Continuous vs Intermittent Dosing of Antibiotics in Critically-Ill Patients

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Critical Care Canada Forum – 1 November 2016
Conflicts of Interest

• None to report
Introduction

• Increasing antibiotic resistance and lack of new antimicrobials makes optimal use of current antibiotics essential

• Interest is growing in alternative antimicrobial dosing strategies that are better aligned with the antimicrobial’s pharmacodynamic properties, and the potential of this approach to improve patient outcomes.

• In particular, continuous or extended infusions of β-lactam antibiotics has been suggested as a way to improve their efficacy
Contents

• Brief Review of Antibiotic Pharmacokinetics and Pharmacodynamics in ICU

• Empiric Data of Continuous vs Intermittent β-lactam Infusions
  – Are higher antibiotic concentrations associated with better outcomes?
  – Do continuous infusions of β-lactam antibiotics lead to
    • higher concentration/MIC ratios?
    • better clinical outcomes?
      – Multicentre BLING II RCT
      – Meta-analysis of RCTs and Cohort Studies
      – Independent Patient Data Meta-Analysis of Blinded RCTs

• Summary and Conclusions
Pharmacokinetics and Pharmacodynamics

- For antibiotic therapy, two parameters are important
  - Concentration of antibiotic in plasma ("pharmacokinetics")
  - Effect of the antibiotic on the bacteria ("pharmacodynamics")
Pharmacokinetics

- Critically ill patients with severe sepsis undergo pathophysiologic changes that may result in different antibiotic concentrations compared to non-critically ill patients
  - Renal failure is common: reduced clearance
    - Increased drug concentration (beneficial)
    - Potentially increased toxicity (harmful)
  - Augmented renal clearance: increased clearance
    - Observational study measuring trough levels β-lactams
      
      | CrCl mL/min | <MIC (42%) | >MIC (58%) |
      |-------------|------------|------------|
      | 188         | 95         |

- For patients with CrCl >130 mL/min 82% <MIC
- Multiple other factors (e.g. protein binding)

Pharmacodynamics and MIC

• MIC is defined as the lowest or minimum antimicrobial concentration that inhibits visible microbial growth in artificial media after a fixed incubation time
  – Growth inhibition not killing
  – Static measure that does not account for fluctuating drug concentrations
  – Concentrations in plasma are often not acceptable proxies for free concentrations at the site of infection.
    • For example, for meropenem, median concentrations achieved in the epithelial lining fluid were only 25% of those observed in the plasma among patients with VAP in one study

• Available data suggest that MIC targets for resistance prevention are generally higher than MIC targets for treatment success.

Pharmacodynamics and MIC

- Certain antibiotics are termed **concentration dependent**
  - their effects correlate best with peak concentration/MIC ratio and/or area under the concentration-time curve/MIC ratio
    - fluoroquinolones, aminoglycosides
- β–lactam antibiotics are termed **time dependent**
  - their effects correlate best with the duration of time that the serum concentration of the antimicrobial is above the MIC of the microorganism.
    - penicillins, cephalopsporins, carbapenems
  - may be more effective as continuous or extended infusions

Time-Dependent $\beta$–Lactams

- $\beta$–lactams work by acylating the $\beta$–lactam–binding proteins
  - This reaction is not instantaneous but takes place over time
  - Consequently drug concentrations do not need to exceed the MIC for the full dosing interval
- Animal and outpatient human data suggest (assumed to be applicable to critically ill patients):

<table>
<thead>
<tr>
<th>Time Duration &gt; MIC</th>
<th>Bacterial Stasis</th>
<th>Maximal bacterial kill</th>
</tr>
</thead>
<tbody>
<tr>
<td>penicillins</td>
<td>~ 30%</td>
<td>~ 50%</td>
</tr>
<tr>
<td>cephalosporins</td>
<td>~ 40%</td>
<td>~ 60-70%</td>
</tr>
<tr>
<td>carbapenems</td>
<td>~ 20%</td>
<td>~ 40%</td>
</tr>
</tbody>
</table>

Time-Dependent β–Lactams

- Simulation suggests similar achievement of 50% time duration >MIC for both continuous and 4h extended infusions (vs 0.5h intermittent infusions)

Clinical Data

• Unclear how clinically applicable this is to critically-ill patients in the ICU
Defined Antibiotic Levels in ICU patients (DALI) Study

• Observational Study
  – 68 ICUs, 361 patients, 8 different β-lactam abx
    • 55% penicillins
    • 38% carbapenems
    • 17% cephalosporins
  – Measured drug concentrations at
    • 50% (midpoint) of the dosing interval
    • 100% of the dosing interval (i.e. trough level)
  – related it to MIC of the bacteria being treated

Ref: Roberts et al. DALI CID 2014; 58:1072
Defined Antibiotic Levels in ICU patients (DALI)

- Observational Study
  - 73% had organism recovered
  - 34% had MIC determined
    - For missing MIC they used highest breakpoint reported (worst case scenario)
  - Did not assess concomitant antibiotics that were used in 62% of infected patients
  - Necessary limitations

Ref: Roberts et al. DALI CID 2014; 58:1072
Defined Antibiotic Levels in ICU patients (DALI) –
High variability in antibiotic concentrations

50% (midpoint) dosing interval

100% (end) [trough] dosing interval.
Defined Antibiotic Levels in ICU patients (DALI) – Similar high variability in drug concentration/MIC

- 50% (midpoint) dosing interval
- 100% (end) [trough] dosing interval

16% of patients did not achieve drug concentration/MIC > 1

40% of patients did not achieve drug concentration/MIC > 1
Defined Antibiotic Levels in ICU (DALI) Study

Used logistic regression to examine the relationship of drug concentration to MIC ratio with positive clinical outcome.

Probability of cure by 50% (midpoint) of dosing interval ratio of drug concentration to MIC in patients with low (black) and high (grey) APACHE II [non-RRT patients]
Defined Antibiotic Levels in ICU (DALI) Study

Used logistic regression to examine the relationship of drug concentration to MIC ratio with positive clinical outcome.

Probability of cure by 50% (midpoint) of dosing interval ratio of drug concentration to MIC in patients with low (black) and high (grey) APACHE II [all patients]
Pilot RCT

• Same research group tried to determine whether continuous infusions vs intermittent boluses leads to increased drug concentration/MIC ratios

Ref: Dulhunty, Roberts et al CID 2013;56(2):236–44
Dulhunty et al Pilot RCT

• RCT (5 ICUs) Included 60 patients with
  – confirmed or presumed infection with organ dysfunction
  – planned or started (<24h) piperacillin-tazobactam, ticarcillin-clavulin, or meropenem
  – Expected ICU stay >48h

– Exclusion criteria
  • CRRT
  • no multi-lumen catheter (dedicated infusion port)
  • allergy to study medications
  • received drug >24h

Ref: Dulhunty et al, CID 2013; 56: 236
Dulhunty et al Pilot RCT

• Randomized
  – Active infusion + placebo bolus or placebo infusion + active bolus (blinded intervention)
    • Pip-tazo, ticar-clav q24h infusions
    • meropenem q8h infusions
  • Plasma trough level prior to bolus dose on day 3 and 4

• Group
  
  Continuous               Intermittent
  Trough  82% (18/22)      29% (6/21)
  Level >MIC               \( p=0.001 \)

Ref: Dulhunty et al, CID 2013; 56: 236
BLING II Multicentre RCT

• RCT
  – Loading dose then continuous vs intermittent (30 minute) infusion
    • piperacillin-tazobactam
    • ticarcillin-clavulan
    • meropenem
  – in severe sepsis
    • suspected or confirmed infection with at least one organ failure

• 432 patients, 25 ICUs

Ref: Dulhunty et al, BLING II Investigators, ANZICS CTG. AJRCCM 2015; 192:1298
BLING II Multicentre RCT

• High Methodologic Quality:
  – Multicentre
  – Allocation concealment (sealed opaque envelopes)
  – Double blind (double dummy)
    • Pilot RCT demonstrated blinding was achieved
  – Enrolled target sample size (no early stopping)
  – Intention to treat analysis
  – Median 12.5h open-label antibiotics prior to study drug
  – Similar treatment duration (median 3.2 vs 3.7d)
    • 66% received blinded study drug >3d
    • 2% did not receive blinded study drug

Dulhunty et al, BLING II Investigators, ANZICS CTG. AJRCCM 2015; 192:1298.
Dulhunty et al, CID 2013; 56: 236.
**BLING II Multicentre RCT**

<table>
<thead>
<tr>
<th></th>
<th>Cont (n=212)</th>
<th>Int (n=220)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>64 (54-72)</td>
<td>65 (53-72)</td>
</tr>
<tr>
<td><strong>Sex, female</strong></td>
<td>39%</td>
<td>39%</td>
</tr>
<tr>
<td><strong>APACHE II</strong></td>
<td>21 (17-26)</td>
<td>20 (16-25)</td>
</tr>
<tr>
<td><strong>Infection Site</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Lung</td>
<td>54%</td>
<td>55%</td>
</tr>
<tr>
<td>– Intraabdominal</td>
<td>25%</td>
<td>26%</td>
</tr>
<tr>
<td>– 1° Bloodstream</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>– Urinary</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Organ Failure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Cardiovascular</td>
<td>73%</td>
<td>74% (Shock)</td>
</tr>
<tr>
<td>– Respiratory</td>
<td>64%</td>
<td>63% (P/F&lt;200)</td>
</tr>
<tr>
<td>– Metabolic Acidosis</td>
<td>32%</td>
<td>32% (pH&lt;7.30)</td>
</tr>
<tr>
<td>– Renal</td>
<td>23%</td>
<td>24% (Cr&gt;1.5×,↓UO)</td>
</tr>
<tr>
<td>– Hematologic</td>
<td>12%</td>
<td>10% (platelets&lt;80)</td>
</tr>
</tbody>
</table>
### BLING II Multicentre RCT

**Study Drug**

<table>
<thead>
<tr>
<th></th>
<th>Cont (n=212)</th>
<th>Int (n=220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pip-Tazo</td>
<td>69%</td>
<td>71%</td>
</tr>
<tr>
<td>Meropenem</td>
<td>30%</td>
<td>27%</td>
</tr>
<tr>
<td>Ticar-Clav</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Change</td>
<td>9%</td>
<td>12% (usually to meropenem)</td>
</tr>
</tbody>
</table>

**Pathogen Isolated**

<table>
<thead>
<tr>
<th></th>
<th>Cont (n=212)</th>
<th>Int (n=220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram +ve</td>
<td>27%</td>
<td>26%</td>
</tr>
<tr>
<td>Gram –ve</td>
<td>73%</td>
<td>72%</td>
</tr>
<tr>
<td>Susceptible</td>
<td>98%</td>
<td>86%</td>
</tr>
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</table>

**Concomitant antibiotics**

<table>
<thead>
<tr>
<th></th>
<th>Cont (n=212)</th>
<th>Int (n=220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycopeptide</td>
<td>36%</td>
<td>31%</td>
</tr>
<tr>
<td>Macrolides</td>
<td>20%</td>
<td>23%</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>11%</td>
<td>15%</td>
</tr>
<tr>
<td>Quinolones</td>
<td>9%</td>
<td>14%</td>
</tr>
</tbody>
</table>
BLING II Multicentre RCT

• Cont (n=212)  Int (n=220)

• Primary Outcome (to 28d)
  – ICU-Free Days 18 (2-24)  20 (3-24)  \( p=0.38 \)

• Survival
  – 90 Day 74%  73%  \( p=0.67 \)
  – ICU 85%  83%  \( p=0.54 \)
  – Hospital 79%  75%  \( p=0.28 \)

• 14d Clinical Cure 52%  50%  \( p=0.56 \)

• Serious AEs 9%  11%  \( p=0.41 \)
BLING II Multicentre RCT

- **Cont** (n=212)  **Int** (n=220)
- Dialysis During Study
  
  26%  27%  \( p=\text{n.s.} \)

- Dialysis may reduce antibiotic clearance and thereby reduce differential effect of continuous vs intermittent dosing.
Meta-Analysis of Studies Comparing Continuous/Extended to Intermittent Infusions

- Restricted to critically-ill patients
  - Other meta-analyses included non-critically ill patient studies
- Searched multiple databases
  - MEDLINE, EMBASE, Cochrane, CINAHL
  - No language restrictions
- Duplicate citation review and data extraction
- Quality assessment of included studies
- Ref: Chant, Leung, Friedrich Crit Care 2013; 17: R279
Meta-Analysis

- 1319 citations → 26 included studies
  - 10 Europe, 11 USA, 3 Asia, 2 Australia
    - Mainly pneumonia (n=12) or any sepsis (n=11)
    - 8 cephalosp, 6 carbapenem, 5 piperacillin, 7 combo or other
  - Generally small, single centre
  - 13 RCTs (782 pts)
    - Risk of bias measures (ITT, allocation concealment) typically not described; only 1 blinded RCT
  - 13 non-randomized cohort studies (2117 pts)
    - 4 prospective
    - 6 concurrent controls
    - 6 with comparable controls

Ref: Chant, Leung, Friedrich Crit Care 2013; 17: R279
Clinical Failure (lack of cure or improvement)
RCTs RR 0.80 (95% CI 0.67-0.95, p=0.01, I²=6%)
Mortality: Decrease Not Statistically Significant

RCTs RR 0.86 (p=0.20) [Incl Cohort RR 0.85 (p=0.03)]; $I^2=0$

| Study or Subgroup | Experimental Events | Control Events | Risk Ratio | Risk Ratio
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Total</td>
<td>Weight</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>1.1.1 RCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wysocki 2001 [15]</td>
<td>21</td>
<td>61</td>
<td>58</td>
<td>8.2%</td>
</tr>
<tr>
<td>Buik 2002 [16]</td>
<td>3</td>
<td>12</td>
<td>6</td>
<td>1.0%</td>
</tr>
<tr>
<td>Georges 2005 [17]</td>
<td>3</td>
<td>26</td>
<td>3</td>
<td>1.0%</td>
</tr>
<tr>
<td>Rafati 2006 [18]</td>
<td>5</td>
<td>20</td>
<td>6</td>
<td>2.2%</td>
</tr>
<tr>
<td>Roberts 2007 [19]</td>
<td>3</td>
<td>29</td>
<td>0</td>
<td>0.3%</td>
</tr>
<tr>
<td>Sakk 2007 [20]</td>
<td>1</td>
<td>10</td>
<td>2</td>
<td>0.5%</td>
</tr>
<tr>
<td>Adembri 2008 [21]</td>
<td>2</td>
<td>8</td>
<td>2</td>
<td>0.8%</td>
</tr>
<tr>
<td>Chytra 2012 [22]</td>
<td>18</td>
<td>120</td>
<td>25</td>
<td>7.1%</td>
</tr>
<tr>
<td>Dulhunty 2013 [29]</td>
<td>2</td>
<td>30</td>
<td>4</td>
<td>0.9%</td>
</tr>
<tr>
<td>Dulhunty/BLING II 2015</td>
<td>32</td>
<td>212</td>
<td>39</td>
<td>10.8%</td>
</tr>
<tr>
<td>Abdul-Azziz/BLISS 2016</td>
<td>13</td>
<td>70</td>
<td>17</td>
<td>5.3%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>598</td>
<td>594</td>
<td>38.2%</td>
<td>0.86 [0.68, 1.08]</td>
</tr>
</tbody>
</table>

Total events 103
Heterogeneity: Tau² = 0.00; Chi² = 3.79, df = 10 (P = 0.96); $I^2 = 0$

Test for overall effect: Z = 1.29 (P = 0.20)

1.1.2 Cohort

| Study or Subgroup | Experimental Events | Control Events | Risk Ratio | Risk Ratio
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Total</td>
<td>Weight</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>Itabashi 2007 [33]</td>
<td>1</td>
<td>18</td>
<td>9</td>
<td>0.6%</td>
</tr>
<tr>
<td>Lodise 2007 [25]</td>
<td>9</td>
<td>102</td>
<td>14</td>
<td>3.6%</td>
</tr>
<tr>
<td>Lorent 2009 [31]</td>
<td>8</td>
<td>37</td>
<td>14</td>
<td>4.0%</td>
</tr>
<tr>
<td>Nicasio 2010 [27]</td>
<td>27</td>
<td>94</td>
<td>26</td>
<td>10.3%</td>
</tr>
<tr>
<td>Dow 2011 [30]</td>
<td>8</td>
<td>67</td>
<td>11</td>
<td>3.2%</td>
</tr>
<tr>
<td>Yost 2011 [28]</td>
<td>15</td>
<td>101</td>
<td>26</td>
<td>6.5%</td>
</tr>
<tr>
<td>Akers 2012 [34]</td>
<td>29</td>
<td>90</td>
<td>17</td>
<td>7.9%</td>
</tr>
<tr>
<td>Lee 2012 [35]</td>
<td>13</td>
<td>68</td>
<td>30</td>
<td>6.7%</td>
</tr>
<tr>
<td>Arnold 2013 [36]</td>
<td>60</td>
<td>261</td>
<td>47</td>
<td>16.0%</td>
</tr>
<tr>
<td>Hsaiy 2013 [37]</td>
<td>7</td>
<td>44</td>
<td>10</td>
<td>3.0%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>882</td>
<td>852</td>
<td>61.8%</td>
<td>0.78 [0.59, 1.03]</td>
</tr>
</tbody>
</table>

Total events 177
Heterogeneity: Tau² = 0.09; Chi² = 17.68, df = 9 (P = 0.04); $I^2 = 49$

Test for overall effect: Z = 1.74 (P = 0.08)

Test for subgroup differences: Chi² = 0.24, df = 1 (P = 0.62), $I^2 = 0$

Test for overall effect: Z = 2.11 (P = 0.03)
By antibiotic:

Pip-Tazo (4/5 Cohort)

Cephalosp. (0/3 Cohort)

Carbapenem (2/4 Cohort)

demonstrated mortality reduction but based mainly on cohort studies
Mortality: **Continuous** vs **Extended Infusions**

<table>
<thead>
<tr>
<th>RR</th>
<th>0.93</th>
<th>0.72</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% CI</td>
<td>0.75-1.14, p=0.47</td>
<td>0.54-0.96, p=0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Total Weight</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wysoki 2008 [15]</td>
<td>21</td>
<td>61</td>
<td>58</td>
<td>9.2%</td>
<td>1.05 [0.63, 1.74]</td>
</tr>
<tr>
<td>Buijk 2002 [16]</td>
<td>3</td>
<td>12</td>
<td>2</td>
<td>1.0%</td>
<td>0.75 [0.17, 3.35]</td>
</tr>
<tr>
<td>Georges 2005 [17]</td>
<td>3</td>
<td>26</td>
<td>34</td>
<td>1.0%</td>
<td>0.82 [0.21, 3.14]</td>
</tr>
<tr>
<td>Ranati 2006 [18]</td>
<td>5</td>
<td>20</td>
<td>25</td>
<td>2.2%</td>
<td>0.88 [0.30, 2.29]</td>
</tr>
<tr>
<td>Roberts 2007 [19]</td>
<td>3</td>
<td>28</td>
<td>29</td>
<td>0.3%</td>
<td>6.77 [0.25, 125.32]</td>
</tr>
<tr>
<td>Sakka 2007 [20]</td>
<td>1</td>
<td>10</td>
<td>11</td>
<td>0.5%</td>
<td>0.50 [0.05, 4.67]</td>
</tr>
<tr>
<td>Adembri 2009 [21]</td>
<td>2</td>
<td>8</td>
<td>2</td>
<td>0.8%</td>
<td>1.00 [0.18, 5.46]</td>
</tr>
<tr>
<td>Loreto 2000 [31]</td>
<td>8</td>
<td>37</td>
<td>45</td>
<td>4.0%</td>
<td>0.71 [0.32, 1.61]</td>
</tr>
<tr>
<td>Akers 2012 [34]</td>
<td>29</td>
<td>90</td>
<td>119</td>
<td>7.9%</td>
<td>1.54 [0.91, 2.68]</td>
</tr>
<tr>
<td>Chytra 2012 [22]</td>
<td>18</td>
<td>120</td>
<td>138</td>
<td>7.1%</td>
<td>0.72 [0.42, 1.25]</td>
</tr>
<tr>
<td>Duhurty 2013 [23]</td>
<td>2</td>
<td>30</td>
<td>32</td>
<td>0.0%</td>
<td>0.50 [0.10, 2.63]</td>
</tr>
<tr>
<td>Duhurby ELLING II 2015</td>
<td>32</td>
<td>212</td>
<td>244</td>
<td>10.8%</td>
<td>0.87 [0.57, 1.34]</td>
</tr>
<tr>
<td>Abdul-AZIZI ELLING 2016</td>
<td>13</td>
<td>70</td>
<td>83</td>
<td>5.3%</td>
<td>0.76 [0.40, 1.45]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>725</strong></td>
<td><strong>721</strong></td>
<td><strong>50.0%</strong></td>
<td><strong>0.93 [0.75, 1.14]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events 140 149
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 8.35, df = 12$ ($p = 0.75$); $R^2 = 0$
Test for overall effect: $Z = 0.73 (p = 0.47)$

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
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<th>Total Events</th>
<th>Total Weight</th>
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<tr>
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<td>18</td>
<td>54</td>
<td>0.6%</td>
<td>0.15 [0.02, 1.07]</td>
</tr>
<tr>
<td>Lodise 2007 [25]</td>
<td>9</td>
<td>102</td>
<td>111</td>
<td>3.6%</td>
<td>0.53 [0.26, 1.28]</td>
</tr>
<tr>
<td>Nicasio 2010 [27]</td>
<td>27</td>
<td>84</td>
<td>111</td>
<td>10.3%</td>
<td>0.82 [0.52, 1.37]</td>
</tr>
<tr>
<td>Dow 2011 [30]</td>
<td>8</td>
<td>67</td>
<td>75</td>
<td>3.2%</td>
<td>0.59 [0.26, 1.36]</td>
</tr>
<tr>
<td>Yosi 2011 [20]</td>
<td>15</td>
<td>181</td>
<td>196</td>
<td>6.5%</td>
<td>0.87 [0.36, 2.19]</td>
</tr>
<tr>
<td>Lee 2012 [35]</td>
<td>13</td>
<td>66</td>
<td>79</td>
<td>4.7%</td>
<td>0.51 [0.25, 0.98]</td>
</tr>
<tr>
<td>Arnold 2013 [36]</td>
<td>60</td>
<td>261</td>
<td>221</td>
<td>18.0%</td>
<td>1.13 [0.64, 1.45]</td>
</tr>
<tr>
<td>Hsaky 2013 [37]</td>
<td>7</td>
<td>44</td>
<td>51</td>
<td>3.0%</td>
<td>0.87 [0.26, 1.59]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>755</strong></td>
<td><strong>725</strong></td>
<td><strong>50.0%</strong></td>
<td><strong>0.72 [0.54, 0.96]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events 140 173
Heterogeneity: $\tau^2 = 0.07$; $\chi^2 = 12.09, df = 7$ ($p = 0.10$); $R^2 = 42$
Test for overall effect: $Z = 2.22 (p = 0.03)$

Total (95% CI) 1480 1446 100.0%
Total events 280 322
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 21.46, df = 20$ ($p = 0.37$); $R^2 = 7$
Test for overall effect: $Z = 2.11 (p = 0.03)$
Test for subgroup differences: $\chi^2 = 1.94, df = 1$ ($p = 0.16$), $R^2 = 48.6$
Meta-Analysis – Summary of Results

• Data from primarily small single-centre RCTs suggest that continuous or extended infusions of antibiotics
  – Reduce clinical failure rates
  – Do not reduce mortality rates
    • Reduced mortality rates only achieve statistical significance if results of higher-risk-of-bias cohort studies are included

• Ref: Chant, Leung, Friedrich Crit Care 2013; 17: R279
Meta-Analysis – Summary of Results

• Subgroup analyses suggest mortality reduction strongest for
  – Piperacillin-tazobactam
  – Carbapenems
  – (Paradoxically) extended rather than continuous infusions

• Driven by the more positive results of the higher-risk-of-bias cohort studies

• Ref: Chant, Leung, Friedrich Crit Care 2013; 17: R279
Individual Patient Data (IPD) Meta-Analysis

• Included only RCTs with blinded outcome assessors
  – Dulhunty 2013 Pilot RCT (n=60)
  – Dulhunty 2015 BLING II (n=432)
  – Abdul-Aziz 2016 BLISS (n=140)

• Hospital Mortality Better
  – 20 vs 26% (RR 0.74, 95% CI 0.56-1.00, p=0.045)

• Clinical Cure not Improved after Adjusting for between-study heterogeneity
  – 55 vs 46% (RR 1.32, 95% CI 0.97-1.80, p=0.07)

Ref: Roberts et al. AJRCCM 2016; 194(6):681-91
Individual Patient Data (IPD) Meta-Analysis

- Greatest benefit in infections with non-fermenting bacteria (pseudomonas, acinetobacter)
  - Tend to have higher MIC’s
    - Continuous infusions are more likely to achieve therapeutic targets for these higher MIC bacteria
- Patients receiving renal replacement therapy did not appear to derive significant benefit
  - Reduced drug clearance hence higher serum antibiotic concentrations making continuous infusions less important in dialysis patients

Ref: Roberts et al. AJRCCM 2016; 194(6):681-91
Summary and Conclusions

• Lack of new antibiotics and increasing resistance increases the importance of using current antibiotics in the most optimum manner possible

• This is particularly important for patients in ICU who are the most vulnerable to infection and are exposed to the most resistant organisms
Summary and Conclusions

• Emerging data is suggestive that continuous or extended infusions of β-lactam antibiotics may improve outcomes though there are no definitively beneficial RCTs

• Conducting efficacy studies in this field is challenging
  – Frequently no infective organisms are cultured
  – Measured MICs of some automated techniques have poor accuracy
  – Relevancy of plasma (rather than tissue) levels is unclear
  – Antibiotic clearance in patients highly variable
    • not routinely measured
  – Confounding effect of concomitant antibiotics
  – Subjectivity of clinical cure in persistently critically-ill patients
    • Objective end point of mortality less directly linked to intervention
Summary and Conclusions

• Given the lack of definitive data what can be done by clinicians at the bedside?
  – Encourage reporting of MICs more regularly
  – Measure and target therapeutic drug levels where possible (vancomycin, aminoglycosides)
  – Given the lack of harm, consider extending infusion durations of β-lactams in select patients with particularly severe infections and/or more resistant bacteria

• given practical difficulties of continuous infusions (dedicated IV access [compatibility], stability) and similarity of effect, extended infusions may be easier to implement than continuous infusions
The End

• Questions?