Should we be personalising antibiotic dosing for critically ill patients?

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Disclosures (previous 24 months)

- **Grants** – NHMRC, ANZ ICF, ANZCA, RBWH Foundation, Queensland Health, MSD, The Medicines Company, Cardeas Pharma
- **Consultancies** – MSD, Bayer, Astellas, bioMerieux, Accelerate Diagnostics
Contents

1. Effective antibiotic dosing?
2. ICU PK
3. ICU PD
4. Is current dosing in ICU acceptable?
5. How do we personalise dosing?
6. Conclusion
Effective antibacterial therapy

- Early and effective appropriate antibacterial therapy is a significant determinant of clinical outcome in ICU.
- Once correct antibacterial 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.

→ Enhances likelihood of positive clinical outcomes
How to maximise positive outcomes?

The ‘players’ in treatment of infection

PK

Immune system

PK/PD

"Personalised antimicrobial dosing in ICU" CCSSA Congress, Sun City 2017
Consequences of inaccurate dosing?

• Each are well described consequences in ICU patients:
  • Therapeutic failure
  • Emergence of resistance
  • Drug toxicity
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Drug dosing studies aren’t done in most of our patients
Dosing complexities

• High level of sickness severity increases importance of achieving optimal therapy BUT also decreases the likelihood

• Little data to guide dosing for many patients
  – ICU patients (others e.g. transplant, burns, obese, paeds)
  – Other organ failures (e.g. CVS, Renal, Hepatic)
  – Extracorporeal circuits? (e.g. RRT, ECMO, TPE)

• Many drugs can be titrated to measurable PD

• Changes in clinical markers for infection can take days → hence PK/PD targets

Interrelationship between PK and PD is key!
Sources of PK variability

CRITICAL ILLNESS

Hyperdynamic
- Cardiac output
  - ↑ CL
  - ↓ Plasma concentrations

Altered fluid balance
- Third spacing &/or altered protein binding
  - ↑ Vd
  - ↓ Plasma concentrations

No organ dysfunction
- Unchanged Vd and CL
  - ‘Normal’ plasma concentrations

Renal &/or hepatic dysfunction
- ↑ Vd & ↓ CL
  - ↑ Plasma concentrations

Organ support
- RRT &/or ECMO
  - ↑ Vd and ?CL
  - ↓ Or ↑ Plasma concentrations

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

Sub-optimal patient outcomes

“Personalised antimicrobial dosing in ICU” CCSSA Congress, Sun City 2017
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&lt;sub&gt;d&lt;/sub&gt; 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>

The Clinical Relevance of Plasma Protein Binding Changes

"Personalised antimicrobial dosing in ICU" CCSSA Congress, Sun City 2017
Beta-lactam PK variability in ICU patients

![Boxplot showing concentration (mg/L) for various antibiotics including Amoxicillin, Ampicillin, Cefazolin, Cefepime, Ceftriaxone, Doripenem, Meropenem, and Piperacillin.](image)
Major drive for altered PK is change in CrCL
Data from a single centre observational study

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

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

<table>
<thead>
<tr>
<th>PD kill characteristics</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>$C_{\text{max}}:\text{MIC}$</td>
<td>$AUC_{0-24}:\text{MIC}$</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

**Data supporting ‘right’ dosing**

<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&lt;sub&gt;max&lt;/sub&gt;/MIC ≥8</td>
<td>Increased clinical cure for <em>Pseudomonas aeruginosa</em> blood stream infections</td>
<td>JAC 2003;52(4): 668-674.</td>
</tr>
<tr>
<td></td>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt;/MIC ≥72</td>
<td>Increased clinical cure for lower respiratory tract infections</td>
<td>JAC 1999;43 Suppl A:55-63</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>C&lt;sub&gt;min&lt;/sub&gt;/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&lt;sub&gt;MIC&lt;/sub&gt;</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>AUC&lt;sub&gt;0-24&lt;/sub&gt;/MIC ≥ 125</td>
<td>Increased microbiological &amp; clinical cure in critically ill patients</td>
<td>AAC 1993;37(5): 1073-1081</td>
</tr>
<tr>
<td>Linezolid</td>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt;/MIC ≥ 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>fAUC&lt;sub&gt;0-24&lt;/sub&gt;/MIC ≥ 0.9</td>
<td>Increased clinical success in hospital acquired pneumonia</td>
<td>AAC 2012;56(1): 130-136</td>
</tr>
</tbody>
</table>
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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

Does contemporary vancomycin dosing achieve therapeutic targets in a heterogeneous clinical cohort of critically ill patients? Data from the multinational DALI study.

Stijn Biot¹, Despoina Kourou³,²,³, Musat Alova³, Matteo Bassetti⁵, Jan J De Waerdt⁴, George Dimopoulos¹, Kiri-Maja Kaukonen⁶, Claude Martin⁷, Philippe Montaurové⁵, Jordi Rello⁵, Andrew Rhodes⁸, Therese Star³,¹, Steven C. Walls⁷, Jeffrey Lipman⁷ and Jason A. Roberts²,³

“Personalised antimicrobial dosing in ICU” CCSSA Congress, Sun City 2017
Teicoplanin

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

Solid lines D1-2; dashed lines – D2+

Variability in protein binding of teicoplanin and achievement of therapeutic drug monitoring targets in critically ill patients: Lessons from the DALI Study

“Personalised antimicrobial dosing in ICU” CCSSA Congress, Sun City 2017
Colistin
The effect of varying renal function on piperacillin PD

- Hollow fibre dynamic *in vitro* infection model
- *P. aeruginosa* isolate (MIC = 4mg/L) over 7-days
- ICU PK simulated of renal functions (30, 110, 250 mL/min); various doses
- Inoculum $10^7$
- Susceptible & resistant populations
Effect of different renal function on antibacterial effects of piperacillin against Pseudomonas aeruginosa evaluated via the hollow-fibre infection model and mechanism-based modelling.

Philip J. Bergen\textsuperscript{1}, Jürgen B. Bulitko\textsuperscript{2}, Carl M. J. Kirkpatrick\textsuperscript{1}, Kate E. Rogers\textsuperscript{3}, Megan J. McGregor\textsuperscript{3}, Steven C. Wallin\textsuperscript{2}, David L. Peterson\textsuperscript{3}, Jeffrey Lipman\textsuperscript{4,5}, Jason A. Roberts\textsuperscript{1,6,7} and Cornelius B. Lendersdorfer\textsuperscript{1,8}

"Personalised antimicrobial dosing in ICU" CCSSA Congress, Sun City 2017
Piperacillin – $C_{\text{min}}$/MIC targets to suppress resistance?

**Conclusions:** Only high piperacillin concentrations prevented regrowth of *P. aeruginosa*. Individualized dosing regimens that account for altered pharmacokinetics and aim for higher-than-standard antibiotic exposures achieve an $fC_{\text{min}}$ of $\geq 5 \times$ MIC were required to maximize bacterial killing and suppress emergence of resistance.

$fC_{\text{min}} > 5 \times$MIC resulted in $3-4 \log_{10}$ bacterial killing and suppressing emergence of resistance $< 2 \log_{10}$.
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Options for more personlaised 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
1. Unit level intervention: beta-lactam continuous infusion regimen
1. Beta-lactam continuous infusion: clinical testing

<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>Total (95% CI)</td>
<td>312</td>
<td>320</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.73 [0.55, 0.98]</td>
</tr>
</tbody>
</table>

Total events: 61, 85
Heterogeneity: Chi² = 0.69, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.11 (P = 0.03)

Original Article

Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis
A Meta-analysis of Individual Patient Data from Randomized Trials
Jason A. Roberts1,2,3,4, Mohd-Hafiz Abdul-Aziz2,5, Joshua S. Davis6,7, Joel M. Dulhunty1,2,8, Menino O. Cotta1,2,3,4, John Myburgh1,9, Rinaldo Bellomo7,11,12, and Jeffrey Libman1,12
American Journal of Respiratory and Critical Care Medicine Volume 194 Number 6 | September 15 2016

“Personalised antimicrobial dosing in ICU” CCSSA Congress, Sun City 2017
2. Dosing nomograms accounting for ICU PK

Vancomycin Dosing in Critically Ill Patients: Robust Methods for Improved Continuous-Infusion Regimens
Jason A. Roberts,1,2 Fabio Silvio Tacconil,1,3 Andrew A. Uly,1 Jean-Louis Vincent,2 Frédérique Jacobs,2 and Jeffrey Lipman1

Decreasing the time to achieve therapeutic vancomycin concentrations in critically ill patients: developing and testing of a dosing nomogram
Júlio Pedro Baptista1,2, Jason A. Roberts1,2,3, Eduardo Sousa1,2, Ricardio Fentse1, Nuno Ceneves1 and Jorge Pinheiro1

“Personalised antimicrobial dosing in ICU” CCSSA Congress, Sun City 2017
2. Nomograms → dosing regimens in ICU

% of patients at target concentration

Conventional  ICU nomogram

P<0.005

“Personalised antimicrobial dosing in ICU” CCSSA Congress, Sun City 2017
3. Dosing software for empiric dosing

- PK model with embedded covariates
  - can account for different renal function or body weight or MICs in the individual patient etc

- Case study for meropenem dosing

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>19</td>
<td>72</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>105</td>
<td>55</td>
</tr>
<tr>
<td>SeCr (umol/L)</td>
<td>55</td>
<td>95</td>
</tr>
</tbody>
</table>
3. Dosing software

30% vs 69% $f_{T > \text{MIC}}$ for MIC = 4
4. TDM (+/- adaptive feedback)

- Aminoglycosides
- Glycopeptides
- Quinolones
- Beta-lactams
- Daptomycin
- Linezolid
- Colistin

No RCT has demonstrated a mortality benefit of TDM
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Conclusions

- Clear concentration-effect relationships exist for antibiotics
  - For efficacy
  - For emergence of resistance
  - For toxicity (sort of)

- Underdosing leads to resistance and failure

- Non-customised dosing in ICU is common because we don’t understand the PK or don’t know how

- SHOULD WE?
  - YES – But ‘personalised’ doses to be tested in clinical trials to include ICU-specific dosing regimens +/- TDM
Personalised antimicrobial dosing in ICU
CCSSA Congress, Sun City 2017

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