td>
<td>5.1%</td>
</tr>
<tr>
<td>5</td>
<td>2 (0.02)</td>
<td>1.53</td>
<td>0.088</td>
<td>5.7%</td>
<td>0.87</td>
<td>0.048</td>
<td>5.5%</td>
</tr>
<tr>
<td>Children</td>
<td>1</td>
<td>4.8 (0.06)</td>
<td>0.29</td>
<td>0.06</td>
<td>19.3%</td>
<td>0.19</td>
<td>0.05</td>
</tr>
<tr>
<td>1</td>
<td>10.4 (0.13)</td>
<td>1.46</td>
<td>0.05</td>
<td>34.4%</td>
<td>0.52</td>
<td>0.06</td>
<td>11.1%</td>
</tr>
<tr>
<td>1 **</td>
<td>16 (0.2)</td>
<td>1.13</td>
<td>0.46</td>
<td>34.8%</td>
<td>0.73</td>
<td>0.50</td>
<td>52.7%</td>
</tr>
<tr>
<td>2</td>
<td>16 (0.2)</td>
<td>1.60</td>
<td>0.11</td>
<td>7.2%</td>
<td>0.97</td>
<td>0.15</td>
<td>16.1%</td>
</tr>
<tr>
<td>3</td>
<td>18 (0.23)</td>
<td>2.20</td>
<td>0.07</td>
<td>3.2%</td>
<td>2.29</td>
<td>0.07</td>
<td>3%</td>
</tr>
</tbody>
</table>

* Meningitis ** meningitis with inflammation. 1 Markantonis et al. AAC 2009; 2 Antachopoulos et al. AAC 2010

### IV vs. IV + intrathecal colistin

- Two tertiary university hospitals in Madrid
- All cases of adult neurosurgical *A. baumannii* meningitis

<table>
<thead>
<tr>
<th></th>
<th>N patients</th>
<th>N deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV beta-lactam +/- IV aminoglycoside*</td>
<td>29</td>
<td>11 (37.9%)</td>
</tr>
<tr>
<td>IV carbapenem + IT aminoglycoside</td>
<td>9</td>
<td>2 (22.2%)</td>
</tr>
<tr>
<td>IV colistin + IT colistin</td>
<td>8</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

* Mostly carbapenems (24) or ampicillin-sulbactam (4) monotherapy. Combination with IV aminoglycoside in 2 cases.


### Intrathecal/ intraventricular colistin

- Case series and literature review 1,2
- Concomitant IV antibiotics usually

<table>
<thead>
<tr>
<th></th>
<th>Intrathecal N=15</th>
<th>Intraventricular N=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Relapse</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Chemical meningitis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Other neurological toxicity</td>
<td>1/8</td>
<td>1</td>
</tr>
</tbody>
</table>

* In a systematic review of case reports on all IT/IV polymyxins, cure in 51/64 (80%) and major toxicity in 17/60 (28%) 3


|     | 25 |
The Future: registered RCTs

- Colistin vs. colistin+imipenem for treatment of documented carbapenem-resistant bacteremia or VAP (2 trials, AIDA, NIH)
- Colistin vs. meropenem as empirical treatment for VAP with suspicion of multi-resistant Gram-negative bacteria (MAGIC BULLET)
- Colistin vs. colistin+fosfomycin for A. baumannii infections
- Colistin vs. colistin+rifampin for A. baumannii or P. aeruginosa infections
- IV vs. nebulized+IV colistin for VAP/ HAP (2 trials)
- Colistin vs. colistin+ascorbic acid for prevention of colistin-associated nephrotoxicity