Continuous vs intermittent dosing of beta-lactam antibiotics

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- **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 infusions in the ICU

- Infection in the ICU
- Importance of PK/PD
- Surrogate data supporting CI
- RCT data
- Conclusions
Introduction

• Infection in ICU
  • Mortality rates for sepsis and septic shock reported at 20-80%
  • Primary cause of 50% of AKI which has a 50% in-hospital mortality
  • Significant costs to healthcare system

• Antibiotic therapy common in ICU (EPIC II)
  – 51% ICU patients infected;
  – 71% receiving antibiotic

Continuous beta-lactam infusions in the ICU

- Infection in the ICU
- Importance of PK/PD
- Surrogate data supporting CI
- RCT data
- Conclusions
Drug dosing studies aren’t done in ICU patients

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


"Continuous vs intermittent dosing of beta-lactams" CCSSA Congress, Sun City 2017
## 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>Carabapenems</th>
<th>Metronidazole</th>
<th>Aminoglycosides</th>
<th>Azithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Linezolid</td>
<td>Fluoroquinolones</td>
<td>Telithromycin</td>
<td>Erythromycin</td>
<td>Quinupristin/dalfopristin</td>
<td>Tigecycline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>Daptomycin</td>
<td>Glycopeptides</td>
<td>Clarithromycin</td>
<td>Quinupristin/dalfopristin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lincosamides</td>
<td>Quinupristin/dalfopristin</td>
<td>Tetracyclines</td>
<td>Lincosamides</td>
<td></td>
<td></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>$C_{\text{max}}$:MIC</td>
<td>$\text{AUC}_{0-24}$:MIC</td>
</tr>
</tbody>
</table>

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

- Decreased susceptibility of organisms in 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

Continuous beta-lactam infusions in the ICU

- Infection in the ICU
- Importance of PK/PD
- Surrogate data supporting CI
- RCT data
- Conclusions
**In vitro** bacterial killing data

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

![Graph showing meropenem concentrations over time for continuous, extended, and bolus infusions compared to the MIC level of 2 mg/L.](https://example.com/graph.png)
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 infusions in the ICU

- Infection in the ICU
- Importance of PK/PD
- Surrogate data supporting CI
- RCT data
- Conclusions
Continuous infusion: single-centre studies

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

<table>
<thead>
<tr>
<th></th>
<th>AOR^a</th>
<th>95% CI^a</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical cure</strong></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><strong>Hosmer Lemeshow ( \chi^2 = 2.78; P = 0.95 )</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proven bacterial eradication^b</strong></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><strong>Hosmer Lemeshow ( \chi^2 = 5.41; P = 0.71 )</strong></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

"Continuous vs intermittent dosing of beta-lactams" CCSSA Congress, Sun City 2017
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
Continuous vs intermittent dosing of beta-lactams

BLING 1 – Concentration:MIC ratio

Piperacillin
Meropenem
Ticarcillin
### 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%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 (28.6%)&lt;sup&gt;a&lt;/sup&gt;</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)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16.5 (7–28)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>.14</td>
</tr>
<tr>
<td>Time to resolution of CRP (days)</td>
<td>6 (2.5–22.5)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5 (3–27)&lt;sup&gt;c&lt;/sup&gt;</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)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>18 (12.75–22)&lt;sup&gt;d&lt;/sup&gt;</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>

<sup>a</sup> Observations were made on ICU discharge, which was the primary endpoint of the study. The difference in plasma antibiotic concentration between the intervention and control groups was statistically significant with a P-value of .001, indicating that continuous dosing of beta-lactams led to higher concentrations compared to intermittent dosing.

<sup>b</sup> Time to clinical resolution was measured from the initiation of treatment. The median time to resolution was significantly shorter in the intervention group (11 days) compared to the control group (16.5 days), with a P-value of .14.

<sup>c</sup> Time to resolution of C-reactive protein (CRP) was assessed postrandomization. The median time to resolution was similar between the groups, with P-values over .05 indicating no significant difference.

<sup>d</sup> ICU survivors were those who survived the initial 30 days post-discharge. The difference in ICU survivors between the groups was not statistically significant, with a P-value of .22.
BLISS

- Same methods as BLING I
- N=2 sites and N=140 patients
- Primary Outcome – PK/PD target attainment for continuous vs intermittent dosing
BLISS

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>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>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 site of infection, n (%)</td>
<td>13 (52)</td>
<td>6 (25)</td>
<td>27 (−0.5 to 0.1)</td>
<td>0.052</td>
</tr>
<tr>
<td>Lung</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)

“Continuous vs intermittent dosing of beta-lactams” CCSSA Congress, Sun City 2017
Continuous vs intermittent dosing of beta-lactams

\textbf{BLING I + BLISS}

1. In vitro data
2. Animal data
3. Observational data
4. Human models
5. Proof of concept clinical trial
6. Phase 2 clinical trial
7. Phase 3 clinical trial

McAuley et al. \textit{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
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, dǁ</td>
<td>7 (3–13)</td>
<td>6 (3–11)</td>
<td>0.042</td>
</tr>
<tr>
<td>Hospital length of stay, dǁ</td>
<td>16 (8–32)</td>
<td>14 (8–27)</td>
<td>0.25</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)
Continuous vs intermittent dosing of beta-lactams

CCSSA Congress, Sun City 2017

Proof of concept clinical trial

Observational data

Human models

Animal data

In vitro data

Phase 3 clinical trial

Phase 2 clinical trial

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Infusion n/N</th>
<th>Bolus n/N</th>
<th>OR (random) 95% CI</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bodey 1979 (46)</td>
<td>48/74</td>
<td>52/92</td>
<td>2.90 (0.76, 2.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lagast 1983 (48)</td>
<td>14/20</td>
<td>20/25</td>
<td>6.17 (0.15, 2.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanes 2000 (47)</td>
<td>9/16</td>
<td>10/14</td>
<td>4.99 (0.11, 2.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicolau 2001 (49)</td>
<td>7/17</td>
<td>6/18</td>
<td>6.11 (0.35, 5.54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pedebosq 2001 (44)</td>
<td>3/3</td>
<td>4/4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buck 2005 (20)</td>
<td>8/12</td>
<td>8/12</td>
<td>4.02 (0.15, 0.46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Georges 2005 (21)</td>
<td>22/26</td>
<td>16/24</td>
<td>6.24 (0.70, 10.74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lau 2006 (22)</td>
<td>96/128</td>
<td>94/130</td>
<td>33.56 (0.42, 1.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Zanten 2007 (26)</td>
<td>31/40</td>
<td>40/43</td>
<td>4.19 (0.18, 4.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roberts 2007 (24)</td>
<td>25/29</td>
<td>23/28</td>
<td>5.65 (0.32, 5.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>365</strong></td>
<td><strong>390</strong></td>
<td></td>
<td><strong>100.00</strong></td>
<td><strong>1.04 (0.74, 1.46)</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 5.93, df = 8 (P = 0.66), I² = 0%
Test for overall effect: Z = 0.21 (P = 0.83)

---

Clinical cure

<table>
<thead>
<tr>
<th>Study</th>
<th>Infusion n/N</th>
<th>Bolus n/N</th>
<th>OR (random) 95% CI</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kojika 2005 (50)</td>
<td>1/5</td>
<td>0/5</td>
<td>4.22 (0.12, 113.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lahest 1983 (48)</td>
<td>5/20</td>
<td>4/25</td>
<td>18.40 (0.40, 7.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angus 2000 (45)</td>
<td>3/10</td>
<td>9/11</td>
<td>10.82 (0.01, 0.74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicolau 2001 (49)</td>
<td>2/17</td>
<td>2/18</td>
<td>10.47 (0.13, 8.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pedebosq 2001 (44)</td>
<td>0/3</td>
<td>0/4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Georges 2006 (21)</td>
<td>3/25</td>
<td>3/23</td>
<td>14.55 (0.16, 5.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lau 2006 (22)</td>
<td>3/128</td>
<td>1/130</td>
<td>8.97 (0.32, 30.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rafati 2006 (23)</td>
<td>5/20</td>
<td>6/20</td>
<td>20.00 (0.19, 3.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roberts 2007 (24)</td>
<td>3/29</td>
<td>0/28</td>
<td>5.41 (0.37, 152.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saikka 2007 (25)</td>
<td>1/10</td>
<td>2/10</td>
<td>7.16 (0.03, 5.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>267</strong></td>
<td><strong>274</strong></td>
<td></td>
<td><strong>100.00</strong></td>
<td><strong>1.00 (0.48, 2.06)</strong></td>
</tr>
</tbody>
</table>

Total events: 26 (Infusion), 27 (Bolus)
Test for heterogeneity: Chi² = 9.38, df = 8 (P = 0.31), I² = 14.8%
Test for overall effect: Z = 0.00 (P = 1.00)

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Mortality
Continuous versus Intermittent \( \beta \)-Lactam Infusion in Severe Sepsis
A Meta-analysis of Individual Patient Data from Randomized Trials

Jason A. Roberts\(^1,2,3,4\), Mohd-Hafiz Abdul-Aziz\(^2,5\), Joshua S. Davis\(^6,7\), Joel M. Dulhunty\(^1,2,8\), Menino O. Cotta\(^1,2,3,4\), John Myburgh\(^9,10\), Rinaldo Bellomo\(^11,12\), and Jeffrey Lipman\(^1,2\)
Continuous vs intermittent dosing of beta-lactams

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BLING III

7

BLING II

6

BLING I + BLISS

5

Proof of concept clinical trial

Phase 3 clinical trial

Phase 2 clinical trial

Human models

Observational data

In vitro data

McAuley et al. Crit Care Med 2010: 38; S523-S527
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)
Continuous beta-lactam infusions in the ICU

- Infection in the ICU
- Importance of PK/PD
- Surrogate data supporting CI
- RCT data
- Conclusions
Conclusions

• CI appears to be advantageous in defined patient groups
  – High sickness severity
  – Not on RRT

• CI has not been shown to be harmful in previous studies

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