Optimal dosing and continuous or prolonged infusion of beta-lactams and vancomycin – what is the evidence?

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Disclosures

• **Grants** – NHMRC, ANZ ICF, ANZCA, RBWH Foundation, Queensland Health, MSD, The Medicines Company, Cardeas Pharma

• **Consultancies** – MSD, Bayer, Astellas, bioMerieux, Accelerate Diagnostics
Continuous beta-lactam and vancomycin infusions

- Introduction
  - Importance of PK/PD
  - Surrogate data supporting CI
  - RCT data
  - Practical tips
- Conclusions
Introduction - continuous infusions

- Method for dose optimisation
- In ICU to improve patient outcomes
  - Mortality rates for sepsis and septic shock reported at 20-80%
- In wards for infections caused by less-susceptible pathogens or for easier TDM
- Outside hospital (HITH/OPAT) for convenience of administration

Continuous beta-lactam and vancomycin infusions

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- Importance of PK/PD
- Surrogate data supporting CI
- RCT data
- Practical tips
- Conclusions
Drug dosing studies aren’t done in all patient groups

PK/PD can propose answers to the remaining questions

Titrating to clinical effect won’t work…
Spectrum of organ function

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

Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions


"CI of beta-lactams and vancomycin" ESCMID Postgraduate Education Course, Rotterdam 2019

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## Antibiotic pharmacodynamics

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

**PD kill characteristics**
- Time-dependent
- Concentration-dependent
- Concentration-dependent with time-dependence

**Optimal PD parameter**
- $T > \text{MIC}$
- $C_{\text{max}}:\text{MIC}$
- $AUC_{0-24}:\text{MIC}$

MIC, minimum inhibitory concentration; AUC, area under curve; PD, pharmacodynamics; $C_{\text{max}}$, maximum concentration.

Crit Care Med 2009; 37: 840-51
PD: Susceptibility Patterns

- Decreased susceptibility of organisms in some parts of hospital
- Increased doses or different dosing approaches 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
- How to change dosing in response to high MICs?

Continuous beta-lactam and vancomycin infusions

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- Importance of PK/PD
- Surrogate data supporting CI
- RCT data
- Practical tips
- Conclusions
**In vitro** bacterial killing data: ceftazidime

- **Bacterial counts after 4\(^{th}\) bolus dose:**
  - Bolus = 2.8 log\(_{10}\)
  - Infusion = 2.2 log\(_{10}\)
Meropenem – bolus vs EI vs CI

Tissue concentrations

- Low penetration with high sickness
- Severe sepsis and septic shock (n=10)
- Meropenem (plasma and ISF)
Proof of concept clinical trial

Phase 2 clinical trial

Phase 3 clinical trial

Human models

Observational data

Animal data

In vitro data

McAuley et al. Crit Care Med 2010: 38; S523-S527
Continuous beta-lactam and vancomycin infusions

- Introduction
- Importance of PK/PD
- Surrogate data supporting CI
- RCT data
- Practical tips
- Conclusions
Observational data (n=182)

Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved pharmacokinetic/pharmacodynamic and patient outcomes? An observation from the Defining Antibiotic Levels in Intensive care unit patients (DALI) cohort

Mohd H. Abdul-Aziz1, Jeffrey Lipman1,2, Murat Akova1, Matteo Bassetti2, Jan J. De Woele5, George Dimopoulos6, Joel Dulhunty2, Kirsi-Maija Kaukonen2, Despoina Koulenti1,6, Claude Martin1,8, Philippe Montravers12, Jordi Rello13, Andrew Rhodes11, Therese Starr1, Steven C. Wallis1 and Jason A. Roberts1,4 on behalf of the DALI Study Group

Figure 2. Method of piperacillin/tazobactam and meropenem administration according to participating countries.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clinical cure</th>
<th>Significance P valuea,b</th>
<th>30 day survival</th>
<th>P valuea,b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yes (n=106)</td>
<td>no (n=39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant antibiotics, n (%)</td>
<td>58 (54.7)</td>
<td>32 (82.1)</td>
<td><strong>0.020c</strong></td>
<td></td>
</tr>
<tr>
<td>Dosing method, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prolonged infusion</td>
<td>44 (41.5)</td>
<td>14 (35.9)</td>
<td>0.641c</td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>62 (58.5)</td>
<td>25 (64.1)</td>
<td>0.023c</td>
<td></td>
</tr>
<tr>
<td>PK/PD ratiod, median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% fT&gt;MIC</td>
<td>7.1 (2.2–13.0)</td>
<td>3.5 (2.1–10.0)</td>
<td><strong>0.097c</strong></td>
<td></td>
</tr>
<tr>
<td>100% fT&gt;MIC</td>
<td>2.2 (0.6–7.1)</td>
<td>1.7 (0.5–3.1)</td>
<td>0.280</td>
<td></td>
</tr>
</tbody>
</table>
Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved pharmacokinetic/pharmacodynamic and patient outcomes? An observation from the Defining Antibiotic Levels in Intensive care unit patients (DALI) cohort

Mohd H. Abdul-Aziz1, Jeffrey Lipman2, Murat Akova1, Matteo Bassetti2, Jan J. De Waele3, George Dimopoulos4, Joel Duhany1,2, Kirsu-Majja Kaakinen7, Despoina Koulenti1,5, Claude Martin5,6, Philippe Montravers19, Jordi Rello13, Andrew Rhodes13, Therese Starr1, Steven C. Wallis1 and Jason A. Roberts1,2* on behalf of the DALI Study Group†
Continuous infusion: single-centre RCT

Study 1: RCT = n=57 ITT (n=57 a priori) outcome analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>AOR^a</th>
<th>95% CI^a</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical cure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>infusion group</td>
<td>22.8</td>
<td>2.24–232.3</td>
<td>0.008</td>
</tr>
<tr>
<td>lower admission APACHE II</td>
<td>0.70</td>
<td>0.54–0.91</td>
<td>0.008</td>
</tr>
<tr>
<td>Hosmer Lemeshow ( \chi^2 = 2.78; P = 0.95 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proven bacterial eradication^b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>infusion group</td>
<td>8.25</td>
<td>1.34–50.77</td>
<td>0.02</td>
</tr>
<tr>
<td>lower admission APACHE II</td>
<td>0.79</td>
<td>0.65–0.97</td>
<td>0.02</td>
</tr>
<tr>
<td>Hosmer Lemeshow ( \chi^2 = 5.41; P = 0.71 )</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


doi:10.1093/jac/dkl478

Advance Access publication 28 November 2006

Is continuous infusion ceftriaxone better than once-a-day dosing in intensive care? A randomized controlled pilot study

Jason A. Roberts^1^2, Rob Boots^1^2, Claire M. Rickard^3, Peter Thomas^1, Jo Quinn^1, Darren M. Roberts^1, Brent Richards^4 and Jeffrey Lipman^1^2^9
BLING 1 – severe sepsis

- Prospective, double-blind, double-dummy RCT (n=60)
- Continuous infusion vs bolus dosing
  - Piperacillin/tazobactam, Meropenem, Ticarcillin/clavulanate
- 5 ICUs in Australasia
- Primary outcome – PK
  - Secondary – clinical outcome
BLING 1 – Concentration:MIC ratio

- Piperacillin
- Meropenem
- Ticarcillin

$P = .054$

$P = .14$

$P = .012$
# BLING 1 – Study Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Intervention Group</th>
<th>Control Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma antibiotic concentration &gt; MIC</td>
<td>18 (81.8%)a</td>
<td>6 (28.6%)a</td>
<td>.001</td>
</tr>
<tr>
<td>Clinical cure (test of cure date)</td>
<td>23 (76.7%)</td>
<td>15 (50.0%)</td>
<td>.032</td>
</tr>
<tr>
<td>Clinical cure (test of cure date with treatment exclusions)</td>
<td>21 (70.0%)</td>
<td>13 (43.3%)</td>
<td>.037</td>
</tr>
<tr>
<td>Clinical cure (last day of blinding)</td>
<td>9 (30.0%)</td>
<td>6 (20.0%)</td>
<td>.37</td>
</tr>
<tr>
<td>Time to clinical resolution (days)</td>
<td>11 (6.75–24.25)b</td>
<td>16.5 (7–28)b</td>
<td>.14</td>
</tr>
<tr>
<td>Time to resolution of CRP (days)</td>
<td>6 (2.5–22.5)c</td>
<td>5 (3–27)c</td>
<td>.79</td>
</tr>
<tr>
<td>ICU length of stay (postrandomization)</td>
<td>7.5 (4–12)</td>
<td>9 (5–14.25)</td>
<td>.50</td>
</tr>
<tr>
<td>ICU-free days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>19.5 (12.75–24)</td>
<td>17 (.75–22)</td>
<td>.14</td>
</tr>
<tr>
<td>ICU survivors</td>
<td>20.5 (16–24)d</td>
<td>18 (12.75–22)d</td>
<td>.22</td>
</tr>
<tr>
<td>ICU survival</td>
<td>28 (93.3%)</td>
<td>26 (86.7%)</td>
<td>.67</td>
</tr>
<tr>
<td>Hospital survival</td>
<td>27 (90.0%)</td>
<td>24 (80.0%)</td>
<td>.47</td>
</tr>
</tbody>
</table>
BLISS

• Same methods as BLING I
• N=2 sites and N=140 patients
• Primary Outcome – PK/PD target attainment for continuous vs intermittent dosing
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 (%)</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>14 (67)</td>
<td>8 (38)</td>
<td>29 (−0.5 to 0.1)</td>
<td>0.064</td>
</tr>
<tr>
<td>Meropenem</td>
<td>3 (27)</td>
<td>1 (50)</td>
<td>23 (−0.3 to 0.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Clinical cure by concomitant antibiotic treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14 (42)</td>
<td>13 (39)</td>
<td>3 (−0.3 to 0.2)</td>
<td>0.802</td>
</tr>
<tr>
<td>No</td>
<td>25 (68)</td>
<td>11 (30)</td>
<td>38 (−0.6 to −0.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Clinical cure by site of infection, n (%)</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 (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (52)</td>
<td>6 (25)</td>
<td>27 (−0.5 to 0.1)</td>
<td>0.052</td>
</tr>
<tr>
<td>No</td>
<td>10 (44)</td>
<td>12 (38)</td>
<td>6 (−0.3 to 0.2)</td>
<td>0.655</td>
</tr>
</tbody>
</table>

Beta-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis

Awarded paper of the year for Intensive Care Medicine in 2016 (ESICM, Vienna 2017)
Phase 3 clinical trial

Phase 2 clinical trial

Proof of concept clinical trial

Human models

Observational data

Animal data

In vitro data

BLING I + BLISS

McAuley et al. Crit Care Med 2010: 38; S523-S527
BLING 2

- Same methods as BLING I
- N=26 sites and N=432 patients
- Primary Outcome – ICU-free days alive at day 28
### BLING 2 data

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

<table>
<thead>
<tr>
<th>Outcome</th>
<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>
<td>0.38</td>
</tr>
<tr>
<td>ICU survivors</td>
<td>21 (12–24)</td>
<td>22 (14–25)</td>
<td>0.12</td>
</tr>
<tr>
<td>Day-90 survival*†</td>
<td>156 (74.3)</td>
<td>158 (72.5)</td>
<td>0.67</td>
</tr>
<tr>
<td>ICU survival†</td>
<td>180 (84.9)</td>
<td>182 (82.7)</td>
<td>0.54</td>
</tr>
<tr>
<td>Hospital survival††</td>
<td>168 (79.2)</td>
<td>164 (74.9)</td>
<td>0.28</td>
</tr>
<tr>
<td>Clinical cure</td>
<td>111 (52.4)</td>
<td>109 (49.5)</td>
<td>0.56</td>
</tr>
<tr>
<td>Organ failure–free days</td>
<td>6 (0–10)</td>
<td>6 (0–11)</td>
<td>0.27</td>
</tr>
<tr>
<td>Duration of bacteremia, d§</td>
<td>0 (0–0)</td>
<td>0 (0–1)</td>
<td>0.24</td>
</tr>
<tr>
<td>ICU length of stay, d</td>
<td></td>
<td></td>
<td>7 (3–13)</td>
</tr>
<tr>
<td>Hospital length of stay, d</td>
<td></td>
<td></td>
<td>16 (8–32)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>20 (9.4)</td>
<td>28 (12.7)</td>
<td>0.28</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>19 (9.0)</td>
<td>25 (11.4)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

>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)
Phase 3 clinical trial

Phase 2 clinical trial

Proof of concept clinical trial

Human models

Observational data

Animal data

In vitro data

BLING II

BLING I + BLISS

McAuley et al. Crit Care Med 2010: 38; S523-S527
Meta-analysis of hospitalised patients

Clinical cure

Mortality
IPDMA of Cl vs IB RCTs

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cl 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></td>
<td></td>
<td><strong>0.73 [0.55, 0.98]</strong></td>
</tr>
</tbody>
</table>

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

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-Aziz⁵, Joshua S. Davis⁶,⁷, Joel M. Dulhunty¹,²,⁸, Menino O. Cotta¹,²,³,⁴, John Myburgh⁹,¹⁰, Rinaldo Bellomo¹¹,¹², and Jeffrey Lipman¹,²

"CI of beta-lactams and vancomycin" ESCMID Postgraduate Education Course, Rotterdam 2019
CI of beta-lactams and vancomycin

1. In vitro data
2. Animal data
3. Observational data
4. Human models
5. Proof of concept clinical trial
6. BLING I + BLISS
7. BLING III
BLING 3 - Study methods

- Prospective, multicentre, phase III RCT
- International (70-100 centres)
- **Open label** administration of piperacillin-tazobactam or meropenem
- Randomisation to continuous or intermittent beta-lactam infusion
- **Primary outcome:**
  - Death from all causes within 90 days after randomisation
- **Secondary outcomes:**
  - ICU & hospital mortality
  - Clinical cure at Day 14
  - New acquisition, colonisation or infection with an MRO
- **Tertiary outcomes:**
  - Health-related quality of life (EQ-5D-5L) at Day 90
  - Cost effectiveness at Day 90 (nested Australian cohort)
Jason Roberts @jasonroberts_pk

Well done - a terrific milestone. 6000 patients to go...

Joshua Davis @Guru_JoshD
Congrats to the #BLING3 team for 1000th patient randomized last night! Answering: do beta-lactam infusions —> lower mortality in sepsis?

2:54 PM - 4 Apr 2019 from Brisbane, Queensland

4 Retweets 17 Likes
Vancomycin multicenter RCT

- N=119 ICU patients
- Micro and clinical outcomes similar
- CI reached therapeutic targets faster (36 +/- 31 vs 51 +/- 39 h, P=0.029)
- CI fewer samples for TDM (7.7 +/- 2.2 vs 11.8 +/- 3.9 per treatment, P < 0.0001)
- Lower PK exposure variability (~4-fold)
Vancomycin meta-analysis - Nephrotoxicity

Patients treated with CIV had a significantly lower incidence of nephrotoxicity [risk ratio (RR) = 0.61, 95% confidence interval (CI) 0.47–0.80; P < 0.001]
Vancomycin meta-analysis - Mortality

Mortality between patients receiving CIV and patients receiving IIIV was similar (RR = 1.15, 95% CI 0.85–1.54; P = 0.365)
Continuous beta-lactam and vancomycin infusions

- Introduction
- Importance of PK/PD
- Surrogate data supporting CI
- RCT data
- Practical tips
- Conclusions
Practical tips

• Loading dose
• Drug stability considerations
• Dead-space in infusion tubing
• Drug-drug incompatibility
Continuous beta-lactam and vancomycin infusions

- Introduction
- Importance of PK/PD
- Surrogate data supporting CI
- RCT data
- Practical tips
- Conclusions
Conclusions

• CI appears to be advantageous in defined patient groups
  – High sickness severity
  – Not on RRT
  Convenience (outside ICU)

• CI has not been shown to be harmful

• BLING 3 – important study that will inform dosing in ICUs globally