Application of Pharmacokinetic and Pharmacodynamic Principles in Antimicrobial Stewardship

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Disclosures

• Serves on the advisory board and speaker’s bureau for Allergan and advisory board for Cubist (Merck).
Learning Objectives

• At the end of this lecture, the learner will be able to:
  – Classify antibiotics based upon pharmacodynamic efficacy characteristics
  – Devise 3 examples of dose optimization initiatives based on PK/PD principles
  – Design and defend a beta-lactam dosing protocol utilizing extended infusion
Seven Steps to Preserve the Miracle of Antibiotics

• Establish a US database for antibiotic use and resistance comparable to the EU
• Restrict use of antibiotics in agriculture
• Prevent selected nosocomial infections
• Aggressively promote antimicrobial stewardship
• Promote use of new diagnostics with emphasis on point-of-care molecular methods
• Reduce FDA antibiotic barrier
• Facilitate public-private partnerships for antibiotic development

Antimicrobial Stewardship

• Primary goal
  – To optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, selection of pathogenic organisms, and emergence of resistance
  – Includes appropriate antibiotic selection, dosing, route, and duration of therapy → judicious use

• Secondary goal
  – To reduce healthcare costs without adversely impacting quality of care

Antimicrobial Stewardship
Core Strategies

• Core strategies
  – Prospective audit of antimicrobial use with direct feedback to the prescriber
  – Formulary restriction and preauthorization

• Additional components
  – Education
  – Evidence-based practice guidelines/clinical pathways
  – Streamlining or de-escalation of therapy
  – Dose optimization based on PK/PD
  – Parenteral to oral conversion

# Pharmacodynamic Properties of Different Antibacterial Classes

<table>
<thead>
<tr>
<th>Drug/Class</th>
<th>Bactericidal Activity</th>
<th>PAE (Gram-negatives)</th>
<th>PD Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams</td>
<td>Time-dependent (<strong>concentration-dependent</strong> up to 4xMIC)</td>
<td>Little to none (exception: carbapenems)</td>
<td>$fT&gt;MIC$</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Concentration-dependent</td>
<td>Yes</td>
<td>AUC/MIC/Peak/MIC</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Concentration-dependent</td>
<td>Yes</td>
<td>Peak/MIC</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Time-dependent</td>
<td>Yes</td>
<td>AUC/MIC</td>
</tr>
</tbody>
</table>

**β-Lactam Antibiotics**

- Commonly recommended PK/PD targets
  - Carbapenem – $fT>MIC \geq 40\%$
  - Penicillins – $fT>MIC \geq 50\%$
  - Cephalosporins – $fT>MIC \geq 60\%$
  - Aztreonam – $fT>MIC \geq 50$-$60\%$

- Other “proposed” or “evaluated” targets
  - $fT>MIC \geq 100\%$
  - $fT>4xMIC \geq 50\%$
  - $fT>4xMIC \geq 100\%$ (Cmin/MIC $\geq 4$)
Clinical Pharmacodynamics of β-Lactams in Different Patient Populations

• Cefepime, Ceftazidime
  – VAP: $fT>MIC > 53\%$ (microbiologic success)$^1$

• Cefepime
  – Gram-negative infections: $T>4.3\times MIC$ (83-95% for microbiologic success of 80-90%)$^2$
    – $P. aeruginosa$: $fT>MIC > 60\%$ (microbiologic success)$^3$

• Meropenem
  – LRTI: $fT>MIC > 54\%, fCmin/MIC > 5$ (microbiologic success)$^4$
  – FN with bacteremia: $T>MIC 83\%$ (clinical response)$^5$

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Goal of Dosing β-Lactam Antibiotics

• Ensure adequate PD exposures by maximizing or optimizing $fT>MIC$
• Why not use current FDA-approved doses?
  – Decreased susceptibility for many nosocomial pathogens
  – Work-horse agents (pip/tazo, cefepime, meropenem) FDA-approved prior to clinical application of PK/PD principles
  – Limited number of dosing regimens studied for each approved indication
• “Therapeutically equivalent” if $fT>MIC$ for alternative regimen $\approx fT>MIC$ for FDA-approved regimen (surrogate marker)
Strategies to Optimize PD Exposures for β-Lactams

• Increase dose, same interval
  – 0.5 g q8h vs. 1 g q8h

• Same dose, shorter interval
  – 1 g q12h vs. 1 g q6h

• Prolonged infusions
  – Infuse dose over 3-4 hours

• Continuous infusion
  – Stability issues
  – Need dedicated IV line
  – Ideal concentration/MIC ratio? ≥ 4xMIC?
Increase Dose, Same Interval

- 500 mg q8h
- 1 g q8h

Concentration (mg/L)

Time (hours)
Same Dose, Shorter Interval

Graph showing concentration over time for two different dosing intervals: 1 g q12h (every 12 hours) and 1 g q6h (every 6 hours). The graph compares the concentration levels, with the q12h dose resulting in lower peaks and the q6h dose showing higher peaks and shorter half-lives.
Same Dose, Prolonged Infusion

- 1 g q8h (0.5 h)
- 1 g q8h (4 h)
National Survey on Continuous and Extended Infusions of Antibiotics

* Random sample of 1,000 acute care hospitals

Pharmacokinetics of Piperacillin, with Tazobactam, in Hospitalized Patients

- Patients received 4.5 g q8h (4 h)
- Free concentrations (PB 30%)
- CLcr 83 ± 42 ml/min (23-148)

Pharmacokinetics of Piperacillin, with Tazobactam, in Hospitalized Patients

Patients received 4.5 g q8h, infused over 4 h
Free concentrations (PB 30%)

Probability of Target Attainment of Piperacillin in Hospitalized Patients

PD target: $fT > \text{MIC} \geq 50%$

Pharmacokinetics of PI Cefepime in Hospitalized Patients

Patients received 1 g q8h (4 h)
Free concentrations (PB 20%)
CLcr 86 ± 31 ml/min (50-137)

Pharmacokinetics of PI Cefepime in Hospitalized Patients

Patients received 1 g q8h, infused over 4 h
Free concentrations (PB 20%)

Probability of Target Attainment of Cefepime in Hospitalized Patients

PTA (%) vs MIC (mg/L)

- 1 g q8h (4 h infusion)
- 2 g q8h (4 h infusion)
- 1 q q12h (4 h infusion)
- 2 g q12h (4 h infusion)
- 1 g q6h (3 h infusion)
- 2 g q6h (3 h infusion)

PD target: fT>MIC ≥ 60%

Cumulative Fraction of Response of Cefepime in Hospitalized Patients

<table>
<thead>
<tr>
<th>Regimen</th>
<th>E. coli</th>
<th>K. pneumoniae</th>
<th>P. aeruginosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 g q12h (4 h)</td>
<td>96.9</td>
<td>88.6</td>
<td>73.8</td>
</tr>
<tr>
<td>2 g q12h (4 h)</td>
<td>97.8</td>
<td>91.1</td>
<td>87.1</td>
</tr>
<tr>
<td>1 g q8h (4 h)</td>
<td>97.7</td>
<td>90.9</td>
<td>88.6</td>
</tr>
<tr>
<td>2 g q8h (4 h)</td>
<td>98.9</td>
<td>95.4</td>
<td>96.2</td>
</tr>
<tr>
<td>1 g q6h (3 h)</td>
<td>98.2</td>
<td>92.6</td>
<td>92.7</td>
</tr>
<tr>
<td>2 g q6h (3 h)</td>
<td>99.4</td>
<td>97.5</td>
<td>98.2</td>
</tr>
</tbody>
</table>

PD target: $fT>MIC \geq 60\%$

Potential Reasons for Not Adopting Prolonged Infusion Dosing

• “This dosing is not approved by the FDA.”
  – Do you only use drugs/doses as approved by FDA?
  – Treatment for HAP/VAP? No drugs FDA-approved

• “I want to see randomized, prospective, clinical studies first.”
  – Funding source?
  – Sample size needed to detect a significant difference?
  – Target less susceptible bacteria?
  – Ethical considerations?

• “It’s not better than what we are currently doing.”
  – Does it have to be “better”?
## Piperacillin/Tazobactam Extended Infusion Dosing for *P. aeruginosa*

<table>
<thead>
<tr>
<th></th>
<th>APACHE II &lt; 17 (n=115)</th>
<th>APACHE II ≥ 17 (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14-day mortality</td>
<td>5.2%</td>
<td>21.5% <em>(p=0.001)</em></td>
</tr>
<tr>
<td>Median LOS</td>
<td>18 days</td>
<td>27.5 days <em>(p=0.02)</em></td>
</tr>
<tr>
<td>14-day mortality</td>
<td>3.7%</td>
<td>6.6%</td>
</tr>
<tr>
<td></td>
<td><em>p=0.5</em></td>
<td><em>p=0.04</em></td>
</tr>
<tr>
<td>Median LOS</td>
<td>18 days</td>
<td>18 days</td>
</tr>
<tr>
<td></td>
<td><em>p=0.5</em></td>
<td></td>
</tr>
</tbody>
</table>

3.375 g q4-6h, infused over 30 minutes
3.375 g q8h, infused over 4 hours

Retrospective Cohort of Extended-Infusion Piperacillin/Tazobactam

EI: 3.375 g q8h, infused over 4 hours

# Extended-Infusion Cefepime in Patients with *P. aeruginosa* Infections

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intermittent (n=54)</th>
<th>Extended (n=33)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>11 (20)</td>
<td>1 (3)</td>
<td>0.03</td>
</tr>
<tr>
<td>LOS (days, median)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>14.5</td>
<td>11</td>
<td>0.36</td>
</tr>
<tr>
<td>Infection-related</td>
<td>12</td>
<td>10</td>
<td>0.45</td>
</tr>
<tr>
<td>ICU</td>
<td>18.5</td>
<td>8</td>
<td>0.04</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (days)</td>
<td>14.5</td>
<td>10.5</td>
<td>0.42</td>
</tr>
<tr>
<td>Total hospital costs</td>
<td>$ 51,231</td>
<td>$ 28,048</td>
<td>0.13</td>
</tr>
<tr>
<td>Infection-related hospital cost</td>
<td>$ 15,322</td>
<td>$ 13,736</td>
<td>0.78</td>
</tr>
</tbody>
</table>

2 g q8h, infused over 30 minutes; 2 g q8h, infused over 4 hours

Clinical Outcomes with PI Vs. Intermittent Infusions – Meta-Analysis

- 29 studies with 2,206 patients included in the meta analysis
- Carbapenems, cephalosporins, and penicillins evaluated
- PI: EI ≥ 3 hours, CI 24 hours; intermittent 20-60 minutes

<table>
<thead>
<tr>
<th>Study Group</th>
<th>EI or CI</th>
<th>Intermittent</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI vs. Intermittent</td>
<td>96</td>
<td>859</td>
<td>137</td>
</tr>
<tr>
<td>Clinical Success</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI vs. Intermittent</td>
<td>617</td>
<td>747</td>
<td>578</td>
</tr>
</tbody>
</table>

Antibiotic-related adverse events were comparable between groups.

Clinical Outcomes with PI Vs. Intermittent Infusions – Meta-Analysis

<table>
<thead>
<tr>
<th>Study Subgroups</th>
<th>No. of Studies</th>
<th>No. of Patients</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCTs</td>
<td>10</td>
<td>779</td>
<td>0.83 (0.57, 1.21)</td>
</tr>
<tr>
<td>Non-RCTs</td>
<td>9</td>
<td>841</td>
<td>0.57 (0.43, 0.76)</td>
</tr>
<tr>
<td>Penicillins</td>
<td>8</td>
<td>974</td>
<td>0.60 (0.45, 0.82)</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>5</td>
<td>191</td>
<td>0.92 (0.52, 1.63)</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>4</td>
<td>274</td>
<td>0.74 (0.42, 1.28)</td>
</tr>
<tr>
<td>Equivalent Daily Dose</td>
<td>10</td>
<td>813</td>
<td>0.82 (0.56, 1.20)</td>
</tr>
<tr>
<td>APACHE II ≥ 15</td>
<td>10</td>
<td>861</td>
<td>0.63 (0.48, 0.81)</td>
</tr>
<tr>
<td>All Studies</td>
<td>19</td>
<td>1620</td>
<td>0.66 (0.53, 0.83)</td>
</tr>
</tbody>
</table>

# Clinical Outcomes with PI Vs. Intermittent Infusions – Meta-Analysis

<table>
<thead>
<tr>
<th>Study Subgroups</th>
<th>No. of Studies</th>
<th>No. of Patients</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Success</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCTs</td>
<td>14</td>
<td>1125</td>
<td>1.05 (0.99, 1.12)</td>
</tr>
<tr>
<td>Non-RCTs</td>
<td>5</td>
<td>421</td>
<td>1.34 (1.02, 1.76)</td>
</tr>
<tr>
<td>Penicillins</td>
<td>6</td>
<td>491</td>
<td>1.08 (0.94, 1.25)</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>9</td>
<td>662</td>
<td>1.11 (0.98, 1.25)</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>3</td>
<td>333</td>
<td>1.16 (0.93, 1.46)</td>
</tr>
<tr>
<td>Equivalent Daily Dose</td>
<td>10</td>
<td>934</td>
<td>1.22 (1.05, 1.43)</td>
</tr>
<tr>
<td>APACHE II ≥ 15</td>
<td>8</td>
<td>663</td>
<td>1.26 (1.06, 1.50)</td>
</tr>
<tr>
<td>All Studies</td>
<td>19</td>
<td>1546</td>
<td>1.12 (1.03, 1.21)</td>
</tr>
</tbody>
</table>

Clinical Outcomes with EI or CI Vs. Short-Term Infusions – Meta-Analysis

- 14 studies with 1,229 patients included in the analysis
- Carbapenems and piperacillin/tazobactam evaluated
- EI ≥ 3 hours; CI 24 hours; short-term 20-60 minutes

<table>
<thead>
<tr>
<th>Study Group</th>
<th>EI or CI</th>
<th>Short-Term</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths</td>
<td>Total</td>
<td>Deaths</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EI vs. Short-term*</td>
<td>34</td>
<td>314</td>
<td>46</td>
</tr>
<tr>
<td>CI vs. Short-term*</td>
<td>10</td>
<td>257</td>
<td>24</td>
</tr>
<tr>
<td>Total*</td>
<td>44</td>
<td>571</td>
<td>70</td>
</tr>
</tbody>
</table>

* Carbapenems and piperacillin/tazobactam combined

Pneumonia: RR 0.50 (95% CI, 0.26, 0.96)
Unspecified infection: RR 0.63 (95% CI 0.41, 0.95)

# Clinical Outcomes with EI or CI Vs. Short-Term Infusions – Meta-Analysis

<table>
<thead>
<tr>
<th>Study Group</th>
<th>EI or CI</th>
<th>Short-Term</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>El or CI vs. Short-term</td>
<td>14</td>
<td>110</td>
<td>0.66 (0.34, 1.30)</td>
</tr>
<tr>
<td>Piperacillin/Tazo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>El or CI vs. Short-term</td>
<td>22</td>
<td>394</td>
<td>0.55 (0.34, 0.89)</td>
</tr>
<tr>
<td>Carbapenem or P/T</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>El or CI vs. Short-term</td>
<td>8</td>
<td>67</td>
<td>0.59 (0.25, 1.35)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>44</td>
<td>571</td>
<td>0.59 (0.41, 0.83)</td>
</tr>
</tbody>
</table>

### Clinical Outcomes with EI or CI Vs. Short-Term Infusions – Meta-Analysis

<table>
<thead>
<tr>
<th>Study Group</th>
<th>EI or CI</th>
<th>Short-Term</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Cure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Success</td>
<td>Total</td>
<td>Success</td>
</tr>
<tr>
<td>Carbapenems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>El or CI vs. Short-term</td>
<td>73</td>
<td>82</td>
<td>62</td>
</tr>
<tr>
<td>Piperacillin/Tazo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>El or CI vs. Short-term</td>
<td>163</td>
<td>185</td>
<td>160</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>236</td>
<td>267</td>
<td>222</td>
</tr>
</tbody>
</table>

* Adverse Events*  
  - 20% (5/25)  
  - 16.9% (22/130)  
  - 24% (6/25)  
  - 13.6% (18/132)  

* No adverse events reported in 3 of 5 studies with data regarding AEs

Clinical Outcomes with Alternative Dosing Strategies for Piperacillin/Tazobactam

- 14 studies with 1,786 patients included in the meta analysis
- Intermittent: 2.25-4.5 g q6-8h, infused over 20-30 minutes
- PI: EI ≥ 3 hours, CI 24 hours; dose range 6.75-13.5 g daily

<table>
<thead>
<tr>
<th>Study Group</th>
<th>EI or CI</th>
<th>Intermittent</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI vs. Intermittent</td>
<td>112</td>
<td>815</td>
<td>Events</td>
</tr>
<tr>
<td><strong>Clinical Success</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI vs. Intermittent</td>
<td>287</td>
<td>345</td>
<td>Events</td>
</tr>
<tr>
<td><strong>Bacteriologic Success</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI vs. Intermittent</td>
<td>111</td>
<td>151</td>
<td>Events</td>
</tr>
</tbody>
</table>

# Clinical Outcomes with PI and Intermittent Infusion in Hospitalized Patients

14 studies with 1,491 patients included in the meta analysis (1979-2008)
- 8 of 14 studies with \( \leq 50 \) patients
- Carbapenems, cephalosporins, penicillins
- PI: EI \( \geq 3 \) hours, CI 24 hours; Intermittent package insert recommendations

<table>
<thead>
<tr>
<th>Study Group</th>
<th>EI or CI</th>
<th>Intermittent</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI vs. Intermittent</td>
<td>53</td>
<td>487</td>
<td>56</td>
</tr>
<tr>
<td><strong>Clinical Cure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI vs. Intermittent</td>
<td>470</td>
<td>677</td>
<td>479</td>
</tr>
</tbody>
</table>

# Prolonged Infusions for Suspected GN Infections in the ICU

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intermittent (n=242)</th>
<th>Prolonged (n=261)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment success</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically evaluable</td>
<td>137 (56.6%)</td>
<td>133 (51.0%)</td>
<td>0.204</td>
</tr>
<tr>
<td>Micro evaluable</td>
<td>58/105 (55.2%)</td>
<td>50/101 (49.5%)</td>
<td>0.486</td>
</tr>
<tr>
<td>14-day mortality</td>
<td>32 (13.2%)</td>
<td>47 (18.0%)</td>
<td>0.141</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>57 (23.6%)</td>
<td>67 (25.7%)</td>
<td>0.582</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>47 (19.4%)</td>
<td>60 (23.0%)</td>
<td>0.329</td>
</tr>
<tr>
<td>ICU LOS (days)*</td>
<td>9.3</td>
<td>10.8</td>
<td>0.138</td>
</tr>
<tr>
<td>Hospital LOS (days)*</td>
<td>17.0</td>
<td>15.6</td>
<td>0.281</td>
</tr>
<tr>
<td>Time from infection onset to:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU discharge*</td>
<td>7.8</td>
<td>8.4</td>
<td>0.293</td>
</tr>
<tr>
<td>Hospital discharge*</td>
<td>13.2</td>
<td>12.4</td>
<td>0.481</td>
</tr>
<tr>
<td>Death*</td>
<td>36</td>
<td>19</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* Median

Applying Prolonged Infusion Dosing to Clinical Practice

• Where will greatest benefit be achieved?
  – Hospital wide vs. specific unit vs. specific patient type
• Ability to interpret PK/PD literature
• Determine which antibiotics and dosing regimens are optimal for your institution
• Access to MIC data at your institution
• Ability to work with a multidisciplinary team to implement dosing protocol
• Educate hospital staff to minimize errors and maximize compliance

Target Population for Prolonged Infusion Dosing Regimens

• Critically ill patients (e.g., ICU, burn)
  – Younger patients
  – Augmented renal clearance or metabolism
    • Creatinine clearance  120 ml/min? 150 ml/min? 200 ml/min?
  – Increased volume of distribution
  – Increased body weight
• Patients likely to be infected with pathogens with elevated MICs
• Site of infection
## Risk Factors for β-lactam Non-Target Attainment in Critically Ill Patients

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=343)</th>
<th>Patient Not Achieving 50% $f_T&gt;MIC$ (n=66)</th>
<th>Patients Achieving 50% $f_T&gt;MIC$ (n=277)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 (47-73)</td>
<td>52 (39-65)</td>
<td>63 (49-75)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>APACHE II</td>
<td>18 (13-24)</td>
<td>15 (8-21)</td>
<td>19 (14-25)</td>
<td>0.001</td>
</tr>
<tr>
<td>SOFA</td>
<td>5 (2-8)</td>
<td>3 (1-6)</td>
<td>6 (3-9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CLcr (ml/min)</td>
<td>91 (54-141)</td>
<td>119 (84-164)</td>
<td>82 (48-124)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RRT</td>
<td>33 (9.6%)</td>
<td>1 (1.5%)</td>
<td>32 (11.6%)</td>
<td>0.013</td>
</tr>
<tr>
<td>El or Cl</td>
<td>86 (25.1%)</td>
<td>7 (10.6%)</td>
<td>79 (28.5%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

## Risk Factors for β-lactam Non-Target Attainment in Critically Ill Patients

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=343)</th>
<th>Patient Not Achieving 100% $f_T&gt;MIC$ (n=142)</th>
<th>Patients Achieving 100% $f_T&gt;MIC$ (n=201)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 (47-73)</td>
<td>55 (40-66)</td>
<td>64 (51-76)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>APACHE II</td>
<td>18 (13-24)</td>
<td>16 (10-23)</td>
<td>19 (15-25)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SOFA</td>
<td>5 (2-8)</td>
<td>3 (2-6.5)</td>
<td>6 (3-9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CLcr (ml/min)</td>
<td>91 (54-141)</td>
<td>118 (86-169)</td>
<td>70 (42-108)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Trauma (admit)</td>
<td>44 (12.8%)</td>
<td>32 (22.5%)</td>
<td>12 (5.9%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Surgery (24h prior)</td>
<td>78 (22.7%)</td>
<td>41 (28.9%)</td>
<td>37 (18.4%)</td>
<td>0.024</td>
</tr>
<tr>
<td>RRT</td>
<td>33 (9.6%)</td>
<td>2 (1.4%)</td>
<td>31 (15.4%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>El or CI</td>
<td>86 (25.1%)</td>
<td>18 (12.7%)</td>
<td>68 (33.8%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Implementation of a Prolonged Infusion Dosing Strategy

• Assess the institution’s available resources
  – How should the protocol be implemented?
  – Under what circumstances?
  – Who is ultimately responsible?
  – What is each department’s involvement and responsibility?

• Develop the prolonged infusion dosing protocol
  – Simple formatting
  – Easily accessible
  – Explicitly define patient populations
  – Employ appropriate antibiotic pharmacodynamics
  – Provide credible source information

Implementation of a Prolonged Infusion Dosing Strategy

• Assess causative pathogens
  – Institution-specific and/or unit-based

• Incorporate local resistance rates
  – Utilize antibiograms to select appropriate agents
  – Incorporate MIC data (obtain from microbiology lab)

• Multidisciplinary approach
  – Providers, infectious diseases, AST, pharmacy, microbiology, nursing, infection control, IT

• Develop an implementation plan
  – Standardized platform (CPOE)
  – Delegate “enforcer” of the program (AST, ID Pharm.D.)

Implementation of a Prolonged Infusion Dosing Strategy

• Education
  – Education and engagement of hospital staff
  – Combination of interventions
    • In-services, presentations, newsletters, order alerts

• Evaluate progress
  – Prospective monitoring to assess compliance and identify barriers
  – Routine surveillance to identify changes in local epidemiology and/or resistance patterns
  – Clinical outcomes

## Challenges and Solutions to Implementation

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Strategic Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of provider buy-in</td>
<td>Involve skeptical providers as members of protocol development team.</td>
</tr>
<tr>
<td></td>
<td>Obtain approval/support from key opinion leaders at the institution.</td>
</tr>
<tr>
<td></td>
<td>Generate CFR data using institution-specific MIC data.</td>
</tr>
<tr>
<td>Limited resources</td>
<td>Provide evidence-based information on potential benefits (clinical and economic)</td>
</tr>
<tr>
<td>Compliance issues</td>
<td>Automatic substitution (P&amp;T, MEC)</td>
</tr>
<tr>
<td>Inappropriate use</td>
<td>Explicitly define inclusion and exclusion criteria for use.</td>
</tr>
<tr>
<td></td>
<td>Implement dosing strategies using CPOE-derived protocols</td>
</tr>
</tbody>
</table>

# Challenges and Solutions to Implementation

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Strategic Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncertainty/confusion with procedures</td>
<td>Provide education up-front and develop initial roll-out plan with contact information for trouble-shooting or questions.</td>
</tr>
<tr>
<td>Medication errors</td>
<td>Electronic alerts, product labels, standardize volumes, “smart” pumps, CPOE</td>
</tr>
<tr>
<td>Decreasing utilization over time</td>
<td>Continue education sessions. Re-evaluate MIC data to determine need for refinement of drug selection or dosing. Collect outcome data to demonstrate improvements at the institution.</td>
</tr>
</tbody>
</table>

What About the First Dose?

• Most PK/PD analyses have focused on steady-state serum drug concentrations.
• Bacterial inoculum is largest prior to first dose.
• Resistant subpopulations may be present.
• Need to maximize bactericidal activity to reduce bacterial load and decrease risk for selection of resistant strains.
• What is the PD target for the first dose?
  – 50% $fT>MIC$? $C_{\text{max}}/\text{MIC} > 4$? $C_{\text{min}}/\text{MIC} > 4$?

First Dose Concentrations of Free Piperacillin in Hospitalized Patients

Concentration (mg/L) vs. Time (hours)

- 3.375 g
- 4.5 g
- 6.75 g

Cmax/BP 5.4
Cmax/BP 3.6
Cmax/BP 2.7
First Dose Concentrations of Free Piperacillin in Hospitalized Patients

Concentration (mg/L) vs Time (hours)

- 3.375 g
- 4.5 g

fCmax/BP = 6.7 for 3.375 g
fCmax/BP = 5.0 for 4.5 g
Application of PD Principles to a Specific Patient (β-Lactam)

Intermittent Infusion

\[
\%T>MIC = \ln\left(\frac{\text{Dose} \times f}{V_d \times \text{MIC}} \times \frac{V_d}{\text{Cl}_T} \times \frac{100}{\text{DI}}\right)
\]

Prolonged Infusion

\[
\int_{t=0}^{T_{\text{INF}}} f(t) > \text{MIC} (\%) = T_{\text{INF}} - \left(\ln\left(\frac{R_0}{\text{Cl}}\right) + \frac{\text{Cl}}{V} \right) + \left(\ln\left(\frac{R_0}{\text{Cl} - \text{MIC}}\right) - \ln(\text{MIC}) \times \frac{\text{Cl}}{V} \right) \times \frac{100}{\text{DI}}
\]

where \( T_{\text{INF}} \) is the infusion time; \( R_0 \) is the infusion rate calculated as \((\text{dose} \times \text{fraction unbound})/T_{\text{INF}}\); \( \text{Cl} \) is systemic clearance (L/h); \( V \) is volume of distribution; \( \text{DI} \) is dosing interval.
Where Do You Find the PK Data?

• Two-stage PK modeling
  – PK parameters are independent of each other
  – Individual patients can influence parameter estimates

• Population PK modeling
  – Estimates covariance between PK parameters and interindividual/residual variability
  – Outliers have less influence on parameter estimates ➔ more robust estimates
  – Can estimate PK parameters in patients with limited drug concentrations
Where Do You Find the PK Data?

• Is your patient represented in the published study?
  – ICU vs. non-ICU
  – Burn injury
  – Morbidly obese
  – Cystic fibrosis
Estimate Systemic Clearance from the Patient’s Creatinine Clearance

Piperacillin

\[ y = 0.065x + 3.191 \]

\[ R^2 = 0.857 \]

\[ p<0.0001 \]

Clinical Application

• 49 year old white male admitted to Methodist Hospital on January 8, 2016 following semi vs. tree MVA (ventilator)
• No significant past medical history
• On 1/15, he develops fever with increased purulent sputum production, hypoxemic.
• Temperature 102.3°F; WBC 17,800/mm³
• He is 70 inches tall, weighs 105 kg, BMI 33.2 kg/m², and his estimated CLcr is 90 ml/min.
Clinical Application

• Sputum gram-stain: gram-negative bacilli
• He was started on piperacillin/tazobactam 3.375 g q8h (infused over 4 h), tobramycin 560 mg IV q24h, and vancomycin 1500 mg IV q12h.
• Sputum culture is positive for *P. aeruginosa*, susceptible to piperacillin/tazobactam (8 μg/ml) and tobramycin (1 μg/ml).
• Are his doses appropriate for his infection?
Clinical Application

- Estimate clearance (CL) and volume (Vd)
  - Non-obese study
    - CL = (0.0651 * 90) + 3.191 = 9.05 L/h
    - Vd = 0.28 ± 0.06 L/kg * 105 kg = 29.4 L
  - Population PK study
    - CL = 11.3 + [0.0646 * (CLcr – 105)] + [0.0579 * (BMI – 35)] = 10.2 L/h
    - Vd = 31.3 + [0.132 * (TBW – 120)] = 29.3 L

Clinical Application
Piperacillin/Tazobactam

• 4 h infusion
  – $T_{INF} = 4 \, h$
  – $R_0 = (3000 \times 0.7)/4 = 525 \, mg/h$
  – $CL = 10.2 \, L/h$
  – $Vd = 29.3 \, L$
  – $fT> MIC \approx 110\%$

• 0.5 h infusion
  – $fT> MIC \approx 105\%$
Clinical Application
Piperacillin/Tazobactam

• Estimated V 29.3 L, CL 10.2 L/h
• If we wanted to give a continuous infusion:
  – $K_0 \text{ (mg/h)} = C_{ss} \text{ (mg/L)} \times CL \text{ (L/h)}$
• MIC 8 mg/L
• $K_0 \text{ (mg/h)} = 32 \text{ mg/L} \times 10.2 \text{ L/h} = 326.4 \text{ mg/h}$
  ➔ 7,834 mg/d ➔ 8 g of piperacillin/day as continuous infusion
Conclusions

• Pharmacodynamic principles and optimal targets have been scientifically validated in numerous in vitro, animal, and human studies.
• An important goal of all ASPs is dose optimization of all antibiotics, especially in patients at risk for subtherapeutic concentrations.
• Prolonged infusions of β-lactams increases PTA compared to standard infusions and may allow for reduction in total daily doses.
• Recently published meta-analyses have shown decreased mortality and increased clinical success with prolonged and continuous infusions.
Early Observations Regarding Drug Concentrations, Bacterial Killing & Resistance

“It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body . . . . Moral: If you use penicillin, use enough.”

Alexander Fleming, 1945 Nobel Prize acceptance speech