Critically Ill Patients versus Healthy Volunteers

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 (grant)
• bioMerieux (consultancy)
• Astellas (consultancy)
• Bayer (consultancy)
• The Medicines Company (grant)
Contents

1. What is critical illness?
2. ICU PK
   a. Renal function
   b. RRT
   c. ECMO
3. ICU PD
4. Importance of ICU PK for clinical trials
5. Are we chronically underdosing in ICU?
6. Conclusions
What is critical illness?

- By definition, critically-ill patients have a medical emergency requiring the constant attendance of a physician.
- High severity of illness
- Frequently require different treatment regimens compared with other hospitalized patients, due to:
  - Pathophysiological changes
  - Treatment interventions
- Infections and use of antibiotics common
  - >70% of ICU patients
Effective antibacterial therapy

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

• Dosing is highly important as enables antibiotic to work!

• 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
Importance of appropriate antibiotic therapy

## Importance of antibiotic exposure on patient outcome

<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>$C_{\text{max}}/\text{MIC} \geq 8$</td>
<td>Increased clinical cure for <em>Pseudomonas aeruginosa</em> bloodstream infections</td>
<td>JAC 2003;52(4): 668-674.</td>
</tr>
<tr>
<td></td>
<td>$AUC_{0-24}/\text{MIC} \geq 72$</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>$C_{\text{min}}/\text{MIC} &gt; 5$</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>$100% T_{\geq \text{MIC}}$</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>$AUC_{0-24}/\text{MIC} \geq 125$</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>$AUC_{0-24}/\text{MIC} \geq 451$</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>$AUC_{0-24}/\text{MIC} \geq 85$</td>
<td>Increased clinical cure in severely ill patients with bloodstream infections</td>
<td>Clin Pharmacokinet 2003;42(15): 1411-1423</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>$f AUC_{0-24}/\text{MIC} \geq 0.9$</td>
<td>Increased clinical success in hospital acquired pneumonia</td>
<td>AAC 2012;56(1): 130-136</td>
</tr>
</tbody>
</table>
Contents

1. What is critical illness?
2. ICU PK
   a. Renal function
   b. RRT
   c. ECMO
3. ICU PD
4. Importance of ICU PK for clinical trials
5. Are we chronically underdosing in ICU?
6. Conclusions
Drug dosing studies aren’t done in most of our patients.
Dosing uncertainties

• 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 \(\rightarrow\) hence PK/PD targets

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

- **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
PK changes in ICU patients relative to healthy volunteers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in clearance in ICU patients</th>
<th>Change in $V_d$ in ICU patients</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
Jason A. Roberts · Federico Pea · Jeffrey Lipman
Beta-lactam PK variability in ICU patients
Contents

1. What is critical illness?
2. ICU PK
   a. Renal function
   b. RRT
   c. ECMO
3. ICU PD
4. Importance of ICU PK for clinical trials
5. Are we chronically underdosing in ICU?
6. Conclusions
Major drive for altered PK is change in CrCL
Augmented Renal Clearance

Ref.: Clinical Pharmacokinetics (2010); 49(1) 1-16.
ARC Risk Factors

Intensive Care Med 2013; 39: 1247-52
ARC Risk Score
(out of 10)

- Age ≤ 50 years (six points)
- Trauma (three points)
- SOFA Score ≤ 4 (one point)

Crit Care 2013; 17: R35
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
Contents

1. What is critical illness?
2. ICU PK
   a. Renal function
   b. RRT
   c. ECMO
3. ICU PD
4. Importance of ICU PK for clinical trials
5. Are we chronically underdosing in ICU?
6. Conclusions
Extent of AKI and type of RRT and RRT Settings

- CrCL and UO can describe endogenous renal function
- Different forms of RRT have different effects on PK
  - PD (continuous)
  - IHD (3-4 hrs)
  - EDD (8-12 hrs)
  - CRRT (24 hrs)
Factors affecting PK in RRT

- **Type of RRT**
  - Treatment time
  - Pump speed
  - Presence of replacement fluid

- **RRT Settings**
  - Ultrafiltrate flow rate
  - Blood flow rate
  - Filter surface area

- **Drug Factors**
  - Vd
  - Protein binding
  - Molecular weight
  - Adsorption to filter
  - Drug charge
**CVVHDF**

Convection + diffusion

Combined CL not additive

<table>
<thead>
<tr>
<th></th>
<th>Piperacillin CL (L/hr)</th>
<th>Meropenem CL (L/hr)</th>
<th>Fluconazole CL (L/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVVH</td>
<td>3.9</td>
<td>3.3</td>
<td>0.6</td>
</tr>
<tr>
<td>CVVHDF - 1 L/hr (dialysate flow rate)</td>
<td>5.1</td>
<td>4.7</td>
<td>1.5</td>
</tr>
<tr>
<td>CVVHDF (2 L/hr) (dialysate flow rate)</td>
<td>5.5</td>
<td>5.7</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Figure 1: Pharmacokinetic profile of meropenem for patients receiving continuous renal replacement therapy. Data shown as mean serum concentrations (with standard deviation) measured in samples taken < 48 hours (circles) and > 48 hours (diamonds) from the start of the treatment. Dotted line, 2 µg/ml; dashed line, 8 µg/ml.

Figure 2: Pharmacokinetic profile of piperacillin for patients receiving continuous renal replacement therapy. Data shown as mean serum concentrations (with standard deviation) measured in samples taken < 48 hours (circles) and > 48 hours (diamonds) from the start of the treatment. Dotted line, 16 µg/ml; dashed line, 64 µg/ml.

Figure 3: Pharmacokinetic profile of cefepime for patients receiving continuous renal replacement therapy. Data shown as mean serum concentrations (with standard deviation) measured in samples taken < 48 hours (circles) and > 48 hours (diamonds) from the start of the treatment. Dotted line, 8 µg/ml; dashed line, 32 µg/ml.

Figure 4: Pharmacokinetic profile of ceftazidime for patients receiving continuous renal replacement therapy. Data shown as mean serum concentrations (with standard deviation) measured in samples taken < 48 hours (circles) and > 48 hours (diamonds) from the start of the treatment. Dotted line, 8 µg/ml; dashed line, 32 µg/ml.
Contents

1. What is critical illness?
2. ICU PK
   a. Renal function
   b. RRT
   c. ECMO
3. ICU PD
4. Importance of ICU PK for clinical trials
5. Are we chronically underdosing in ICU?
6. Conclusions
ECMO effects - circuit sequestration/destruction of drugs?
Contents

1. What is critical illness?
2. ICU PK
   a. Renal function
   b. RRT
   c. ECMO
3. ICU PD
4. Importance of ICU PK for clinical trials
5. Are we chronically underdosing in ICU?
6. Conclusions
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>Carbapenems</td>
<td>Metronidazole</td>
<td>Fluoroquinolones</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Fluoroquinolones</td>
<td>Aminoglycosides</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Telithromycin</td>
<td>Glycopeptides</td>
<td>Tigecycline</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Daptomycin</td>
<td>Quinupristin/dalfopristin</td>
<td>Quinupristin/dalfopristin</td>
</tr>
<tr>
<td>Lincosamides</td>
<td>Quinupristin/dalfopristin</td>
<td>Tigecycline</td>
<td>Linezolid</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>$C_{max}$:MIC</td>
<td>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. What is critical illness?
2. ICU PK
   a. Renal function
   b. RRT
   c. ECMO
3. ICU PD
4. Importance of ICU PK for clinical trials
5. Are we chronically underdosing in ICU?
6. Conclusions
Case study - doripenem

- Phase III, multicentre, double blind RCT
- Fixed 7/7 doripenem (1g q8h 4h inf) vs fixed 10/7 imipenem-cilastatin (1g q8h 1h inf) for VAP
- Terminated with 274/524 patients recruited
- Duration of treatment?
Was doripenem dosing sufficient?

- MIC breakpoints:
  - USA = 8mg/L
  - Australia = 4mg/L
  - Malaysia = 2mg/L

83% PK/PD target attainment at 150ml/min – but not above!
Contents

1. What is critical illness?
2. ICU PK
   a. Renal function
   b. RRT
   c. ECMO
3. ICU PD
4. Importance of ICU PK for clinical trials
5. Are we chronically underdosing in ICU?
6. Conclusions
Beta-lactams
Vancomycin

![Graph showing vancomycin trough concentration (Cmin) vs. vancomycin dose (mg/kg/24h). The graph includes various data points and a shaded area indicating a therapeutic range.]
Teicoplanin

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

Solid lines D1-2; dashed lines – D2+

(a)
Colistin
Toxicity? (beta-lactams)

Figure 3. Proportion of therapeutic drug monitorings (TDMs) associated with worsening neurological status (NWS) for the different $C_{\text{min}}/\text{MIC}$ categories in all patients (A) and when patients with neurological disease were excluded (B).
Contents

1. What is critical illness?
2. ICU PK
   a. Renal function
   b. RRT
   c. ECMO
3. ICU PD
4. Importance of ICU PK for clinical trials
5. Are we chronically underdosing in ICU?
6. Conclusions
Conclusions

- Concentration-effect relationships exist for antibiotics
  - For efficacy
  - For emergence of resistance
  - For toxicity
- Most dosing is based on PK data from non-critically ill patients
- Sub-optimal dosing in ICU is common because we haven’t characterised the PK
Acknowledgements