Importance of the loading dose: CMS vs Polymyxin B

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How should CMS (colistin) and Polymyxin B be administered?

- **Dose**
  - **Conc**
  - **Bacterial kill**
  - **PK**
    - **Need for loading dose?**
  - **PD**
    - Maintenance dosing?
    - **Toxicity**
How should CMS (colistin) be administered?

Maintenance dosing? Need for loading dose?

- Dose (CMS)
- CMS
- Colistin
- Bacterial kill
- Toxicity
Quantitative analysis of colistin A and colistin B in plasma and culture medium using a simple precipitation step followed by LC/MS/MS

Britt Jansson, Matti Karvanen, Otto Cars, Diamantis Plachouras, Lena E. Friberg

- Low degradation of CMS to colistin during work-up (< 1%)
  - Important for characterization of initial concentrations, i.e. when CMS is high and colistin is low
- Measure colistin A and colistin B (only)
- ”CMS” = Colistin(A+B) after hydrolysis – Colistin(A+B) before hydrolysis
Pharmacokinetics of CMS and colistin
3MU q8h

Population Pharmacokinetic Analysis of Colistin Methanesulfonate and Colistin after Intravenous Administration in Critically Ill Patients with Infections Caused by Gram-Negative Bacteria,


4th Department of Internal Medicine and 2nd Department of Critical Care Medicine, Medical School, Athens University, Athens, Greece, and Department of Clinical Sciences and Department of Pharmaceutical Sciences, Uppsala University, Uppsala, Sweden

All modeling performed using molar units
A loading dose of CMS suggested

Plachouras et al., AAC, 2009
A loading dose of 6MU (+ 3MU q8h)

Application of a Loading Dose of Colistin Methanesulfonate in Critically Ill Patients: Population Pharmacokinetics, Protein Binding, and Prediction of Bacterial Kill

Ami F. Mohamed, Ilías Karaiskos, Diamantis Plachouras, Matti Karvanen, Konstantinos Pontikis, Britt Jansson, Evangelos Papadomichelakis, Anastasia Antoniadou, Helen Giamarelou, Apostolos Armaganidis, Otto Cars and Lena E. Friberg

Is application of a loading dose likely to affect bacterial killing?

PK-model based on studies in critically ill

PKPD-model based on in vitro experiments (P. Aeroginosa)

CMS Dose

CMS

CMS

Colistin

AR

AR

B = Bacteria

AR = Adaptive resistance

Mohamed et al., AAC 2012, WCoP 2012

Loading dose then 240 mg (3MU) q8h (Typical individual)
When to start maintenance dosing?  
3MU q8h or 4.5MU q12h?

D. Loading dose then 240 mg (3MU) q8h after 1st 12 h (Typical individual)

E. Loading dose then 240 mg (3MU) q8h after 1st 24 h (Typical individual)

F. Loading dose then 360 mg (4.5MU) q12h (Typical individual)

Mohamed et al., AAC 2012
A loading dose of 9MU (+4.5MU q12h)

High-Dose, Extended-Interval Colistin Administration in Critically Ill Patients: Is This the Right Dosing Strategy? A Preliminary Study

Lidia Dalfino, Filomena Puntillo, Adriana Mosca, Rosa Monno, Maria Luigia Spada, Sergio Coppolecchia, Giuseppe Miragliotta, Francesco Bruno, and Nicola Brienza

1Anesthesia and Intensive Care Unit, Department of Emergency and Organ Transplantation; and 2Microbiology Section, Department of Interdisciplinary Medicine, University of Bari, Italy

Conclusions. Our study shows that in severe infections due to COS gram-negative bacteria, the high-dose, extended-interval CMS regimen has a high efficacy, without significant renal toxicity.

Nephrotoxicity – P-12 (Recommend to commence maintenance dosing at 24h after 9MU load)
New data:
PK of CMS and Colistin after 9MU

<table>
<thead>
<tr>
<th>Compound</th>
<th>Plachouras et al., 2009</th>
<th>Mohamed et al., 2012</th>
<th>Karaiskos et al., unpublished data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3MUq8h 0.25h inf</td>
<td>6MU Load, 3MUq8h 0.25h inf</td>
<td>9MU Load, 4.5MUq12h 0.5h inf</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9MU Load, 4.5MUq12h 1h inf</td>
</tr>
</tbody>
</table>

Time after dose (h)

Concentration (µM)

Plots show concentration over time for CMS and Colistin after different dosing regimens.
Model fit without re-estimating parameters

Red lines are medians/trends of observations
Pink fields are 95%CI of median from datasets simulated from the model

CMS conc underpredicted initially

CMS conc underpredicted

Previous published model

"CMS" plasma

CMS \(_c\)

CMS \(_p\)

Colistin

CMS Dose

F = 1

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Current best model

CMS Dose
F (Study1&2) = 78%
F (Study3) = 146%

"Derivatives" Dose
F (All studies) = 22%

All 3 studies:
- Same CMS brand (Norma, Greece)
- Similar patient population
- Same assay
- Calculations made in the same way

Analyze Colistin A & B (only)
- Proportions of A & B to total CMS differ?

Other studies of PK of CMS & colistin in critically ill:
O-5 & P-9

Differences in CMS brands:
P-6 and R. Nation’s talk
Current best model explains observed data much better.

Red lines are medians/trends of observations.
Pink fields are 95%CI of median from datasets simulated from the model.
Individualization of CMS dosing by covariates

Population Pharmacokinetics of Colistin Methanesulfonate and Formed Colistin in Critically Ill Patients from a Multicenter Study Provide Dosing Suggestions for Various Categories of Patients


CMS: $V_1$ – dependent on Body wt
CL – dependent on CrCL

TABLE 3. Suggested loading dose and daily maintenance doses of CMS

<table>
<thead>
<tr>
<th>Dose</th>
<th>Category of critically ill patient</th>
<th>Dosing suggestions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading dose</td>
<td>All patient categories</td>
<td>Equation 9: Loading dose of CBA (mg) = colistin $C_{\text{ss,avg target}}^h \times 2.0 \times \text{body wt (kg)}^c$. See caveat in footnote c. First maintenance dose should be given 24 h later.</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>Not on renal replacement</td>
<td>Equation 10: Daily dose of CBA (mg) = colistin $C_{\text{ss,avg target}}^h \times (1.50 \times \text{CrCL} + 30)^d$. Recommended dosage intervals based on CrCL: $&lt;10$ ml/min/1.73 m$^2$, every 12 h; 10-70 ml/min/1.73 m$^2$ every 12 (or 8) h, and $&gt;70$ ml/min/1.73 m$^2$ every 12 (or 8) h. See important caveat in footnote d.</td>
</tr>
</tbody>
</table>
How does a WT-V₁ relationship for CMS affect concentrations and bacterial killing?

Loading dose proportional to weight
V₁ for CMS proportional to weight
but V₁ has limited influence on conc-time profiles

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Mohamed et al., WCoP 2012
How should Polymyxin B be administered?

- Dose
  - Polymyxin B conc
    - Bacterial kill
      - Toxicity
  - Maintenance dosing? Need for a loading dose?
Pharmacokinetics of Polymyxin B

Population Pharmacokinetics of Intravenous Polymyxin B in Critically Ill Patients: Implications for Selection of Dosage Regimens

Ana M. Sandri,1,* Cornelia B. Landersdorfer,2,3,5 Jovian Jacob,4 Marello M. Boniatti,5 Micheline G. Dalarosa,6 Diego R. Fale,7 Tatiana F. Bele, Rosaura C. Bordinhao,6 Jiping Wang,4 Alan Forrest,3 Roger L. Nation,4 Jian Li,4,7,8 Alexandre P. Zavascki2,9

Studied at steady-state (doses and infusion duration varied)

Polymyxin B:
CL & V terms – dependent on Body wt
No dependence on CrCL (Supported by Zavascki et al., CID, 2008, Abdelraouf, AAC, 2012)
Simulations of dosing regimens

<table>
<thead>
<tr>
<th></th>
<th>$C_{\text{max}}$ (mg/L)$^b$</th>
<th>$C_{\text{min}}$ (mg/L)$^b$</th>
<th>AUC$_{0-24h}$ (mg·h/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P10</td>
<td>P50</td>
<td>P90</td>
</tr>
<tr>
<td>1.25 mg/kg q12h as 1-h infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>2.59</td>
<td>5.17</td>
<td>9.38</td>
</tr>
<tr>
<td>Day 4</td>
<td>4.34</td>
<td>7.09</td>
<td>11.3</td>
</tr>
<tr>
<td>2 mg/kg loading as 2-h infusion, followed by 1.25 mg/kg q12h as 1-h infusion$^c$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>3.06</td>
<td>5.71</td>
<td>10.5</td>
</tr>
<tr>
<td>Day 4</td>
<td>4.35</td>
<td>7.06</td>
<td>11.3</td>
</tr>
<tr>
<td>1.5 mg/kg q12h as 1-h infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>3.11</td>
<td>6.21</td>
<td>11.25</td>
</tr>
<tr>
<td>Day 4</td>
<td>5.20</td>
<td>8.51</td>
<td>13.56</td>
</tr>
<tr>
<td>2.5 mg/kg loading as 2-h infusion followed by 1.5 mg/kg q12h as 1-h infusion$^c$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>3.95</td>
<td>7.39</td>
<td>13.5</td>
</tr>
<tr>
<td>Day 4</td>
<td>5.40</td>
<td>8.76</td>
<td>14.0</td>
</tr>
</tbody>
</table>
How should Polymyxin B be administered?

- **Dose**
- **Polymyxin B conc**
- **Bacterial kill**
- **PK and Effects after a loading dose?**
- **Toxicity**

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Conclusions
Loading dose in Critically ill patients

CMS / Colistin
- Slow formation + Long half-life → A clear need for a loading dose
- Flat fixed: 9MU CMS (a weight-based loading dose may result in underexposure in low weight patients)
- Some PKPD-information available
- Variability in composition

Polymyxin B
- Long half-life → A loading dose is recommended
- Weight-based: 2-2.5 mg/kg
- In need of more PKPD information
- Less variability in composition (?)
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