Therapeutic Drug Monitoring of Beta-Lactam Antibiotics: Does it Lead to “Beta” Outcomes?

Jessica F. Morales, PharmD
PGY2 Infectious Diseases Pharmacy Resident
South Texas Veterans Health Care System, San Antonio, Texas
Division of Pharmacotherapy, The University of Texas at Austin College of Pharmacy
Pharmacotherapy Education and Research Center,
University of Texas Health Science Center San Antonio

October 30, 2015

Learning Objectives:
1. Discuss the necessity of developing new strategies for the treatment of bacterial infections
2. Specify the criteria identifying drugs for which therapeutic drug monitoring would be most useful
3. Describe how pathophysiological changes can alter pharmacokinetic and pharmacodynamic properties
4. Based on a review of the literature, identify patients that may derive the most benefit from therapeutic drug monitoring of beta-lactams
I. Background

A. Infection-related morbidity and mortality\textsuperscript{1,2}
   i. Infections can affect anyone – the young and old, the healthy and the chronically ill
   ii. Infectious diseases account for 43% of the global burden of disease
   iii. Approximately 2 million Americans develop an infection and 90,000 die each year
   iv. Approximately 50% of intensive care unit patients have infection, doubling mortality risk

B. Antibiotic resistance\textsuperscript{2-5}
   i. Antibiotic-resistant bacteria present a serious threat to public health and the economy
   ii. Approximately 2 million illnesses and 23,000 deaths in the United States have been attributed to antibiotic-resistant bacteria

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure1.png}
\caption{Increasing Prevalence of Resistant \textit{Klebsiella pneumoniae} in All Patient Settings\textsuperscript{4,6}}
\end{figure}

C. Bad bugs, no drugs\textsuperscript{7}
   i. Pharmaceutical pipeline for antibiotics has become less productive over time
   ii. Antibiotics not as profitable as medications for chronic medical conditions

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure2.png}
\caption{Number of New Systemic Antibiotics Approved in the United States\textsuperscript{8}}
\end{figure}

*Adapted from Spellberg, et al., \textit{Clinical Infectious Diseases}, May 2004
i. Loss of effective antibiotics and increase in infection-related morbidity and mortality

ii. Centers for Disease Control and Infection proposed following measures to help fight antibiotic resistance:
   a. Prevention of infection and spread of antibiotic resistance
   b. Implementation of surveillance for resistant bacteria
   c. Development of strategies to optimize activity of currently available antibiotics
   d. Facilitation of the development of novel agents and new diagnostic tests

iii. Therapeutic drug monitoring (TDM) proposed as a strategy to optimize pharmacokinetics (PK) and pharmacodynamics (PD) of existing antibiotics
   a. Limitations of standard dosing regimens
      1. Studied in young, healthy volunteers
      2. Many established prior to extensive knowledge of PK/PD of antibiotics
   b. Patient populations in which the PK of drugs has not been fully studied
      1. Critically ill
      2. Obese
      3. Elderly
      4. Cystic fibrosis
      5. Intravenous drug users

II. Therapeutic Drug Monitoring

A. Proposed goals of TDM

   - Increased efficacy
   - Decreased toxicity
   - Decreased antibiotic resistance

   Figure 3. Proposed Goals of TDM

B. Criteria for TDM

   i. Lack of easily measured clinical parameter of efficacy
      a. No clinical parameter available to gauge drug efficacy
      b. Example: blood pressure as a measure of vasopressor efficacy

   ii. Variable pharmacokinetics
      a. Fixed dose results in different concentration-time curves between/within patients
      b. Due to large between-subject differences and/or non-linear PK
      c. Unpredictable relationship between dose and clinical response

   iii. Narrow therapeutic index
      a. Increased risk of toxicity or failure with concentrations outside narrow range
      b. Drug toxicity may lead to hospitalization, irreversible organ damage, or death

   iv. Correlation between serum concentration and response
      a. Response can be efficacy, toxicity, or both

   v. Availability of commercial assay
III. Beta-Lactam Antibiotics

A. Background
i. Most commonly used class of antibiotics
ii. Includes penicillins, cephalosporins, monobactams, and carbapenems

B. Pharmacokinetics
i. Concentration-time profile in serum for a specific drug dose and its absorption, distribution, and elimination
ii. Lower volume of distribution
iii. Eliminated primarily by glomerular filtration and hepatobiliary system
iv. Variable protein binding
v. Only free (non-protein bound) concentration pharmacologically active; serum concentration may not equal concentration at site of infection
vi. Lowest concentration of an antibiotic that inhibits the visible growth of a microorganism is the minimum inhibitory concentration (MIC)

C. Pharmacodynamics
i. Relationship between drug concentration or exposure and effect
ii. Higher the MIC, the less effect a fixed drug exposure will have

D. PK/PD
i. Relationship between drug exposure, organism susceptibility, and host response
ii. Time above the MIC (T>MIC) most closely correlates with efficacy of beta-lactams
iii. Goal of beta-lactam dosing regimens is to optimize duration of drug exposure
iv. Fraction of time (%T>MIC) correlating with efficacy differs between beta lactams

Table 1. Target %T>MIC Parameters for Different Beta-Lactam Agents

<table>
<thead>
<tr>
<th></th>
<th>Bacteriostatic</th>
<th>Bacteriocidal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>30%</td>
<td>50%</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>35-40%</td>
<td>60-70%</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>20%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Figure 4. Bactericidal Activity of Ticarcillin

Figure 5. PK/PD Properties of Beta-Lactams
Some retrospective studies have suggested larger drug exposures are required\textsuperscript{20,21,24}:

i. Microbiological eradication 89% with 100\%T>MIC vs. 0% if below 100\%T>MIC
ii. Clinical cure and microbiological eradication lower if below 100\%T>MIC (33\% and 44\% vs. 82\% and 97\%, $p < .05$)

IV. Patient Populations and Pathophysiological Changes

A. Factors associated with antibiotic concentrations below MIC\textsuperscript{25,26}
   i. Younger age
   ii. Increased creatinine clearance (CrCL)
   iii. High organism MIC

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{pathophysiological_changes.png}
\caption{Pathophysiological Changes and PK Effects in Septic Patients\textsuperscript{8}}
\end{figure}
B. Critically ill patients\textsuperscript{27}
   i. Variable elimination half-life ($t_{1/2}$)
   ii. Variable clearance (CL)
   iii. Increased volume of distribution (Vd)
   iv. Translesional diffusion of antibiotic in burn patients\textsuperscript{28,29}

![Diagram of Endotoxins, Vascular endothelium, Maldistribution of blood flow, Endothelial damage, Increased capillary permeability, Fluid shifts (intravascular → interstitial)]

\textbf{Figure 8. Development of Capillary Leak Syndrome\textsuperscript{9}}

C. Capillary leak syndrome
   i. Bacterial endotoxins stimulate production of endogenous mediators that increase capillary permeability
   ii. Fluid shifts from intravascular space to interstitial space result in increased Vd of drugs

D. Altered protein binding\textsuperscript{30,31}
   i. Albumin responsible for binding of most drugs
   ii. Hypoalbuminemia occurs in \textasciitilde50\% of critically ill patients
      a. Higher levels of unbound drug means more is available for distribution, glomerular filtration, and hepatic clearance
      b. Highly protein-bound antibiotics may be most affected\textsuperscript{32}
         1. Two-fold increases in Vd and CL\textsuperscript{33}
         2. Associated with failure to attain PD targets\textsuperscript{30}

\textbf{Table 2. Variations in Vd and CL of Highly Albumin-bound Antibiotics in Critically Ill Patients\textsuperscript{30}}

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Study Group</th>
<th>No.</th>
<th>APACHE II Score</th>
<th>CrCL (mL/min)</th>
<th>Albumin (g/L)</th>
<th>CrCL (mL/min)</th>
<th>Vd (L/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRIAX</td>
<td>Healthy adults</td>
<td>6</td>
<td>NA</td>
<td>Within reference values</td>
<td>13 ± 2.6</td>
<td>0</td>
<td>0.12 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>Critically ill patients</td>
<td>18</td>
<td>NA</td>
<td>112 ± 29</td>
<td>NA</td>
<td>18 ± 5.5</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Critically ill patients with severe sepsis</td>
<td>11</td>
<td>21.7 ± 3.8</td>
<td>98 ± 50</td>
<td>22.2 ± 6.1</td>
<td>25.8</td>
<td>99</td>
</tr>
<tr>
<td>ERTA</td>
<td>Healthy adults</td>
<td>10</td>
<td>NA</td>
<td>Within reference values</td>
<td>20.2 ± 0.16</td>
<td>0</td>
<td>0.07 ± 0.003</td>
</tr>
<tr>
<td></td>
<td>Critically ill patients with VAP</td>
<td>17</td>
<td>23.1 ± 4.2</td>
<td>94 ± 52</td>
<td>15.9 ±5.7</td>
<td>43.2 ± 23.7</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td>Critically ill patients with severe sepsis</td>
<td>8</td>
<td>8.9 ± 5.1</td>
<td>89 ± 36</td>
<td>26.9 ± 9</td>
<td>200.5 ± 306.9</td>
<td>893</td>
</tr>
</tbody>
</table>

TRIAX, ceftriaxone; ERTA, ertapenem; CrCL, creatinine clearance; Vd, volume of distribution
E. Augmented renal clearance (ARC) \(^{10,25,34}\)
   i. Defined as Cockcroft-Gault estimated CrCL ≥ 130 mL/min
   ii. Renal perfusion often increased secondary to intravenous fluid administration and vasopressor initiation
   iii. Development of ARC rarely considered in critically ill patients
     a. Sensitivity of serum creatinine for identifying ARC is limited, making appropriate dosing in critically ill patients with seemingly normal renal function difficult
     b. At highest risk of developing ARC:
        1. Younger age
        2. Polytrauma patients\(^5\)
        3. Patients with traumatic brain injury\(^36\)
        4. Critically ill postoperative patients\(^37\)

Table 3. PK Parameters PD Target Achievement in Critically Ill Patients Without Renal Dysfunction\(^38\)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>No.</th>
<th>Dose</th>
<th>Vd (L/kg)</th>
<th>CL (mL/min)</th>
<th>(t_{1/2}) (h)</th>
<th>MIC target</th>
<th>PD target achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIP</td>
<td>27</td>
<td>4g q6h</td>
<td>0.38</td>
<td>141</td>
<td>2.58</td>
<td>64</td>
<td>33%T&gt;4xMIC</td>
</tr>
<tr>
<td>TRIAX</td>
<td>54</td>
<td>2g q24h</td>
<td>0.28</td>
<td>14.7</td>
<td>9.6</td>
<td>8</td>
<td>16%T&gt;MIC</td>
</tr>
<tr>
<td>FEP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>2g q12h</td>
<td>0.34</td>
<td>123</td>
<td>3.2</td>
<td>4</td>
<td></td>
<td>77%T&gt;MIC</td>
</tr>
<tr>
<td>19</td>
<td>2g q8h</td>
<td>0.36</td>
<td>88</td>
<td>3.37</td>
<td>32</td>
<td>44%T&gt;2xMIC</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>2g q12h</td>
<td>0.32</td>
<td>134</td>
<td>2.5</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2g q12h</td>
<td>0.47</td>
<td>125</td>
<td>3.42</td>
<td>7</td>
<td>80%T&gt;MIC</td>
<td></td>
</tr>
<tr>
<td>MERO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2g q8h</td>
<td>0.38</td>
<td>157</td>
<td>2.4</td>
<td>-</td>
<td>-</td>
<td>100%T&gt;MIC</td>
</tr>
<tr>
<td>7</td>
<td>2g LD + 3g CI/day</td>
<td>0.37</td>
<td>128</td>
<td>-</td>
<td>-</td>
<td>100%T&gt;MIC</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>1g q8h</td>
<td>0.43</td>
<td>131</td>
<td>2.05</td>
<td>8</td>
<td>57%T&gt;4xMIC</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1g q8h</td>
<td>0.39</td>
<td>191</td>
<td>2.13</td>
<td>0.25-1</td>
<td></td>
<td>100%T&gt;MIC</td>
</tr>
</tbody>
</table>

PIP, piperacillin-tazobactam; TRIAX, ceftriaxone; FEP, cefepime; MERO, meropenem; CI, continuous infusion; LD, loading dose; Vd, volume of distribution; CL, clearance; \(t_{1/2}\), half-life; Cmax, peak serum concentration; AUC, area under the curve; MIC, minimum inhibitory concentration; PD, pharmacodynamic

Figure 9. Development of Augmented Renal Clearance

Figure 10. Effect of Organism MIC on Achievement of PK/PD Parameters with Beta-Lactams
F. Less susceptible pathogens with high MICs
   i. Insufficient dosing is a particular concern for pathogens with a high MIC
   ii. Even with increased doses, attainment of PD targets is unreliable because of time-dependent activity of beta-lactams

V. Alternative strategies

A. Dosing based on estimation of creatinine clearance
   i. Suboptimal in patients with augmented renal function
   ii. Not always reliable in estimating true renal function, particularly in patients with rapidly fluctuating serum creatinine levels, low muscle mass, or who are critically ill

B. Prolonged infusions
   i. Theoretically more likely to attain target PK/PD parameters
   ii. Even prolonged infusions may fail to consistently achieve target exposures
      a. DALI study – percentage not achieving 50%T>MIC
         1. Extended or continuous infusions: 7%
         2. Intermittent dosing: 20%
      b. Double blind, randomized, controlled study
         1. Trough antibiotic concentration samples drawn at steady state
         2. Concentration/MIC ratios not significantly different between continuous infusion and intermittent bolus until 3rd sample
   iii. To date, high-quality, randomized controlled trials to support this practice are lacking
      a. Small sample sizes
      b. Variability in dosing strategies
      c. Patients with low severity of illness and/or highly susceptible pathogens
   iv. Studies suggestive of greatest benefit in:
      a. Critically ill patients with higher severity of illness
      b. Patients with Pseudomonas aeruginosa infections
      c. Infections with pathogens with higher MICs

<table>
<thead>
<tr>
<th>Study Subgroup</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>Summary RR (95% CI)</th>
<th>I²</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>Summary RR (95% CI)</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Studies</td>
<td>19</td>
<td>1620</td>
<td>0.66 (0.53-0.83)</td>
<td>0</td>
<td>19</td>
<td>1546</td>
<td>1.12 (1.03-1.21)</td>
<td>63</td>
</tr>
<tr>
<td>RCTs</td>
<td>10</td>
<td>779</td>
<td>0.83 (0.57-1.21)</td>
<td>0</td>
<td>14</td>
<td>1125</td>
<td>1.05 (0.99-1.12)</td>
<td>0</td>
</tr>
<tr>
<td>Non-RCTs</td>
<td>9</td>
<td>841</td>
<td>0.57 (0.43-0.76)</td>
<td>0</td>
<td>5</td>
<td>421</td>
<td>1.34 (1.02-1.76)</td>
<td>90</td>
</tr>
<tr>
<td>Penicillins</td>
<td>8</td>
<td>974</td>
<td>0.60 (0.45-0.82)</td>
<td>0</td>
<td>6</td>
<td>491</td>
<td>1.08 (0.94-1.25)</td>
<td>60</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>5</td>
<td>191</td>
<td>0.92 (0.52-1.63)</td>
<td>33</td>
<td>9</td>
<td>662</td>
<td>1.11 (0.98-1.25)</td>
<td>65</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>4</td>
<td>274</td>
<td>0.74 (0.42-1.28)</td>
<td>28</td>
<td>3</td>
<td>333</td>
<td>1.16 (0.93-1.46)</td>
<td>83</td>
</tr>
<tr>
<td>Equivalent daily dose</td>
<td>10</td>
<td>813</td>
<td>0.82 (0.56-1.20)</td>
<td>0</td>
<td>10</td>
<td>934</td>
<td>1.22 (1.05-1.43)</td>
<td>75</td>
</tr>
<tr>
<td>APACHE II score ≥15</td>
<td>10</td>
<td>861</td>
<td>0.63 (0.48-0.81)</td>
<td>9</td>
<td>8</td>
<td>663</td>
<td>1.26 (1.06-1.50)</td>
<td>83</td>
</tr>
</tbody>
</table>

CI, confidence interval; RCT, randomized controlled trial; APACHE, Acute Physiology and Chronic Health Evaluation
VI. Therapeutic Drug Monitoring of Beta-Lactams

A. Lack of easily measurable clinical parameter for resolution of infection
   i. Clearly defined clinical parameter guiding dosage adjustments not available
   ii. The presence or absence of clinical response takes days to weeks to appear
   iii. Development of toxicities is often delayed until antibiotic doses accumulate

B. Variable pharmacokinetics\textsuperscript{9,10,25,30,31}
   i. Pathophysiological changes are present in critically ill and burn patient populations
      a. Increased volume of distribution
      b. Prolonged elimination half-life
      c. Decreased, unchanged, or augmented renal clearance
      d. Enhanced elimination due to hypoalbuminemia
   ii. True PK variability between and within patients

C. Narrow therapeutic index
   i. Historically, beta-lactams have had a lower perceived risk for toxicity
   ii. Beta-lactams can lead to dose-dependent adverse effects\textsuperscript{46-48}

D. Correlation between levels and response
   i. Antimicrobial resistance\textsuperscript{49-51}
      a. Drug exposure preventing amplification of mutant subpopulations in vitro
         1. \textit{P. aeruginosa} and varying meropenem doses\textsuperscript{49}
      b. Concentrations below the MIC for more than half the dosing interval (50\%T>MIC)\textsuperscript{51}
   ii. Toxicity
      a. Hepatic or renal impairment may be associated with toxic drug concentrations\textsuperscript{52}
      b. Neurotoxicity has been reported\textsuperscript{46-48}
         1. Encephalopathy, disorientation, hallucinations, agitation, reversible coma
         2. Myoclonus, non-convulsive status epilepticus, ataxia, asterixis

Table 5. Characteristics of cefepime-induced toxicity in a case series\textsuperscript{46}

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>CrCL (mL/min)</th>
<th>Duration of cefepime at time of symptoms</th>
<th>Dose</th>
<th>Cefepime levels (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>82</td>
<td>27</td>
<td>5 days</td>
<td>2 g daily x 3d, then 1 g daily</td>
<td>48.1 (8 h)</td>
</tr>
<tr>
<td>71</td>
<td>15</td>
<td>3 weeks</td>
<td>4 g bid</td>
<td>160 (20 h)</td>
</tr>
<tr>
<td>75</td>
<td>9</td>
<td>4 days</td>
<td>1 g q48h (after dialysis)</td>
<td>73 (48 h)</td>
</tr>
<tr>
<td>84</td>
<td>&lt;20</td>
<td>6 days</td>
<td>2 g daily</td>
<td>74 (12 h)</td>
</tr>
<tr>
<td>49</td>
<td>12</td>
<td>3 days</td>
<td>2 g tid x 3d, then 2 g bid</td>
<td>37.6 (after HD)</td>
</tr>
<tr>
<td>82</td>
<td>20</td>
<td>2 days</td>
<td>1 g daily</td>
<td>67.2 (24 h)</td>
</tr>
<tr>
<td>77</td>
<td>15</td>
<td>54 hours</td>
<td>3 g daily</td>
<td>41 (31 h)</td>
</tr>
<tr>
<td>81</td>
<td>Anuric</td>
<td>NA</td>
<td>2 g twice daily</td>
<td>224 (12 h)</td>
</tr>
<tr>
<td>61</td>
<td>14</td>
<td>NA</td>
<td>500 mg daily, then 2 g daily</td>
<td>60 (24 h)</td>
</tr>
</tbody>
</table>

iii. Efficacy
   a. In vitro and animal data demonstrate %T>MIC predicts efficacy\textsuperscript{14,16,17}
   b. Observational data suggest a relationship between achievement of these target exposures and clinical outcomes\textsuperscript{40,53}
   c. TDM may be of most benefit in critically ill patients, burn patients, patients with \textit{P. aeruginosa} infections and/or pathogens with high MICs

E. Availability of commercial assay to measure levels
   i. No readily available assay for beta-lactam concentrations
   ii. High-performance liquid chromatography (HPLC) assay is used in research setting
   iii. Approximately 1\% and 2\% of sites surveyed in one study performed TDM for piperacillin-tazobactam and meropenem, respectively\textsuperscript{54}
VII. Literature review


---

**Therapeutic drug monitoring of beta-lactams in critically ill patients: proof of concept.**

<table>
<thead>
<tr>
<th>Objective</th>
<th>To evaluate the practicality and utility of beta-lactam TDM in critically ill patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Prospective 11-month study at a 30-bed tertiary referral critical care unit</td>
</tr>
<tr>
<td>Population</td>
<td>236 patients prescribed beta-lactam antibiotic therapy</td>
</tr>
</tbody>
</table>

**Endpoints**
- Treatment outcome
  - Positive: completion of treatment course without change or addition of antibiotics within 48 hours, or de-escalation of therapy
  - Negative: patient death, escalation of therapy, or cessation of antibiotic secondary to an adverse drug reaction

**Methods**
- Drug serum concentrations determined twice weekly
  - Intermittent dosing: trough drawn after at least 4 doses
  - Continuous infusions: level drawn after at least 4 to 5 half-lives
- Unbound concentrations calculated based on percent protein binding
- PK/PD target of 100%fft > 4-5xMIC
  - Dose/frequency increased if concentration < 4-5xMIC
  - Dose/frequency decreased if concentration > 10xMIC
- Eight-hour urinary CrCL calculated for 47 patients at high risk of having augmented renal clearance for correlation with dose adjustments

**Baseline Characteristics**
- Demographics: 59% male, mean age 53.5 ± 18.3 years, mean weight: 85.4 ± 27.7 kg
- Mean SCr: 1.26 ± 1.03 mg/dL
  - Eight-hour urinary CrCL > 150 mL/min in 21 of 47 patients (44.7%)
- Presence of surgical drains: 25.4%

**Results**
- Overall positive treatment outcomes: 206/236 (87.3%)
- Overall treatment failures: 30/236 (12.7%)
  - 14 deaths
  - 15 cases required escalation of antibiotic therapy
- Mean duration of therapy: 8.5 ± 7.0 days

**Need for dose adjustment after first TDM level by antibiotic indication**

<table>
<thead>
<tr>
<th>Indication</th>
<th>No.</th>
<th>Maintained No. (%)</th>
<th>Increased No. (%)</th>
<th>Decreased No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremia</td>
<td>18</td>
<td>2 (11)</td>
<td>13 (72)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>HAP</td>
<td>89</td>
<td>14 (16)</td>
<td>53 (60)</td>
<td>22 (25)</td>
</tr>
<tr>
<td>CAP</td>
<td>47</td>
<td>21 (45)</td>
<td>15 (32)</td>
<td>11 (23)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>17</td>
<td>7 (41)</td>
<td>8 (47)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Wound</td>
<td>10</td>
<td>1 (10)</td>
<td>9 (90)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SSTI</td>
<td>16</td>
<td>5 (31)</td>
<td>8 (50)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Abdominal</td>
<td>28</td>
<td>7 (25)</td>
<td>10 (36)</td>
<td>11 (39)</td>
</tr>
<tr>
<td>Neutropenic</td>
<td>4</td>
<td>3 (75)</td>
<td>1 (25)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Urosepsis</td>
<td>7</td>
<td>1 (14)</td>
<td>2 (29)</td>
<td>4 (57)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>236</strong></td>
<td><strong>61 (25.8)</strong></td>
<td><strong>119 (50.4)</strong></td>
<td><strong>56 (23.7)</strong></td>
</tr>
</tbody>
</table>

HAP, hospital-acquired pneumonia; CAP, community-acquired pneumonia; SSTI, skin-and-soft-tissue infection
Mortality rate based on achievement of target at initial TDM point

<table>
<thead>
<tr>
<th></th>
<th>Subtherapeutic</th>
<th>Therapeutic</th>
<th>Supratherapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>3.3%</td>
<td>8.2%</td>
<td>9.3%</td>
</tr>
</tbody>
</table>

- Only ↑ APACHE II scores predictive of negative treatment outcome
- Only ↑ APACHE II scores and ↑ serum creatinine predictive of mortality
- At first TDM:
  - Surgical drains: 61.5% required dose increase, 17.3% required dose decrease
  - Renal dysfunction: 80% with concentrations >10xMIC
- Documented ADRs: 1 of 8 patients had antibiotic concentration likely to be associated with toxicity (PIP 137 mg/L; cholestasis)

Strengths
- Inclusion of patients with CVVHD, organ dysfunction, all antibiotic indications
- Many beta-lactam antibiotics included
- Parameters for dose adjustment provided

Weaknesses
- Low incidence of multidrug resistant organisms at study site
- Aggressive PK/PD target of 100%T>4-5xMIC
- Unbound concentrations calculated rather than measured
- Twice-weekly frequency of TDM; only 21.6% of patients had second TDM

Take Home Points
- 74% of patients required dosage adjustments at initial TDM to achieve PK/PD target
- 100% T>4-5xMIC is aggressive and difficult to achieve with standard doses
- CrCL measurements were not always predictive of need for dose adjustment
- Antibiotic concentrations were not found to be predictive of mortality; however, effect may have been blunted by the use of an aggressive PD target and a lower baseline APACHE II score in patients with subtherapeutic concentrations
- Increased empiric doses for patients with surgical drains and/or augmented renal clearance could be considered

Need for dose adjustment after first TDM level by antibiotic

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>No.</th>
<th>Initiation Dose</th>
<th>Same No. (%)</th>
<th>Increased No. (%)</th>
<th>Decreased No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIP</td>
<td>116</td>
<td>4.5 g q6h</td>
<td>27 (23)</td>
<td>57 (49)</td>
<td>32 (28)</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>4</td>
<td>2 g q6h</td>
<td>0 (0)</td>
<td>1 (25)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>51</td>
<td>1 g q8h</td>
<td>8 (16)</td>
<td>29 (57)</td>
<td>14 (27)</td>
</tr>
<tr>
<td>PCN G</td>
<td>9</td>
<td>2.4 g q4h</td>
<td>3 (33)</td>
<td>3 (33)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>6</td>
<td>1 g q8h</td>
<td>0 (0)</td>
<td>6 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>33</td>
<td>1 g q12h</td>
<td>22 (67)</td>
<td>7 (21)</td>
<td>4 (12)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>236</strong></td>
<td>-</td>
<td><strong>61 (25.8)</strong></td>
<td><strong>119 (50.4)</strong></td>
<td><strong>56 (23.7)</strong></td>
</tr>
</tbody>
</table>

PIP, piperacillin-tazobactam; PCN, penicillin

PIPMortality rate based on achievement of target at initial TDM point
Objective To assess the value of TDM for ceftazidime in critically ill patients

Design Prospective multicenter study from 2005 to 2008

Population 92 critically ill non-dialyzed patients receiving ceftazidime as a continuous infusion

Endpoints Achievement of ceftazidime concentration 40±10 mg/L and concentration/MIC ratio ≥5

Methods
- Initial 2 g loading dose followed by continuous infusion of 2 to 6 g/day
- Serum assays obtained at 36-48 hours using agar plate diffusion method
- Target concentration ≥40 ± 10 mg/L or >5xMIC when pathogen isolated

Baseline Characteristics
- Demographics: 70% male, mean age 66 yo (20-94), mean weight: 73 kg (33-122)
- Mean CrCL: 93.5 mL/min (14-258 mL/min)
  - CrCL >30 mL/min: 71/92 (77.2%)
  - CrCL ≤30 mL/min: 21/92 (22.8%)
- Antibiotic indication:
  - Respiratory tract infections 52/92 (56.5%)
  - Urinary tract infections 10/92 (10.9%)
  - Septicemia 8/92 (8.7%)
  - Cutaneous infections 8/92 (8.7%)
  - Abdominal infections 5/92 (5.4%)
  - Other infection 9/92 (9.8%)
- Documented infection: 69/92 (66.3%)
- MICs obtained: 51/92 (55%)
  - P. aeruginosa 41/51 (80.4%)
  - Enterobacteriaceae 8/51 (15.7%)
  - Stenotrophomonas maltophilia 1/51 (2%)
  - Chryseomonas 1/51 (2%)

Results
- Mean CAZ concentration: 46.9 mg/L
- No local or systemic ADRs reported

Concentration-to-MIC Ratios for Subset of Patients with Organism MICs (N= 51)

<table>
<thead>
<tr>
<th>Concentration/MIC Ratio</th>
<th>&lt; 5</th>
<th>≥5</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/51 (15.7%)(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>43/51 (84.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) 6/8 patients had MICs ≥8, antibiotic was changed; 2/8 patients required dose increases

Distribution of ceftazidime concentrations in patients at 36-48 hours
Demographics of patients stratified by ceftazidime concentration

<table>
<thead>
<tr>
<th>Concentration (mg/L)</th>
<th>No. (%)</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Dose (g/24h)</th>
<th>CrCL (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>34 (37)</td>
<td>59.5</td>
<td>68</td>
<td>4</td>
<td>103</td>
</tr>
<tr>
<td>30-50</td>
<td>33 (36)</td>
<td>70</td>
<td>70</td>
<td>6</td>
<td>74</td>
</tr>
<tr>
<td>&gt;50</td>
<td>25 (27)</td>
<td>76</td>
<td>81</td>
<td>4</td>
<td>51</td>
</tr>
</tbody>
</table>

Median values shown

Strengths
- Broad range of infectious diseases treated with ceftazidime included
- Descriptive data on ceftazidime concentration ranges achieved provided
- Target concentration 40 mg/L extrapolated from ceftazidime susceptibility breakpoint of 8 mg/L and maximal cephalosporin activity reported at concentrations ≥5xMIC

Weaknesses
- Hemodialysis patients excluded
- Findings limited to ceftazidime and patients with gram-negative infections
- Use of agar plate diffusion method as serum assay
- No protocol for dosage adjustment and no information provided on dose adjustment
- Primary focus on target attainment, no objective clinical outcomes data

Take Home Points
- Significant degree of variability in ceftazidime concentrations across patients
- Good proportion of patients either at risk for subtherapeutic concentrations despite normal renal function or with high concentrations at risk for inducing toxicity
- No ADRs were noted to occur despite high levels of ceftazidime, however toxicity is more likely to occur with prolonged high concentrations
- TDM is likely necessary to achieve ceftazidime concentrations within a target range, but correlation between target attainment and clinical outcomes was not studied

Therapeutic drug monitoring of beta-lactam antibiotics in burns patients – a one-year prospective study.

Objective
To evaluate the utility of a beta-lactam TDM program in a cohort of burn injury patients

Design
Prospective, 12-month single-center study at a tertiary referral burns center

Population
50 patients treated with beta-lactam antibiotics on admission to the burns unit

Endpoints
- Primary: rate of achievement of 100%T>MIC
- Secondary: rate of achievement of 100%T≥4xMIC
- Treatment outcomes:
  - Positive: completion of treatment course without change/addition of antibiotics
  - Negative: any change in antibiotic therapy or development of resistant infection

Methods
- Flucloxacillin, dicloxacillin, penicillin G, piperacillin-tazobactam, ampicillin, meropenem, ceftriaxone
- Drug concentrations determined by HPLC
- Trough levels drawn at every dosing interval after steady state (≥4 doses)
- Unbound concentrations calculated based on percent protein binding
- Administration frequency rather than dose was adjusted if necessary, up to administration of an extended infusion over 50% of dosing interval

Baseline Characteristics
- Demographics: 82% male, mean age: 49 ± 16 yo
- Mean % total body surface area burn: 17 ± 13%
- Mean serum creatinine concentration: 97 ± 0.23 mg/dL
- Antibiotic indication:
  - Skin-and-soft-tissue infection (SSTI): 44/50 (88%)
  - Urinary tract infection (UTI): 1/50 (2%)

Results
- Achieved a positive clinical outcome: 100%
- Duration of treatment:
  - Patients who achieved trough concentration >MIC: 4.2 ± 1.1 days
  - Patients who did not achieve trough concentration >MIC: 5.3±2.3 days (p=0.03)
### TDM results and MICs by beta-lactam antibiotic prescribed

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Initial Dose</th>
<th>No. of patients</th>
<th>Trough &lt;MIC</th>
<th>100% T&gt;MIC</th>
<th>100% T&gt;4xMIC</th>
<th>MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flucloxacillin</td>
<td>2 g q6h</td>
<td>24 (48%)</td>
<td>12 (50%)</td>
<td>8 (34%)</td>
<td>4 (16%)</td>
<td>2</td>
</tr>
<tr>
<td>Dicloxacillin</td>
<td>2 g q6h</td>
<td>8 (16%)</td>
<td>6 (75%)</td>
<td>0 (0%)</td>
<td>2 (25%)</td>
<td>2</td>
</tr>
<tr>
<td>PCN G</td>
<td>2 g q6h</td>
<td>8 (16%)</td>
<td>5 (63%)</td>
<td>2 (25%)</td>
<td>1 (12%)</td>
<td>0.25</td>
</tr>
<tr>
<td>PIP</td>
<td>4.5 g q6h</td>
<td>6 (16%)</td>
<td>4 (66%)</td>
<td>0 (0%)</td>
<td>2 (34%)</td>
<td>2</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>2 g q6h</td>
<td>2 (4%)</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td>0 (0%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1 g q8h</td>
<td>1 (2%)</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1 g q12h</td>
<td>1 (2%)</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>50 (100%)</strong></td>
<td><strong>30 (60%)</strong></td>
<td><strong>11 (22%)</strong></td>
<td><strong>9 (18%)</strong></td>
<td><strong>-</strong></td>
</tr>
</tbody>
</table>

PCN, penicillin; PIP, piperacillin-tazobactam

### Variation in PIP concentrations in relation to MICs

#### Strengths
- Many beta-lactam antibiotics included
- Frequency of TDM performed at every dosing interval

#### Weaknesses
- Small sample size
- Use of aggressive PD targets of 100% T>MIC and 100% T>4xMIC
- Findings limited to burns patients predominantly with SSTIs
- Unbound concentrations calculated based on antibiotics’ percentage protein binding determine in non-burns populations
- Distribution of concentrations stratified by renal function not provided

#### Take Home Points
- Significant variability in antibiotic concentrations exists in burn patients
- Regardless of initial low or therapeutic concentrations of antibiotics, 100% of patients achieved a positive clinical outcome overall; however, all patients initially not at target did achieve 100% T>MIC after the one subsequent dose adjustment
- Only 18% of patients overall achieved the higher target 100% T>4xMIC
- Patients achieving the 100% T>MIC had shorter durations of therapy compared to those that didn’t
DALI: Defining antibiotic levels in intensive care unit patients: Are current β-lactam antibiotic doses sufficient for critically ill patients?

**Objective**
To determine whether standard beta-lactam antibiotic dosing in critically ill patients achieves concentrations associated with maximal beta-lactam activity and correlate antibiotic concentrations to patient outcomes.

**Design**
Prospective, multinational, pharmacokinetic point-prevalence study.

**Population**
361 critically ill evaluable patients in 68 ICUs across 10 countries.

**Endpoints**
- Rate of achievement of target concentrations at 50%T>MIC and 100%T>MIC.
- Clinical outcome:
  - Positive: completion of treatment course without change or addition of antibiotics.
  - Negative: Any clinical outcome other than positive clinical outcome.

**Methods**
- Concentrations determined at 50% and 100% of dosing interval by HPLC.
- When no pathogen isolated, highest MIC considered susceptible was used.
- De-escalation permitted but excluded from clinical outcome analysis.

**Baseline Characteristics**
- Demographics: 65% male, mean age 61 years (IQR, 48-73 years).
- Median APACHE II score: 18 (IQR, 14-24).
- Median SOFA score: 5 (IQR, 2-9).
- Antibiotic indication:
  - 248/361 (68.7%) treatment of infection.
    - Primarily lung infections (41%) and intra-abdominal infections (14%).
    - 67% intermittent dosing and 33% extended or continuous infusion.
  - 113/361 (31.3%) prophylaxis.
- Beta-lactam monotherapy: 67/361 (18.6%).

**Results**
- Treated for infection: 248/361 (68.7%).
  - Positive clinical outcome: 58.1%.
  - Bacterial pathogen isolated: 72.9%.
    - *P. aeruginosa*: 18%, median MIC 8 mg/L (IQR, 2-16).
    - *Escherichia coli*: 16%, median MIC 4 mg/L (IQR, 1-16).
  - Did not achieve 50%T>MIC: 16%.
    - Extended or continuous infusions: 7%.
    - Intermittent dosing: 20%.
    - 32% less likely to have positive clinical outcome, 95% CI, 0.52-0.91.

**Dosing and achievement of PK/PD target by beta-lactam antibiotic**
% unless otherwise specified.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AMOX</th>
<th>AMP</th>
<th>FAZ</th>
<th>FEP</th>
<th>TRIAX</th>
<th>DOR</th>
<th>PIP</th>
<th>MER</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>24h dose, g</td>
<td>N=71</td>
<td>N=18</td>
<td>N=14</td>
<td>N=14</td>
<td>N=33</td>
<td>N=13</td>
<td>N=109</td>
<td>N=89</td>
<td>N=361</td>
</tr>
<tr>
<td>50%T&gt;MIC</td>
<td>52.1</td>
<td>55.6</td>
<td>100</td>
<td>78.6</td>
<td>97</td>
<td>100</td>
<td>80.6</td>
<td>95</td>
<td>78.9</td>
</tr>
<tr>
<td>50%T&gt;4xMIC</td>
<td>16.9</td>
<td>27.8</td>
<td>50</td>
<td>50</td>
<td>93.9</td>
<td>69.2</td>
<td>48.9</td>
<td>68.8</td>
<td>48.9</td>
</tr>
<tr>
<td>100%T&gt;MIC</td>
<td>18.3</td>
<td>33.3</td>
<td>78.6</td>
<td>78.6</td>
<td>93.9</td>
<td>76.9</td>
<td>67</td>
<td>69.7</td>
<td>60.4</td>
</tr>
<tr>
<td>100%T&gt;4xMIC</td>
<td>11.3</td>
<td>22.2</td>
<td>14.3</td>
<td>71.4</td>
<td>87.9</td>
<td>30.8</td>
<td>30.3</td>
<td>41.6</td>
<td>35</td>
</tr>
</tbody>
</table>

- AMOX, amoxicillin-clavulanate; AMP, ampicillin; FAZ, cefazolin; FEP, cefepime; TRIAX, ceftriaxone; PIP, piperacillin-tazobactam; MER, meropenem.

**Multivariate regression results of clinical outcome** (N=220)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>50% T&gt;MIC</th>
<th></th>
<th>100%T&gt;MIC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P</td>
<td>OR</td>
</tr>
<tr>
<td>APACHE II Score</td>
<td>0.94</td>
<td>0.92-0.96</td>
<td>&lt;.001</td>
<td>0.94</td>
</tr>
<tr>
<td>SOFA Score</td>
<td>0.97</td>
<td>0.94-1.00</td>
<td>0.53</td>
<td>0.97</td>
</tr>
<tr>
<td>50%T&gt;MIC</td>
<td>1.03</td>
<td>1.01-1.04</td>
<td>0.001</td>
<td>-</td>
</tr>
<tr>
<td>100%T&gt;MIC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.02</td>
</tr>
</tbody>
</table>

Patients receiving renal replacement therapy excluded from analysis.
- 30-day mortality rate: 21.9%
- Total infection-related mortality rate: 8.9%
- Higher PK/PD ratios associated with a higher likelihood of a positive clinical outcome
  - 50%T>MIC: OR 1.02; 95% CI, 1.01-1.04
  - 100%T>MIC: OR 1.56; 95% CI, 1.15-2.13
- The probability of achieving a positive clinical outcome in patients with bloodstream infections (n= 24) was significantly correlated with increasing concentrations at 50%T>MIC (OR 1.13; 95% CI, 1.07-1.19)
- Patients with a pathogen with an MIC ≤ 2 mg/L were more likely to achieve a positive clinical outcome (OR 2.27; 95% CI, 1.79-2.87)

### Strengths
- Large sample size
- Severity of illness provided via APACHE II scores and SOFA scores
- Correlated attainment of PK/PD target parameters with clinical outcomes
- Measured unbound plasma concentration of highly-protein bound antibiotics

### Weaknesses
- Point-prevalence study, no dose adjustment based on levels
- PK/PD ratios based on assumptions of worst-case scenario MICs in majority (66%) of patients with an isolated pathogen; only 34% of patients with pathogen MIC

### Take Home Points
- Achievement of PK/PD targets for beta-lactams is inconsistent with standard doses
- The use of prolonged infusions did not guarantee achievement of PK/PD parameters; 7% of patients treated for infection did not achieve concentrations above the MIC
- Higher PK/PD indices of 50%T>MIC and 100%T>MIC (but not ≥4xMIC) were significantly associated with positive clinical outcome
- Patients with bloodstream infections demonstrated an increased probability of achieving a positive clinical outcome with increasing 50%T>MIC ratios
- Patients with pathogens with MIC ≤ 2 mg/L were more likely to achieve a positive clinical outcome

### VIII. Summary

#### A. Background
  i. Antibiotic-resistant bacteria present an ongoing threat and production of novel antibiotics may not be enough to mitigate infection-related morbidity and mortality
  ii. Ensuring appropriate dosing of beta-lactams that is targeted to PK/PD parameters associated with efficacy could optimize their antibacterial activity

#### B. PK/PD variability
  i. Pathophysiological changes leading to alterations in PK/PD parameters have been demonstrated in various patient populations, particularly critically ill patients
  ii. Standard dosing regimens and even prolonged infusions of beta-lactams may fail to consistently achieve target PK/PD parameters in these patients
  iii. Other patient populations with data demonstrating altered PK include obese, elderly, cystic fibrosis, intravenous drug users, febrile neutropenia patients

#### C. Therapeutic Drug Monitoring
  i. TDM is an attractive strategy to help ensure attainment of target PK/PD parameters
  ii. The impact of TDM on clinical outcomes remains to be definitively established

#### D. Clinical data
  i. Current studies relatively small and limited by heterogeneous patient populations and varying target PK/PD parameters
  ii. Studies suggestive of benefit in critically ill patients, bloodstream infections, *P. aeruginosa* infections, and infections caused by pathogens with high MICs
E. Obstacles to widespread implementation of beta-lactam TDM
   i. Absence of a prospective randomized, controlled trial demonstrating benefit
   ii. Chromatography-based assay used to measure beta-lactam concentrations
       a. Turnaround time (6-24 h) relatively longer than for other techniques
       b. Costs associated with equipment, skilled operators, 24/7 availability
   iii. Demonstration of changes such as reduced duration of therapy or patient length of stay is needed to mitigate or negate cost burden associated with TDM
   iv. Establishment of a collaborative approach between clinicians and the laboratory and development of a protocol for sampling and dose modification is strongly recommended

IX. Conclusion and Recommendations

A. Conclusion
   i. Data for TDM of beta-lactams is still very preliminary
   ii. Current studies are small and have many limitations
   iii. Evidence to support beta-lactam TDM thus far remains circumstantial, but logical
       a. Increased attainment of target PK/PD parameters that are associated with beta-lactam efficacy lead to increased likelihood of positive outcome
       b. TDM demonstrated to increase likelihood of attaining target parameters
       c. Therefore, TDM likely increases the likelihood of achieving a positive outcome, but a large randomized controlled trial is needed to test this hypothesis

B. Benefits of beta-lactam TDM
   i. Populations with highly varied and unpredictable pharmacokinetics
      a. Critically ill patients
      b. Burn patients
   ii. With risk factors for augmented renal clearance
      a. Younger age
      b. Postoperative patients
      c. Septic patients
      d. Major trauma patients
   iii. Patients with severe renal dysfunction
   iv. Infections due to multidrug-resistant or high-MIC pathogens
   v. Infections caused by *P. aeruginosa*

C. Recommendations
   i. Pending results of a large randomized controlled trial, it is reasonable to limit TDM to situations in which it would be extremely useful to know concentrations of beta-lactams
      a. Serious infections with multidrug-resistant or high-MIC pathogens
      b. Patients at high risk of morbidity/mortality not improving on antibiotic regimens considered to be appropriately dosed
      c. Patients suspected to be suffering from dose-related beta-lactam toxicity (e.g. neurotoxicity)
References


## Objective
To evaluate the benefit of piperacillin TDM in critically ill patients

## Design
Prospective, observational 11-month study at a single intensive care unit

## Population
24 critically ill patients with evidence of bacterial sepsis

## Endpoints
- Rate of achievement of serum piperacillin concentrations >4xMIC
- Incidence of convulsions, changes in WBC, changes in CrCL, cutaneous intolerance

## Methods
- Initial 66 mg/kg IV bolus followed by continuous infusion (CI) at 200 mg/kg/24 h
- Serum concentrations drawn 1.5 hours post-bolus dose, then daily at steady state
- Target concentration >4xMIC to ≤150 mg/L
  - Dose increased when ≤4xMIC
  - Dose decreased when >150 mg/L

## Baseline Characteristics
- Demographics: 92% male, mean age 62.5 years, mean weight 78.8 kg
- CrCL: ≤30 mL/min 7/22 (29%)
- Antibiotic indications: HAP or cellulitis 22/24 (92%)
- Documented infections: 9/24 (38%)
  - *P. aeruginosa, Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, MRSA, Enterobacter aerogenes*
  - MIC mean (range): 7.6 ± 5.1 mg/L (4-16 mg/L)

## Results
- Mean duration of therapy: 9 ± 5.2 days (3-20 days)

### Distribution of Piperacillin-Tazobactam Concentrations

<table>
<thead>
<tr>
<th></th>
<th>≤4xMIC</th>
<th>&gt;4xMIC and ≤150 mg/L</th>
<th>&gt;150 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At initial TDM point</td>
<td>PIP Concentration</td>
<td>8/24 (33)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T&gt;4xMIC and ≤150 mg/L</td>
<td>12/24 (50)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;150 mg/L</td>
<td>4/24 (17)</td>
<td></td>
</tr>
<tr>
<td>After 1st dosage adjustment</td>
<td>PIP Concentration</td>
<td>6/24 (25)b,c,d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T&gt;4xMIC and ≤150 mg/L</td>
<td>18/24 (75)e</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;150 mg/L</td>
<td>0/24 (0)</td>
<td></td>
</tr>
</tbody>
</table>

### Notes:
- PIP, piperacillin-tazobactam
- a All with baseline severe renal dysfunction; dose subsequently reduced, no ADRs observed
- b Mean %T>4xMIC before and after adjustment: 7.1±5.9% vs 27.3±8.6% (p=0.03)
- c Concentrations >4xMIC never achieved despite multiple dosage adjustments up to 18g PIP/day
- d 5/6 (83%) with extensive cellulitis
- e 50% before adjustment vs 75% after adjustment (p<0.006)

## Strengths
- Initial dosing and dosing adjustments of piperacillin-tazobactam provided
- Good proportion of patients with severe renal dysfunction included (29%)
- Daily frequency of TDM
- Highest MIC considered susceptible used for patients without an isolated pathogen
- Collected information on adverse drug reactions

## Weaknesses
- Small sample size
- Pathogen isolated in only 38% of patients, data on isolated pathogens not reported
- Predominantly included patients with HAP and cellulitis
- Patients’ severity of illness unclear; ‘bacterial sepsis’ undefined
- Determination of ‘toxicity threshold’ of 150 mg/L based on ‘personal data’
- Primary focus on target attainment, no objective clinical outcomes data

## Take Home Points
- Patients with renal dysfunction are at high risk of high serum piperacillin-tazobactam concentrations despite dosage adjustment for calculated CrCL
- TDM implementation resulted in a significantly higher proportion of patients achieving the target PIP concentration >4xMIC (p=0.03)