Do we need beta-lactam TDM or can we just use prolonged infusions?

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Consultancies/Speaking
MSD, Bayer, Astellas, bioMerieux, Accelerate Diagnostics
Contents

1. Introduction
2. Altered PK/PD
3. Dose optimisation of beta-lactams
4. Current status of beta-lactam TDM and PI
5. Conclusions
Introduction

• Beta-lactams are the most commonly prescribed antibiotic class
• Broad uses
  • Narrow to broad spectrum; empiric and directed therapy; prophylaxis
  • Different patient populations
  • Different indications
• Considered very safe antibiotics!
• How appropriate is ‘product information’ dosing?
Where do doses come from?

Are they appropriate for all?
Where might standard doses be inappropriate?

- Where drug behaviour (PK) is different to that seen in registration trials. E.g.
  - ICU…but also:
    - Renal failure
    - Liver failure
    - Obesity
    - Burns
    - Cystic fibrosis
    - Transplant
    - Extracorporeal circuits etc…
  - Many drugs can be titrated to measurable PD
  - Changes in clinical markers for infection can take days → hence PK/PD targets
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Pharmacokinetics

PK

Dose $\rightarrow$ concentration
ARC vs antibiotic concentration

- 51 ICU patients
- Trough concentration beta-lactam TDM
- MIC – Vitek2
- Measured CrCL
Pharmacodynamics

Defines concentration needed for maximal bacterial killing

Most importantly – PD shows that a clear concentration-effect relationship exists for antibiotics

Altered PK leads to altered concentration which leads to altered antibiotic effect
PD: Susceptibility Patterns

• Decreased susceptibility of organisms in some units in hospital
• Increased doses needed to achieve PK/PD targets
• German surveillance study of carbapenem MIC in ICU vs ward
  • Meropenem MIC 8 x higher in ICU
  • Doripenem MIC 4 x higher in ICU
  • Imipenem MIC 4 x higher in ICU

Spectrum of organ function

Need for altered dose depends on concentration and MIC of pathogen
Beta-lactam PK/PD variability in ICU
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5. Conclusions
Options for beta-lactam dose optimisation?

• Depends on antibiotic PK/PD
• Higher doses?
• More frequent doses?
• Prolonged infusions? (extended or continuous)
• Continuous infusions?
• Therapeutic drug monitoring?
Beta-lactam PD

Maximum bacterial killing at 4 x MIC

FIG. 1. Relationship between kill rates of P. aeruginosa ATCC 27853 and increasing concentrations of ceftazidime.

Options for beta-lactam dose optimisation?

- Depends on antibiotic PK/PD
- Higher doses? No
- More frequent doses? Increases T>MIC; convenience?
- Prolonged Infusions:
  - Extended infusions? DALI: IB 62.4%; EI 74.5%; CI 95%
  - Continuous infusions? BLING 82% vs 28% T>MIC
- Therapeutic drug monitoring? Only way to be sure PK/PD targets are being achieved.
Data supporting beta-lactam PK/PD targets
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   – PI
5. Conclusions
How common is beta-lactam TDM?

- Piperacillin TDM – 7%
- Carbapenem TDM – 6%
Figure 1. Frequency with which β-lactam antibiotics were included as part of a TDM programme in surveyed ICUs.
An international, multicentre survey of β-lactam antibiotic therapeutic drug monitoring practice in intensive care units

Gloria Wong1, Alexander Brinkman2, Russell J. Benefield1, Mieke Corliss1, Jan J. De Woele1, Najoua El Halali6, Otto Frey7, Stephan Horbach1, Angela Huthner1, Brett McWhinney1, Benoit Misset1,2, Federico Pea1, Judit Preisengreiber1, Michael S. Roberts1, Thomas A. Robertson1, Amie Roche1, Fakade Bruck Sime2, Fabio Silvio Taccone2, Jacobus P. J. Ungerer1, Jeffrey Lipman1,2 and Jason A. Roberts1,2

Table 4. List of PK/PD targets for dose adjustment adopted by selected ICUs

<table>
<thead>
<tr>
<th>PK/PD targets</th>
<th>Specific conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>For dose increase</td>
<td></td>
</tr>
<tr>
<td>100% $fT_{&gt;\text{MIC}}$ (n=5)</td>
<td>intermittent bolus dosing</td>
</tr>
<tr>
<td>100% $fT_{2\times\text{MIC}}$ (n=1)</td>
<td>continuous infusion</td>
</tr>
<tr>
<td>50% $fT_{&gt;\text{MIC}}$ (n=1)</td>
<td>for meropenem</td>
</tr>
<tr>
<td>100% $fT_{&gt;\text{MIC}}$ (n=2)</td>
<td>for piperacillin, aztreonam and cefuroxime</td>
</tr>
<tr>
<td>40% $fT_{&gt;\text{MIC}}$ (n=1)</td>
<td>for ceftazidime</td>
</tr>
<tr>
<td>50% $fT_{&gt;\text{MIC}}$ (n=1)</td>
<td></td>
</tr>
<tr>
<td>70% $fT_{&gt;\text{MIC}}$ (n=1)</td>
<td></td>
</tr>
<tr>
<td>100% $fT_{&gt;\text{MIC}}$ (n=4)</td>
<td>MIC for Pseudomonas aeruginosa of the antibiotic</td>
</tr>
<tr>
<td>100% $fT_{&gt;\text{MIC}}$ (n=1)</td>
<td>continuous infusion</td>
</tr>
<tr>
<td>100% $fT_{&gt;\text{MIC}}$ (n=1)</td>
<td>in the presence of susceptible pathogens</td>
</tr>
<tr>
<td>100% $fT_{&gt;\text{MIC}}$ (n=1)</td>
<td>continuous infusion</td>
</tr>
<tr>
<td>steady-state concentration exceeding $\times$ maximum exposure expected in general population; e.g. piperacillin $\geq 100$ mg/L (&gt;$\times$2 g/24 h in normal patients), meropenem $&gt;80$ mg/L (&gt;$12$ g/24 h in normal patients) (n=1)</td>
<td></td>
</tr>
</tbody>
</table>

$\% fT_{>\text{MIC}}$, percentage of the dosing period during which the free (unbound) concentration was $\times$ times the MIC for targeted pathogen.
An international, multicentre survey of β-lactam antibiotic therapeutic drug monitoring practice in intensive care units

Gloria Wong1, Alexander Brinkman2, Russell J. Benefield3, Mieke Carlier4,5, Jan J. De Waele5, Najoua El Helali6, Otto Frey2, Stephan Harbarth7, Angela Huttner7, Brett McWhinney8, Benoit Misset9,10, Federico Pea11, Judit Preisenerberger1, Michael S. Roberts12, Thomas A. Robertson13, Anka Roehr14, Fekade Bruck Sime12, Fabio Silvio Taccone11, Jacobus P. J. Ungerer9, Jeffrey Lipman1,14 and Jason A. Roberts1,14

Table 5. Methods for dose adjustment based on initial mode of drug administration

<table>
<thead>
<tr>
<th>Dose adjustment strategy</th>
<th>Increase dose administration frequency by 25%–50%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25%–50% increased dose with same frequency</td>
</tr>
<tr>
<td></td>
<td>change to extended infusion (if concentration within 20%</td>
</tr>
<tr>
<td></td>
<td>of target)</td>
</tr>
<tr>
<td></td>
<td>change to continuous infusion (if at maximum daily dose</td>
</tr>
<tr>
<td></td>
<td>according to product information)</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>decrease frequency of administration at the same dose</td>
</tr>
<tr>
<td></td>
<td>25%–50% decrease in dose with same dosing frequency</td>
</tr>
<tr>
<td></td>
<td>withhold therapy for 1 day</td>
</tr>
</tbody>
</table>
Effect of TDM on achievement of PK/PD targets

**Fig. 2** Percentage of control and intervention patients reaching 100% $fT_{\geq MIC}$ at baseline and on day 3. $fT_{\geq MIC}$ Cumulative percentage of a 24-h period that the free (f) drug concentration exceeded the MIC under steady-state pharmacokinetic conditions.

**Fig. 3** Percentage of control and intervention patients reaching 100% $fT_{>4MIC}$ at baseline and on day 3. $>4MIC$ Fourfold the MIC.
RCT of beta-lactam TDM in febrile neutropenia

Table 2. Comparison of the proportion of patients in each group who attained PK/PD targets after the first baseline measurement and subsequent follow-up measurements.

<table>
<thead>
<tr>
<th>PK/PD target</th>
<th>Patient group</th>
<th>control</th>
<th>intervention</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>First TDM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% $T_{&gt;\text{MIC}}$</td>
<td>31%</td>
<td>44%</td>
<td>0.716</td>
<td></td>
</tr>
<tr>
<td>100% $T_{&gt;\text{MIC}}$</td>
<td>25%</td>
<td>19%</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Second TDM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% $T_{&gt;\text{MIC}}$</td>
<td>31%</td>
<td>96%</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>100% $T_{&gt;\text{MIC}}$</td>
<td>19%</td>
<td>69%</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Third TDM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100% $T_{&gt;\text{MIC}}$</td>
<td>7%</td>
<td>73%</td>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>

Can therapeutic drug monitoring optimize exposure to piperacillin in febrile neutropenic patients with haematological malignancies? A randomized controlled trial.
Relevance of measuring unbound concentration
Beta-lactam TDM: clinical outcome trial data

- None powered to clinical outcome
- 2-3 RCTs reporting improved target attainment
- Only observational studies reporting good outcomes
- E.g. Roberts et al 2010, 87.3% TDM cases positive clinical outcome
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How common is beta-lactam PI?

- Includes EI and CI
- 402 HCPs (328 hospitals; 252 cities; 53 countries).
- 78% were specialists in ICU, 11.9% pharmacists and 7% training
Meropenem – bolus vs EI vs CI

BLISS: IB vs CI target attainment

- RCT
- N=140 ICU patients
- Primary Outcome – PK/PD target attainment for continuous vs intermittent dosing
BLISS: Clinical Outcomes

Table 2 Primary and secondary endpoints by treatment arm in the intention-to-treat population and the subgroups of interest

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Intervention (n = 70)</th>
<th>Control (n = 70)</th>
<th>Absolute difference (95 % CI)</th>
<th>Significance (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical cure for ITT population, n (%)</td>
<td>39 (56)</td>
<td>24 (34)</td>
<td>22 (−0.4 to −0.1)</td>
<td>0.011</td>
</tr>
<tr>
<td>Clinical cure by antibiotic, n (%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>22 (58)</td>
<td>15 (32)</td>
<td>26 (−0.4 to −0.1)</td>
<td>0.016</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td>14 (67)</td>
<td>8 (38)</td>
<td>29 (−0.3 to 0.1)</td>
<td>0.0064</td>
</tr>
<tr>
<td>Cefepime</td>
<td>3 (27)</td>
<td>1 (30)</td>
<td>23 (−0.3 to 0.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Clinical cure by concomitant antibiotic treatment, n (%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>14 (42)</td>
<td>13 (39)</td>
<td>3 (−0.3 to 0.2)</td>
<td>0.802</td>
</tr>
<tr>
<td>Yes</td>
<td>25 (68)</td>
<td>11 (30)</td>
<td>38 (−0.6 to −0.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical cure by site of infection, n (%)&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>27 (59)</td>
<td>12 (33)</td>
<td>25 (−0.4 to −0.1)</td>
<td>0.022</td>
</tr>
<tr>
<td>Clinical cure by A. baumannii or P. aeruginosa infection, n (%)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>13 (52)</td>
<td>6 (25)</td>
<td>27 (−0.5 to 0.1)</td>
<td>0.052</td>
</tr>
<tr>
<td>Yes</td>
<td>10 (44)</td>
<td>12 (38)</td>
<td>6 (−0.3 to 0.2)</td>
<td>0.655</td>
</tr>
</tbody>
</table>

Awarded paper of the year for Intensive Care Medicine in 2016 (ESICM, Vienna 2017)
>3 days therapy mortality: 20.4% for CI and 27.6% for IB (P=0.14)
Non-RRT patients: 14.6 for CI and 18.7% for IB (hazard ratio = 0.78)

**Table 3. Primary and Secondary Outcomes, Clinical Results, and Adverse Events**

<table>
<thead>
<tr>
<th>Continuous (n = 212)</th>
<th>Intermittent (n = 220)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive ICU-free days</td>
<td>18 (2–24)</td>
<td>20 (3–24)</td>
</tr>
<tr>
<td>ICU survivors</td>
<td>21 (12–24)</td>
<td>22 (14–25)</td>
</tr>
<tr>
<td>Day-90 survival†</td>
<td>156 (74.3)</td>
<td>158 (72.5)</td>
</tr>
<tr>
<td>ICU survival†</td>
<td>180 (84.9)</td>
<td>182 (82.7)</td>
</tr>
<tr>
<td>Hospital survival††</td>
<td>168 (79.2)</td>
<td>164 (74.9)</td>
</tr>
<tr>
<td>Clinical cure</td>
<td>111 (52.4)</td>
<td>109 (49.5)</td>
</tr>
<tr>
<td>Organ failure-free days</td>
<td>6 (0–10)</td>
<td>6 (0–11)</td>
</tr>
<tr>
<td>Duration of bacteremia, dº</td>
<td>0 (0–0)</td>
<td>0 (0–1)</td>
</tr>
<tr>
<td>ICU length of stay, d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital length of stay, d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>20 (9.4)</td>
<td>28 (12.7)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>19 (9.0)</td>
<td>25 (11.4)</td>
</tr>
</tbody>
</table>
**IPDMA of CI vs IB RCTs: Hospital survival**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CI Events</th>
<th>Total</th>
<th>II Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdul-Aziz 2016</td>
<td>20</td>
<td>70</td>
<td>28</td>
<td>70</td>
<td>33.3%</td>
<td>0.71 [0.45, 1.14]</td>
</tr>
<tr>
<td>Dulhunty 2015</td>
<td>39</td>
<td>212</td>
<td>52</td>
<td>220</td>
<td>60.7%</td>
<td>0.78 [0.54, 1.13]</td>
</tr>
<tr>
<td>Dulhunty 2013</td>
<td>2</td>
<td>30</td>
<td>5</td>
<td>30</td>
<td>5.9%</td>
<td>0.40 [0.08, 1.90]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>312</strong></td>
<td><strong>320</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>85</strong></td>
<td></td>
<td><strong>0.73 [0.55, 0.98]</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>61</td>
<td>85</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 0.69, \text{df} = 2 (P = 0.71); I^2 = 0\%

Test for overall effect: \( Z = 2.11 (P = 0.03) \)
IPDMA of CI vs IB RCTs: Hospital survival

Cox regression 30-day survival curves for combined study population

Covariates included: age, APACHE II score, cardiovascular dysfunction at randomization, NFGNB infection, respiratory dysfunction at randomization, RRT, study
BLING 3

- RCT: in process
- N=7000 ICU patients
- 70 ICUs
- Primary outcome: 90-day mortality
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When is dose optimization valuable?

Taccone FS, Laupland KB, Montravers P. Continuous infusion of β-lactam antibiotics for all critically ill patients? Intensive Care Med 2016
Conclusions

Q. Do we need TDM or can we just use infusions?

1. Not all patients need dose optimization
2. PI is an easy means of increasing the likelihood of achieving PK/PD targets
3. TDM is the only approach which can ensure all patients achieve PK/PD targets

A. Use PI with TDM!