The use of polymyxins in clinical practice: North America

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Overview

• Systemic polymyxins being used with increased frequency over past decade
• Primarily used for “rescue therapy” for treatment of XDR-Gram-negative Bacilli
  – CRE, Acinetobacter baumannii, Pseudomonas aeruginosa
  – Some empiric use in high endemic regions, in ICUs
  – Inhaled use is inconsistent from institution to institution – often used in combination with intravenous therapy for treatment of pneumonia in the ICU; or infections among CF patients
CMS or Polymyxin B?

- Vast majority of hospitals use CMS as primary polymyxin
  - Major exception – New York area where polymyxin B is predominant formulation
  - Also spotty polymyxin B use in other areas of Northeast, Atlanta
  - VA – approximately 2/3 of polymyxin use is polymyxin B
Dosing CMS – Where did We Start From?

<table>
<thead>
<tr>
<th>Creatinine</th>
<th>0.7 – 1.2</th>
<th>1.3 – 1.5</th>
<th>1.6 – 2.5</th>
<th>2.6 – 4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose in CBA</strong></td>
<td>100 – 150</td>
<td>75-115</td>
<td>66-150</td>
<td>100 – 150</td>
</tr>
<tr>
<td><strong>Times/day</strong></td>
<td>4 to 2</td>
<td>2</td>
<td>2 or 1</td>
<td>Every 36</td>
</tr>
<tr>
<td><strong>Total daily dose</strong></td>
<td>300</td>
<td>150-230</td>
<td>133 – 150</td>
<td>100</td>
</tr>
<tr>
<td><strong>Mg/kg/day</strong></td>
<td>5</td>
<td>2.5 – 3.8</td>
<td>2.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Limitations: Vague; drugs dosed off Clcr rather than serum creatinine; renal dosing guidelines based on combined CMS + Colisitn serum levels; no recommendation for dose for pt > 60 kg;
Dosing CMS – Where we Have Arrived At

- Dosing remains variable, but more uniformity seems to be taking hold over past few years
- Recent changes
  - Loading doses
    - Garonzik et al and Plachouras et al demonstrated delayed time to reach therapeutic levels with maintenance dosing
    - Currently loading doses are being used at many sites

Recent Dosing Changes (2)

- **Renal adjustment**
  - Practices varied with regards to renal dosing
    - Based on package insert information
    - More recent data demonstrating that colistin was not renally excreted – questioning need for any renal adjustment
  - Recent work have shown an increase in colistin half-life in the setting of renal insufficiency, presumably due to increased CMS available for conversion
  - Although this confirmed the need for renal dosing, current practices still vary

- **Weight-based dosing**
  - Garonzik et al data suggest that adjustment is not necessary.
    - However, median weight of study subjects was < 60 kg
  - Two toxicity analyses in the US showed that using ideal body weight was preferable to adjusted or actual with regards to nephrotoxicity

Colistin dosing in Detroit (in mg CBA)

- Ideal body weight used
- Loading dose: 5 mg/kg x 1 (max 300 mg)
- Maintenance dose
  - Clcr $\geq$ 50 mL/min: 1.67 mg/kg q8h (5 mg/kg/day)
  - Clcr 30 – 49 mL/min: 1.75 mg/kg q12h (3.5 mg/kg/day)
  - Clcr 10 - 29 mL/min: 1.25 mg/kg q12h (2.5 mg/kg/day)
  - Clcr < 10 or hemodialysis: 1.5 mg/kg q24h
  - CRRT: full dose
- Maintenance dose should start on the interval that the patient is being dosed
Polymyxin B Dosing in the US

- Only 3 published reports, all based out of New York City
- 2.5 – 3 mg/kg/day base dosing (higher than PI of 1.5 – 2.5 mg/kg/day)
  - Using IBW or TBW have both been described
  - Q12h and q24h dosing have both been described
- All reports dose adjusted if creatinine clearance was < 80 mL/min
  - 1.5 mg/kg/d if clearance was between 30-79 mL/min
  - Various strategies used if clearance drops below 30, ranging from every other day to every 5-7 days
Mono or Combination Therapy?

- No clear data, but most sites seem to combine polymyxins with another agent
  - Second active drug: tigecycline, aminoglycoside;
    - If a drug (i.e., B-lactam) has any *in vitro* activity (i.e., "intermediate susceptibility"), can use it in combination
  - Synergistic drug: rifampin, carbapenems

- NIH 10-0065 RCT addressing mono vs combination therapy (more later)
Questions?