Why do we need to reconsider standard dosing regimens

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Early days of antibiotics

- **1940s:** Penicillin 100,000 to 120,000 units/day iv
- **Today:** 5-24 million units/day iv

<table>
<thead>
<tr>
<th>Type of Case</th>
<th>Average Total Dosage of Penicillin</th>
<th>Average Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>341,000 units</td>
<td>86</td>
</tr>
<tr>
<td>Group 2</td>
<td>728,000 units</td>
<td>162</td>
</tr>
<tr>
<td>Severity:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>317,000 units</td>
<td>66</td>
</tr>
<tr>
<td>Grade 3</td>
<td>477,000 units</td>
<td>107</td>
</tr>
<tr>
<td>Grade 4</td>
<td>735,000 units</td>
<td>148</td>
</tr>
<tr>
<td>All cases</td>
<td>507,000 units</td>
<td>107</td>
</tr>
</tbody>
</table>

Early days of antibiotics

- Amoxicillin, adult dosing
  - 1980s: 3x 250mg/day oral
  - Now: 3x 500-875

- Amoxicillin, paediatric dosing
  - 1980s: 37.51-75 mg/kg divided three times per day
  - Now: 90 mg/kg/day divided two times per day
Old antibiotics

- Europe: National agencies
- EMA since 1995
- Article 30: Harmonisation
- Article 31: Public health interest (Quality, safety, efficacy)
  - Examples: Fluoroquinolones, polymyxins (New SPC valid since 12/2014)
- Article 5(3): Scientific issues
  - Example polymyxins: Revision of the Ph. Eur. Monograph
Dosage creep

- Daptomycin
  - Clinical trials 2mg/kg
  - FDA approved in 2003: 4 mg/kg once daily for the treatment of complicated SSSI caused by specific gram-positive bacteria
  - Post-approval studies: 6 mg/kg
  - Label extension: 4 mg/kg for skin infections and 6 mg/kg for bacteraemia or right-sided endocarditis.
  - Today: ≥10 mg/kg recommended for endocarditis or bacteraemia including those associated with intravascular catheter and implant-related infections
Current additional considerations for dosing regimens

- Special patient populations
  - Obese patients
  - Critically ill patients
- Duration of treatment
- Extra-, intracellular infections, tissue infections
Future dosing challenges

- Non-traditional approaches
  - Non-MIC drugs
  - Complex delivery systems
  - Phages
  - Microbiome-modulating drugs
  - Immunomodulating
  - Nanoparticles

- Traditional approaches
  - Small therapeutic window
  - Emergence of resistance
  - Potentiators