TDM: For all drugs? For all patients?

Jason A Roberts  B Pharm (Hons), PhD, FSHP

Professor of Medicine and Pharmacy
The University of Queensland, Australia
Royal Brisbane and Women’s Hospital, Australia
j.roberts2@uq.edu.au
@jasonroberts_pk
Disclosures

Last 2 years:

- MSD (grants, lectures)
- Cardeas Pharma (grants)
- bioMerieux (consultancy)
- Astellas (consultancy)
- Achaogen (advisory board)
- Bayer (advisory board)
Contents

1. Where do doses come from?
2. Altered PK
3. PD considerations
4. Does current dosing meet PK/PD targets?
5. TDM
6. Scenarios to apply TDM – drugs/patients
7. Conclusion
Principles of antibiotic dosing

- Once appropriate empiric/directed antibiotic has been selected, dose selection occurs.

- The aims of antibiotic dosing are to:
  - Maximise rate and extent of bacterial kill;
  - Minimise possibility of drug toxicity; and
  - Minimise the development of antibacterial resistance.

- Can we rely on singular dosing regimens for complex patients?

→ Enhances likelihood of positive clinical outcomes
The role of infection models and PK/PD modelling for optimising care of critically ill patients with severe infections

Recommendations for individually adjusted dosing and therapeutic drug monitoring (TDM) in critically ill patients
Has the relevant patient group been studied in the dose finding studies?
<table>
<thead>
<tr>
<th>Drug class</th>
<th>Patient group</th>
<th>Target Exposure</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>$C_{\text{max}}$/MIC $\geq 8$</td>
<td>Increased clinical cure for Pseudomonas aeruginosa blood stream infections</td>
<td>JAC 2003;52(4):668-674.</td>
</tr>
<tr>
<td></td>
<td>$\text{AUC}_{0-24}$/MIC $\geq 72$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\text{AUC}_{0-24}$/MIC $\geq 72$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenem</td>
<td>$C_{\text{min}}$/MIC $&gt; 5$</td>
<td>Increased clinical &amp; microbiological cure in lower respiratory tract infections</td>
<td>AAC 2007;51(5):1725-1730</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>100% $T_{&gt;\text{MIC}}$</td>
<td>Increased microbiological &amp; clinical cure in serious infections</td>
<td>IJAA 2008;31(4):345-351</td>
</tr>
<tr>
<td>Quinolones</td>
<td>$\text{AUC}_{0-24}$/MIC $\geq 125$</td>
<td>Increased microbiological &amp; clinical cure in critically ill patients</td>
<td>AAC 1993;37(5):1073-1081</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>$\text{AUC}_{0-24}$/MIC $\geq 451$</td>
<td>Increased survival in critically ill patients associated with MRSA septic shock</td>
<td>IJAA 2013;41(3):255-260</td>
</tr>
<tr>
<td>Linezolid</td>
<td>$\text{AUC}_{0-24}$/MIC $\geq 85$</td>
<td>Increased clinical cure in severely ill patients with blood stream infections</td>
<td>Clin Pharmacokin 2003;42(15):1411-1423</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>f $\text{AUC}_{0-24}$/MIC $\geq 0.9$</td>
<td>Increased clinical success in hospital acquired pneumonia</td>
<td>AAC 2012;56(1):130-136</td>
</tr>
</tbody>
</table>
Contents

1. Where do doses come from?
2. Altered PK
3. PD considerations
4. Does current dosing meet PK/PD targets?
5. TDM
6. Scenarios to apply TDM – drugs/patients
7. Conclusion
Sources of PK variability

If dosing does not account for these changes – sub-optimal therapy!

Sub-optimal patient outcomes

- Obesity,
- Paediatrics (organ maturation, water content)
PK changes in ICU patients relative to healthy volunteers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in clearance in ICU patients&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Change in ( V_d ) in ICU patients&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam [26, 27]</td>
<td>15 % increase</td>
<td>Nil change</td>
</tr>
<tr>
<td>Ceftriaxone [10, 16]</td>
<td>99 % increase</td>
<td>32 % increase</td>
</tr>
<tr>
<td>Daptomycin [28, 29]</td>
<td>151 % increase</td>
<td>10 % increase</td>
</tr>
<tr>
<td>Ertapenem [30, 31]</td>
<td>113 % increase</td>
<td>200 % increase</td>
</tr>
<tr>
<td>Ertapenem [14]</td>
<td>462 % increase</td>
<td>624 % increase</td>
</tr>
<tr>
<td>Flucloxacillin [13, 32]</td>
<td>10 % increase</td>
<td>57 % increase</td>
</tr>
<tr>
<td>Fusidic acid [33, 34]</td>
<td>94 % increase</td>
<td>NA</td>
</tr>
<tr>
<td>Teicoplanin [8, 35]</td>
<td>36 % increase</td>
<td>NA</td>
</tr>
</tbody>
</table>
Beta-lactam PK variability in ICU patients
Major drive for altered PK is change in CrCL
Data from a single centre observational study

<table>
<thead>
<tr>
<th>Drug</th>
<th>No ARC</th>
<th>ARC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with failure</td>
<td>8/62 (12.9%)</td>
<td>18/66 (27.3%)</td>
</tr>
<tr>
<td>Amoxicillin/clavulanic acid</td>
<td>1/24 (4.2)</td>
<td>8/25 (32.0)</td>
</tr>
<tr>
<td>Cefuroxim</td>
<td>2/11 (18.1)</td>
<td>5/23 (21.7)</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>2/17 (11.8)</td>
<td>6/19 (31.6)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>2/7 (28.6)</td>
<td>2/8 (25.0)</td>
</tr>
</tbody>
</table>

ARC: Augmented renal clearance is a 24-hour urinary creatinine clearance >130 mL/min per 1.73 m².

Claus et al, J Crit Care 2013; http://dx.doi.org/10.1016/j.jcrc.2013.03.003
Contents

1. Where do doses come from?
2. Altered PK
3. PD considerations
4. Does current dosing meet PK/PD targets?
5. TDM
6. Scenarios to apply TDM – drugs/patients
7. Conclusion
**PD characteristics of antibacterials**

**Table 1. Pharmacodynamic properties that correlate with efficacy of selected antibiotics**

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>β-lactams</th>
<th>Aminoglycosides</th>
<th>Fluoroquinolones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenems</td>
<td></td>
<td>Metronidazole</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Linezolid</td>
<td></td>
<td>Fluoroquinolones</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
<td>Telithromycin</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td></td>
<td>Daptomycin</td>
<td>Glycopeptides</td>
</tr>
<tr>
<td>Lincosamides</td>
<td></td>
<td>Quinupristin/dalfopristin</td>
<td>Tigecycline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quinupristin/dalfopristin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Linezolid</td>
</tr>
</tbody>
</table>

**PD kill characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Time-dependent</th>
<th>Concentration-dependent</th>
<th>Concentration-dependent with time-dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal PD parameter</td>
<td>T &gt; MIC</td>
<td>$C_{\text{max}}$ : MIC</td>
<td>$\text{AUC}_{0-24}$ : MIC</td>
</tr>
</tbody>
</table>

**Note importance of MIC!**
PD: Susceptibility Patterns

- Decreased susceptibility of organisms in some clinical areas (e.g. ICU)
- 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

Contents

1. Where do doses come from?
2. Altered PK
3. PD considerations
4. Does current dosing meet PK/PD targets?
5. TDM
6. Scenarios to apply TDM – drugs/patients
7. Conclusion
Beta-lactam PK/PD variability in ICU

DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients?
Vancomycin PK/PD variability in ICU
Teicoplanin PK/PD variability in ICU

42% patients did not achieve concentrations between 10-30 mg/L

Solid lines D1-2; dashed lines – D2+
Colistin PK/PD variability in ICU
Contents

1. Where do doses come from?
2. Altered PK
3. PD considerations
4. Does current dosing meet PK/PD targets?
5. TDM
6. Scenarios to apply TDM – drugs/patients
7. Conclusion
Options for more accurate therapy

1. Unit-level interventions
   • Prolonged infusion beta-lactams
   • Extended interval aminoglycosides

2. Dosing nomograms for individual patients
   • Weight-based vancomycin loading doses
   • CrCL-based dosing of renally cleared drugs

3. Dosing software
   • Any drug with an embedded popPK model

4. TDM
   • Any drug with an assay available
TDM

- Measurement of blood concentrations for TDM purposes is mostly used for drugs with narrow therapeutic index
  - i.e., small changes in drug exposure can result in toxicity or loss of efficacy
- TDM is particularly useful when:
  - Altered PK
  - Fixed approaches are likely to fail
  - Doses vary with specific patient needs
Conventional dosing with or without therapeutic drug monitoring (TDM)

- Diagnosis
  - Standard empirical (Product Information) dose
- Drug concentration determination (TDM)
- Dose adjusted based on nomogram
- New dose implementation

Dose unchanged without therapeutic drug monitoring.

Steady state has to be reached for best dose advice, which can cause a substantial delay.

Individualised dosing with therapeutic drug monitoring (TDM)

- Diagnosis
  - Individualised empirical dose
- Drug concentration determination (TDM)
- Dose adjusted based on population PK and patient factors
- New dose implementation

Enhanced chance of reaching PD target with additional drug concentration measurements and dose optimisation.

Fig. 1 Schematic for antimicrobial dosing where dosing is based only on Product Information (orange section), empirical dosing is individualised using relevant patient factors (e.g. renal function or weight; green section) or where dosing is based on collection of therapeutic drug monitoring data (grey sections) and is adapted on the basis of dosing nomograms (top) or adaptive feedback (bottom).
Contents

1. Where do doses come from?
2. Altered PK
3. PD considerations
4. Does current dosing meet PK/PD targets?
5. TDM
6. Scenarios to apply TDM – drugs/patients
7. Conclusion
TDM – patients & scenarios

• Efficacy vs toxicity?

• Uncertain PK
  – ICU, post transplant, burns, obese, paeds
  – Other organ failures (e.g. CVS, Renal, Hepatic)
  – Extracorporeal circuits? (e.g. RRT, ECMO, TPE)

• Known MIC or presence if decreased susceptibility

• Different target exposure
  – Deep-seated infection
  – Part aim of therapy is resistance suppression

Interrelationship between PK and PD is key!
TDM – drugs

- Aminoglycosides
- Glycopeptides
- Quinolones
- Beta-lactams
- Daptomycin
- Linezolid
- Colistin
- Triazole antifungals
- (val)-ganciclovir

No RCT has demonstrated a mortality benefit of TDM
<table>
<thead>
<tr>
<th>Anti-infective</th>
<th>PK/PD index</th>
<th>PK/PD threshold for effectiveness</th>
<th>PK/PD threshold for toxicity</th>
<th>Analytical assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>$C_{\text{max}}$/MIC</td>
<td>$C_{\text{max}}$/MIC $\geq$ 8–10</td>
<td>Gentamicin, tobramycin: $C_{\text{min}} &gt; 1$ mg/L</td>
<td>Immunoassay</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>AUC/MIC</td>
<td>Vancomycin: $C_{\text{max}}$/MIC $\geq$ 400</td>
<td>Amikacin, tobramycin: $C_{\text{min}} &gt; 5$ mg/L</td>
<td>Immunoassay</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II: $C_{\text{min}}$ 10–15 mg/L</td>
<td>Vancomycin: II: $C_{\text{min}} &gt; 20$ mg/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>II, higher MICs: $C_{\text{min}}$ 15–20 mg/L</td>
<td>Cl: $C = 20$–25 mg/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Teicoplanin: II: $C_{\text{min}} &gt; 10$ mg/L</td>
<td>Cl: $C &gt; 25$ mg/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>II, higher MICs: $C_{\text{min}} &gt; 20$ mg/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta$-lactams</td>
<td>$T_{\text{MIC}}$</td>
<td>Not clearly defined</td>
<td>Not clearly defined</td>
<td>LC–MS/MS</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>AUC/MIC</td>
<td>Ciprofloxacin: $C_{\text{max}}$/MIC 8–10</td>
<td>Not clearly defined</td>
<td>HPLC–UV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Levofloxacin: $C_{\text{max}}$/MIC $\geq$ 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colistin</td>
<td>AUC/MIC</td>
<td>$C_{\text{min}} &gt; 2$ mg/L</td>
<td>$C_{\text{min}} &gt; 2.4$ mg/L</td>
<td>HPLC–MS/MS</td>
</tr>
<tr>
<td>Linezolid</td>
<td>AUC/MIC</td>
<td>$C_{\text{min}} &gt; 2$ mg/L</td>
<td>$C_{\text{min}} &gt; 6$ mg/L</td>
<td>HPLC–UV</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>AUC/MIC</td>
<td>$C_{\text{max}} &gt; 100$ mg/L</td>
<td>$C_{\text{min}} &gt; 25$ mg/L</td>
<td>HPLC–UV</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>AUC/MIC</td>
<td>Not clearly defined</td>
<td>Not clearly defined</td>
<td>HPLC–UV</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>AUC/MIC</td>
<td>Prophylaxis: $C_{\text{min}} &gt; 0.5$ mg/L</td>
<td>Not clearly defined</td>
<td>HPLC–UV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment: $C_{\text{min}} &gt; 1.0$ mg/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td>AUC/MIC</td>
<td>Prophylaxis: $C_{\text{min}} &gt; 0.7$ mg/L</td>
<td>Not clearly defined</td>
<td>HPLC–UV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment: $C_{\text{min}} &gt; 1.0$ mg/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>AUC/MIC</td>
<td>$C_{\text{min}} &gt; 2$ mg/L</td>
<td>$C_{\text{min}} &gt; 6$ mg/L</td>
<td>HPLC–UV</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>$T_{\text{MIC}}$</td>
<td>II: $C_{\text{min}} &gt; 25$ mg/L</td>
<td>II: $C_{\text{min}} &gt; 25$ mg/L</td>
<td>HPLC–UV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cl: $C = 50$ mg/L</td>
<td>Cl: $C = 50$ mg/L</td>
<td></td>
</tr>
<tr>
<td>Aciclovir</td>
<td>Not clearly defined</td>
<td>Not clearly defined</td>
<td>Not clearly defined</td>
<td>Immunnoassay</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Not clearly defined</td>
<td>Not clearly defined</td>
<td>Not clearly defined</td>
<td>HPLC–UV</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>AUC/MIC</td>
<td>Not clearly defined</td>
<td>Not clearly defined</td>
<td>HPLC–UV</td>
</tr>
</tbody>
</table>

II: Intermittent infusion; Cl: continuous infusion; $C$: concentration; $C_{\text{max}}$: peak concentration; $C_{\text{min}}$: trough concentration.

Therapeutic drug monitoring of anti-infective agents in critically ill patients

Nynke G. L. Jager, Reiner M. van Hest, Jeffrey Lipman, Fabio S. Taccone & Jason A. Roberts

ECCMID, Vienna 2017
TDM – clinical outcome data

Van Lent Evers (Ther Drug Monit 1999; 21: 63-73)

N=232

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ATM</th>
<th>Nonguided TDM</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of hospital stay (days)</td>
<td>20.0 ± 13.7</td>
<td>26.3 ± 31.5</td>
<td>0.045†</td>
</tr>
<tr>
<td>Signs of infection (days)</td>
<td>4.8 ± 5.1</td>
<td>3.4 ± 3.8</td>
<td>0.003*</td>
</tr>
<tr>
<td>Febrile period (days)</td>
<td>2.8 ± 2.4</td>
<td>2.3 ± 2.9</td>
<td>0.024*</td>
</tr>
<tr>
<td>Days of aminoglycoside therapy</td>
<td>5.9 ± 2.9</td>
<td>8.0 ± 4.9</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Total dose (mg)</td>
<td>1466 ± 1081</td>
<td>1668 ± 1249</td>
<td>0.161*</td>
</tr>
<tr>
<td>Dose adjustments (%)</td>
<td>48.6</td>
<td>80.4</td>
<td>0.016†</td>
</tr>
<tr>
<td>No TDM (n)</td>
<td>0</td>
<td>25 (19.7%)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Change in serum creatinine (µmol/L)</td>
<td>6 ± 30</td>
<td>25 ± 99</td>
<td>0.007*</td>
</tr>
<tr>
<td>Nephrotoxicity (n)</td>
<td>3 (2.8%)</td>
<td>17 (13.4%)</td>
<td>0.003†</td>
</tr>
<tr>
<td>Mortality (n)</td>
<td>9 (8.6%)</td>
<td>18 (14.2%)</td>
<td>0.26†</td>
</tr>
</tbody>
</table>

* Mann-Whitney U test.
† Fisher’s exact test.
‡ Kaplan-Meier analysis.

ATM, active therapeutic monitoring; TDM, therapeutic drug monitoring.
Contents

1. Where do doses come from?
2. Altered PK
3. PD considerations
4. Does current dosing meet PK/PD targets?
5. TDM
6. Scenarios to apply TDM – drugs/patients
7. Conclusion
Conclusions

- Clear concentration-effect relationships exist for antibiotics
  - For efficacy
  - For emergence of resistance
  - For toxicity
- Underdosing leads to resistance and failure
- Non-optimised dosing can occur because we don’t understand the target
- TDM-based therapy to be tested in clinical trials
Acknowledgements