Combating Antimicrobial Resistance with Extended Infusion Beta-lactams

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PGY-1 Pharmacy Practice Resident
Disclosure

• The presenter has no conflicts of interest to disclose with material in this presentation.
Objectives

• Review pharmacokinetic and pharmacodynamic (PK/PD) properties of beta-lactam antibiotics

• Evaluate the literature for using extended infusion beta-lactam antibiotics

• Determine candidates for extended infusion beta-lactam therapy

• Identify obstacles in administering extended infusion beta-lactam therapy
No Longer a Threat: Reality of Resistance

- “Pan-Resistant New Delhi Metallo-Beta-Lactamase-Producing *Klebsiella pneumoniae*” - Washoe County, Nevada
  - Resistant to 26 antibiotics

- 10-50% of patients treated for nosocomial pneumonia develop antimicrobial resistance

- No new classes of antibiotics since the 1980s
## Isolate Susceptibility – Antibiogram 2015

<table>
<thead>
<tr>
<th></th>
<th>Piperacillin-tazobactam</th>
<th>Cefepime</th>
<th>Ertapenem</th>
<th>Meropenem</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P. aeruginosa</strong> <em>(n=1,065)</em></td>
<td>66%</td>
<td>77%</td>
<td>--</td>
<td>66%</td>
</tr>
<tr>
<td><strong>E. coli</strong> <em>(n=3,481)</em></td>
<td>96%</td>
<td>91%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>K. pneumoniae</strong> <em>(n=881)</em></td>
<td>95%</td>
<td>99%</td>
<td>100%</td>
<td>--</td>
</tr>
<tr>
<td><strong>A. baumanii</strong> <em>(n=119)</em></td>
<td>42%</td>
<td>69%</td>
<td>--</td>
<td>79%</td>
</tr>
</tbody>
</table>
Outline

• Common PK/PD parameters

• Monte Carlo simulations

• Literature evaluation

• Practical considerations
Time-Dependent (Time > MIC)

- Longer duration of exposure above the MIC results in greater bactericidal activity
  - Beta-lactam antibiotics

MIC: Minimum Inhibitory Concentration
Concentration-Dependent (Peak / MIC)

- Higher concentrations result in greater bactericidal activity
  - Aminoglycosides

MIC: Minimal inhibitory concentration
AUC-Dependent (AUC/MIC)

- Larger AUCs above the MIC result in greater extent of killing
  - Fluoroquinolones
Beta-lactams: Time-Dependent

• Approved dosing regimens occurred before robust PK / PD studies

• Bactericidal response is predicted by the amount of time above the MIC

• Regrowth occurs rapidly when concentrations are below MIC between administrations
  – Chance for resistance increases
Options for Increasing Time above MIC

• Option 1: Increase the dose
  – Increases risk of concentration-dependent toxicities

• Option 2: Extend the infusion time
Duration Above MIC is Drug-Specific

- Optimal time above MIC by drug class
  - Carbapenems: 30-60%
  - Cephalosporins: 60-70%
  - Penicillins: 50-60%

- PK / PD parameters initially studied in neutropenic animal models

- Validated in healthy adults

Pharmacodynamic Changes in Illness

- Critical Illness
  - Inflammation
  - Hypotension
    - Volume Resuscitation
      - Increased Volume of Distribution
      - Acute Kidney Injury
        - Decreased Clearance
        - Increased Cardiac Output
          - Increased Clearance
Infusion Duration affects Time > MIC

A

Log plasma β-lactam concentration (mg/L)

MIC=8 mg/L

$\text{MIC}=8 \text{ mg/L}$

$\text{MIC}=0.25 \text{ mg/L}$

IB infusion

Time (hours)

IB infusion

B

Log plasma β-lactam concentration (mg/L)

MIC=8 mg/L

$\text{MIC}=8 \text{ mg/L}$

$\text{MIC}=0.25 \text{ mg/L}$

IB infusion

Time (hours)

IB infusion

Extended infusion

Continuous infusion

Therapeutic Drug Monitoring

• Not routine practice for beta-lactams

• Monte Carlo simulations used to determine optimal dosing strategies

• Statistical model to predict achievement of a PK / PD target
  – Probability of target attainment
  – Cumulative fraction of response

Review Question 1

• Which of the following describes the PK / PD parameter for beta-lactam antibiotics?

A. Concentration / MIC

B. Time / MIC

C. AUC / MIC
What is the clinical evidence supporting extended infusion beta-lactam antibiotics?
Extended Infusion vs. Traditional Dosing Piperacillin-tazobactam with *P. aeruginosa*

**Objective**

- Evaluate efficacy of extended infusion piperacillin-tazobactam vs. traditional dosing for *P. aeruginosa* infections

**Outcomes**

- 14-day Mortality
- Length of Hospital Stay

**Dosing**

- Extended Infusion: 3.375g q8h over 4 hours
- Traditional: 3.375g q6h over 30 minutes
Extended Infusion vs. Traditional Dosing
Piperacillin-tazobactam with *P. aeruginosa*

**Inclusion Criteria**
- Adults with confirmed *P. aeruginosa* infections
- Absolute neutrophil count >1000
- Piperacillin-tazobactam given within 72 hours of infection and continued at least 48 hours
- ICU and floor patients

**Exclusion Criteria**
- >1 day of traditional dosing before extended infusion
- Reported resistance
- Dialysis, cystic fibrosis, solid organ or bone marrow transplant patients
- Beta-lactam therapy within 5 days of initiation of piperacillin-tazobactam

Study Design

- Single-center, retrospective cohort study

- No loading dose reported
  - Loading dose: same dose given as an intermittent infusion prior to beginning extended infusion
Justification of Dosing Strategy

- High probability of achieving piperacillin concentrations above MIC for 50% of dosing interval (50% $fT>MIC$)

Lodise TP, et al. CID 2007;44:357-63
Patient Characteristics

- 126 patients (64.9%) in the ICU when therapy started

<table>
<thead>
<tr>
<th>Source of Infection</th>
<th>Extended (n = 102)</th>
<th>Intermittent (n = 92)</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary (%)</td>
<td>55 (53.9)</td>
<td>48 (52.2)</td>
<td>0.8</td>
</tr>
<tr>
<td>Intra-abdominal (%)</td>
<td>4 (3.9)</td>
<td>1 (1.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>Urinary (%)</td>
<td>21 (20.6)</td>
<td>12 (13)</td>
<td>0.2</td>
</tr>
<tr>
<td>Skin &amp; soft tissue (%)</td>
<td>11 (10.8)</td>
<td>23 (25)</td>
<td>0.009</td>
</tr>
<tr>
<td>Bloodstream (%)</td>
<td>3 (2.9)</td>
<td>0 (0)</td>
<td>0.1</td>
</tr>
<tr>
<td>Other (%)</td>
<td>8 (7.8)</td>
<td>8 (8.7)</td>
<td>0.8</td>
</tr>
</tbody>
</table>
Clinical Outcomes

• Classification and Regression Tree (CART) analysis
  – Goal: Find the breakpoint APACHE II score for benefit

• Extended infusion dosing decreased mortality and length of stay (LOS) if APACHE II ≥ 17
  – Average APACHE II score = 15.6

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Extended (n=102)</th>
<th>Traditional (n=92)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (%)</td>
<td>12.2 (5 / 41)</td>
<td>31.6 (12 / 38)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>21 (3 - 91)</td>
<td>38 (6 - 131)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Lodise TP, et al. CID 2007;44:357-63
Limitations

- Retrospective study design
- Potentially suboptimal dose for *P. aeruginosa* in traditional infusion group
- Only *P. aeruginosa* confirmed infections
- No MIC data available
- Variable indications for treatment
- No subgroup analysis based on infection source
Unanswered Questions

• Does the benefit of extended infusion apply to all gram-negative pathogens or only *Pseudomonas*?

• Should the MIC dictate whether extended infusions are necessary?

• Do extended infusion beta lactam dosing strategies improve mortality outcomes beyond 14 days?
Extended Infusion vs. Traditional Dosing with Gram-negative Infections

Objective
• Evaluate efficacy of extended infusion piperacillin-tazobactam vs. traditional dosing for gram-negative infections

Outcomes
• 30-day Mortality
• Length of Hospital Stay
• Results stratified by MIC: <8, 8 to 16, >16 mg/L

Dosing
• Extended Infusion: 3.375g q8h over 4 hours
• Traditional: 3.375g to 4.5g q6-8h over 30 minutes
Extended Infusion vs. Traditional Dosing with Gram-negative Infections

**Inclusion Criteria**
- Age 18 or older, ANC ≥1000
- Confirmed infection with *gram-negative pathogen*
- Piperacillin-tazobactam given within 72 hours of infection continued at least 48 hours

**Exclusion Criteria**
- >1 day of traditional piperacillin-tazobactam before EI
- Reported resistance
- Dialysis, cystic fibrosis, solid organ or bone marrow transplant patients
- Concurrent beta-lactam therapy within 5 days of initiation of piperacillin-tazobactam
Study Design

• Retrospective, multisite cohort study

• Power not set
## Patient Characteristics

<table>
<thead>
<tr>
<th>Source of Infection</th>
<th>Extended (n=70)</th>
<th>Intermittent (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary (%)</td>
<td>17 (20.4)</td>
<td>20 (33.9)</td>
</tr>
<tr>
<td>Intra-abdominal (%)</td>
<td>9 (12.9)</td>
<td>10 (16.9)</td>
</tr>
<tr>
<td>Urinary (%)</td>
<td>27 (38.6)</td>
<td>18 (30.5)</td>
</tr>
<tr>
<td>Skin &amp; soft tissue infection (%)</td>
<td>10 (14.3)</td>
<td>10 (16.9)</td>
</tr>
<tr>
<td>Bloodstream (%)</td>
<td>4 (5.7)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Other (%)</td>
<td>3 (4.3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organisms Present (&gt;10% frequency)</th>
<th>Extended (n=70)</th>
<th>Intermittent (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>27 (28.6)</td>
<td>23 (39)</td>
</tr>
<tr>
<td><em>Psuedomonas aeruginosa</em></td>
<td>14 (20)</td>
<td>14 (23.7)</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>14 (20)</td>
<td>12 (20.3)</td>
</tr>
<tr>
<td><em>Proteus</em> spp.</td>
<td>3 (4.3)</td>
<td>13 (22)</td>
</tr>
</tbody>
</table>

Patel GW, et al. *Diagnostic Microbiology and Infectious Disease* 64 (2009) 236-240
Clinical Outcomes

- No statistical difference in 30 day mortality or length of hospital stay

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Extended (n=70)</th>
<th>Intermittent (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (%)</td>
<td>5.7</td>
<td>8.5</td>
</tr>
<tr>
<td>Hospital LOS (days) - Overall</td>
<td>8 (5.5-15)</td>
<td>8 (5-11)</td>
</tr>
<tr>
<td>Hospital LOS (days) – MIC &lt;8 mg/L (n=76)</td>
<td>8 (5.5-15)</td>
<td>8 (5-11)</td>
</tr>
<tr>
<td>Hospital LOS (days) – MIC 8-16 mg/L (n=52)</td>
<td>5 (4-10.5)</td>
<td>5 (4-9)</td>
</tr>
<tr>
<td>Hospital LOS (days) – MIC &gt;16 mg/L (n=1)</td>
<td>N/A</td>
<td>17 (17)</td>
</tr>
<tr>
<td>APACHE II Score, mean (SD)</td>
<td>10.9 (5.3)</td>
<td>10.5 (5.5)</td>
</tr>
</tbody>
</table>
Why did the study fail to find benefit in using extended infusions?

- Smaller study size (n=129)

- 43% of patients in traditional dosing group had a CrCl <40 mL/min

- 59% of patients in traditional dosing had MIC <8 mg/L

- 35% of patients had a urinary infection
Summary

• More likely to benefit:
  – *Pseudomonal* strains
  – Pulmonary source of infection
  – APACHE II ≥ 17

• Less likely to benefit:
  – Gram-negative infections with lower MICs
  – Patients with urinary tract infections

• Does this phenomenon hold up when compared to all beta-lactams with similar spectrums?
Extended Infusion vs. Traditional Dosed Beta-lactams with Gram-negative Infections

**Objective**
- Compare clinical outcomes for extended infusion piperacillin-tazobactam versus traditional dosing of similar spectrum beta-lactams in gram-negative infections

**Outcomes**
- In-hospital mortality rate
- Length of hospital and ICU stay
- Total duration of antibiotic therapy

**Dosing**
- Extended-infusion piperacillin-tazobactam: 3.375g q8h over 4 hours
- Traditional Dosing: cefepime, ceftazidime, imipenem-cilastatin, meropenem, doripenem, or piperacillin-tazobactam

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Extended Infusion vs. Traditional Dosed Beta-lactams with Gram-negative Infections

Inclusion Criteria
- Adults with confirmed gram-negative infections
- Mixed infections were allowed
- Patients hospitalized for >72 hours
- Antibiotics given for >48 hours

Exclusion Criteria
- >1 day of traditional piperacillin-tazobactam before extended infusion
- Intermediate or resistant to initial therapy
- Concomitant beta-lactam therapy
- Gram-positive or fungal coverage was inappropriate

Study Design

- Multicenter, retrospective study
- Included a multivariate analysis
Clinical Outcomes

- Extended infusion piperacillin-tazobactam reduced in-hospital mortality
- No difference in antibiotic duration, hospital or ICU length of stay

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Extended (n=186)</th>
<th>Intermittent (n=173)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (%)</td>
<td>9.7%</td>
<td>17.9%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multivariate Endpoint</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0.22</td>
<td>0.07-0.76</td>
<td>0.053</td>
</tr>
<tr>
<td>Survival (days)</td>
<td>2.77</td>
<td>0.85-4.7</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

## Source of Infection

<table>
<thead>
<tr>
<th>Source of Infection</th>
<th>Extended (n=186)</th>
<th>Intermittent (n=173)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary (%)</strong></td>
<td>57 (30.7)</td>
<td>75 (43.3)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Urinary (%)</strong></td>
<td>76 (40.9)</td>
<td>63 (36.4)</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>Skin &amp; soft tissue infection (%)</strong></td>
<td>36 (19.4)</td>
<td>35 (20.2)</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Bloodstream (%)</strong></td>
<td>41 (22)</td>
<td>47 (27.2)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Other (%)</strong></td>
<td>13 (7)</td>
<td>28 (16.2)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

# Potential Confounders

<table>
<thead>
<tr>
<th>Group characteristics</th>
<th>Extended (n=186)</th>
<th>Intermittent (n=173)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pseudomonas</em> sp.</td>
<td>42 (22.6%)</td>
<td>69 (39.9%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><em>Streptococcus</em> sp.</td>
<td>3 (1.6%)</td>
<td>13 (7.5%)</td>
<td>0.01</td>
</tr>
<tr>
<td>IV aminoglycosides</td>
<td>11 (5.9%)</td>
<td>28 (16.2%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>APACHE II</td>
<td>--</td>
<td>--</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Does this show extended infusion beta-lactam dosing is superior?

Supportive

• Extended infusion outperformed combination therapy with aminoglycosides (5.9% vs. 16.2%)

Confounding

• More *P. aeruginosa* in traditional dosing group
  – Potential higher MIC

• More respiratory tract infections with traditional dosing group
  – Potentially more difficult to treat
  – No group specific mortality information published
Review Question 2

• Which of the following groups are more likely to benefit from extended infusion beta-lactam therapies?

A. Patients who are more critically ill
B. Patients who have *P. aeruginosa* infections
C. Patients who have urinary tract infections
D. Both A and B
Empiric Coverage for Suspected Gram-negative Infections

Objective
- Determine if extended infusion beta-lactams improve outcomes in critically ill patients with suspected or confirmed gram-negative infections
  - Expect lower rate of mortality based on patient population

Primary Outcome
- Resolution of fever to < 38.3°C and > 36°C for 24 consecutive hours, and/or
  - WBC decrease to < 12,000/μL or 50% decrease within 7 days

Secondary Outcomes
- Time to defervescence
- All-cause hospital-, 14-, and 30-day mortality
- ICU and hospital length of stay

Standardized Dosing Schemes

- All extended infusions occurred over 3 hours

<table>
<thead>
<tr>
<th>Drug</th>
<th>CrCl (ml/min)</th>
<th>IV Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefepime</td>
<td>≥60</td>
<td>2g every 8 hours</td>
</tr>
<tr>
<td></td>
<td>30-60</td>
<td>2g every 12 hours</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≥50</td>
<td>1g every 8 hours</td>
</tr>
<tr>
<td></td>
<td>30-50</td>
<td>1g every 12 hours</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>≥40</td>
<td>4.5g every 6 hours</td>
</tr>
<tr>
<td></td>
<td>30-40</td>
<td>3.375g every 6 hours</td>
</tr>
</tbody>
</table>
Empiric Coverage for Suspected Gram-negative Infections

**Inclusion Criteria**
- ICU status receiving empiric gram-negative coverage
- Suspected health-care associated infection
- Fever (>38.3°C) and/or WBC >12,000/μL
- Cultures drawn within 24 hours of the antibiotic start time

**Exclusion Criteria**
- <48 consecutive hours of antibiotics while in ICU
- CrCl <30 ml/min or renal replacement therapy
- Antibiotic dose outside protocol
- Urinary tract infection
- Only gram-positive, fungal, or viral pathogen identified

Study Design

• Single center, pre/post implementation trial

• 162 patients needed to detect 50% relative risk reduction in treatment failure
## Patient Characteristics

- 503 patients included

<table>
<thead>
<tr>
<th>Group characteristics</th>
<th>Extended (n=261)</th>
<th>Intermittent (n=242)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>57 (21.8%)</td>
<td>81 (33.5%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Cefepime</td>
<td>115 (47.5%)</td>
<td>143 (54.8%)</td>
<td>0.103</td>
</tr>
<tr>
<td>Meropenem</td>
<td>86 (35.5%)</td>
<td>64 (24.5%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>41 (16.9%)</td>
<td>54 (20.7%)</td>
<td>0.283</td>
</tr>
<tr>
<td>APACHE score, median (IQR)</td>
<td>21 (16-25)</td>
<td>19 (17-24)</td>
<td>0.466</td>
</tr>
</tbody>
</table>
Clinical Outcomes

- No statistically significant difference in primary outcome or secondary outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Extended (n=261)</th>
<th>Intermittent (n=242)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution of fever and WBC (%)</td>
<td>51%</td>
<td>56.6%</td>
<td>0.204</td>
</tr>
<tr>
<td>30 day Mortality (%)</td>
<td>25.7%</td>
<td>23.6%</td>
<td>0.542</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>10.8 (5-17)</td>
<td>9.3 (5.6-19.2)</td>
<td>0.138</td>
</tr>
</tbody>
</table>
Limitations

- Only 41% of patients had confirmed infections.

- Limited number of patients with high MIC organisms identified:
  - n=25 of 206 patients with identified organisms
  - Enterobacteriaceae, P. aeruginosa, Acinetobacter

- No loading dose given
  - Low serum concentrations initially could impact outcomes
  - Time to first antibiotic doses are determinants of mortality

Does prospective data show similar results?
# Continuous vs. Intermittent Infusions

## BLING II & BLISS

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>Evaluate efficacy of continuous infusion beta-lactams in critically ill patients with severe sepsis</td>
<td></td>
</tr>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>Number of alive ICU-free days at Day 28</td>
<td>Clinical cure at 14 days after antibiotic cessation</td>
</tr>
</tbody>
</table>
| **Secondary Outcome(s)** | - 90-day mortality  
- Clinical cure at 14 days after antibiotic cessation  
- Alive organ failure-free days at Day 14  
- Duration of bacteremia post randomization | - 14- and 30-day survival  
- PK/PD target attainment  
- ICU and ventilator-free days at 28 days post randomization |

## Continuous vs. Intermittent Infusions

### BLING II & BLISS

|------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| **Study Design** | - Randomized controlled trial  
- Open label                                                                  | - Randomized controlled trial  
- Double-blinded                                                               |
| **Medications**  | Similar spectrum of activity                                                   |                                                                               |
|                  | - Piperacillin/tazobactam  
- Ticarcillin/clavulanate  
- Meropenem                                                                   | - Piperacillin/tazobactam  
- Cefepime  
- Meropenem                                                                   |
| **Dosing**       | Loading dose given  
Allowed concomitant, non-beta-lactam antibiotics                               |                                                                               |
## Continuous vs. Intermittent Infusions

**BLING II & BLISS**

|---------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| **Inclusion Criteria** | ≥18 years old  
Severe sepsis criteria |                                                                                  |
| **Exclusion Criteria** | - >24 hours beta-lactam before randomization  
- Pregnancy  
- Allergy to study drug | - Continuous renal replacement therapy  
- Impaired hepatic function  
- Inadequate central venous access |

## Patient Characteristics

### BLING II

<table>
<thead>
<tr>
<th>Group characteristics</th>
<th>Continuous (n=212)</th>
<th>Intermittent (n=220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identified gram-negatives</td>
<td>29 (72.5%)</td>
<td>31 (72.1%)</td>
</tr>
<tr>
<td>Pulmonary Infection</td>
<td>115 (54.2%)</td>
<td>120 (54.5%)</td>
</tr>
<tr>
<td>APACHE II</td>
<td>21 (17-26)</td>
<td>21 (16-25)</td>
</tr>
</tbody>
</table>
Patient Characteristics

BLISS

- Same total daily dose of antibiotics regardless of infusion strategy

<table>
<thead>
<tr>
<th>Group characteristics</th>
<th>Continuous (n=70)</th>
<th>Intermittent (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. aeruginosa</td>
<td>37%</td>
<td>31%</td>
</tr>
<tr>
<td>A. baumannii</td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td>Pulmonary Infection</td>
<td>46 (66%)</td>
<td>36 (51%)</td>
</tr>
<tr>
<td>Concomitant antibiotic</td>
<td>33 (47%)</td>
<td>33 (47%)</td>
</tr>
<tr>
<td>APACHE II</td>
<td>21 (17-26)</td>
<td>21 (15-26)</td>
</tr>
</tbody>
</table>
Clinical Outcomes
BLING II & BLISS

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Results</td>
<td>- No statistically significant difference between groups in any outcome</td>
<td>- Clinical cure at 14 days higher after cessation of antibiotic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 56% vs. 34%, p=0.011</td>
</tr>
<tr>
<td>Limitations</td>
<td>- 26% of patients had renal replacement therapy</td>
<td>- Median length of treatment: 7 days</td>
</tr>
<tr>
<td></td>
<td>- Median length of treatment: 3 days</td>
<td></td>
</tr>
</tbody>
</table>

Extended Infusion Carbapenems?

- Limited data available – mainly case reports

- Risk documented with extended infusion doripenem
  - Doripenem 1g q8h over 4 hours for 7 days vs. imipenem-cilastatin 1g q8h over 30 minutes for 10 days
  - Study stopped early due to inferior efficacy and increased mortality
  - Limitation: first dose was the extended infusion
Indications

- Confirmed *P. aeruginosa* infections
- Critically ill patients
- Pulmonary infections
- Severe sepsis
- Institution-specific resistance patterns
Dosing Strategy

• Loading dose before using extended infusion or continuous infusion

• Quicker attainment of MIC with loading doses

• Start extended infusion dosing schedule at next interval
Other Hospitals that Use Extended or Continuous Infusions

• Out of 17 responses:
  – All hospitals used extended or continuous infusion beta-lactam therapy
  – All hospitals used piperacillin-tazobactam as an extended infusion
  – Five hospitals used meropenem extended infusion
  – Three hospitals used cefepime extended infusion
Other Hospitals that Use Extended or Continuous Infusions

• University of Missouri Health Care
• Oklahoma Heart Hospital
• University of California – Davis Medical Center
• UC – San Diego Health
• Detroit Medical Center
• University of Chicago
• Beth Israel Deaconess Medical Center
• Gulf Coast Regional Medical Center
• UW Health
• UCLA
• Johns Hopkins
• University of Utah
Obstacles for Extended Infusion Beta-lactam Implementation
IV Medication Compatibility

- Doses can run for 12 hours each day
- Requires multiple peripheral lines or a central line

<table>
<thead>
<tr>
<th>Piperacillin-tazobactam</th>
<th>Cefepime</th>
<th>Meropenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Levofloxacin, vancomycin</td>
<td>- Diltiazem, dobutamine, nicardipine</td>
<td>- Amiodarone, nicardipine</td>
</tr>
<tr>
<td>- Diltiazem, dobutamine, hydralazine, labetalol, nicardipine</td>
<td>- Diphenhydramine, propofol</td>
<td>- Diazepam, propofol</td>
</tr>
<tr>
<td>- Famotidine, prochlorperazine, promethazine, pantoprazole, insulin</td>
<td>- Famotidine, pantoprazole, prochlorperazine, promethazine</td>
<td>- Pantoprazole</td>
</tr>
<tr>
<td>- Midazolam</td>
<td>- Midazolam, dopamine, morphine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Magnesium sulfate</td>
<td></td>
</tr>
</tbody>
</table>

*Not an inclusive list of incompatibilities
Trissel’s 2 Database
Cost Benefits of Extended Infusion Beta-lactams

• Reduced cost of piperacillin-tazobactam
  – Decrease of one dose per day
  – Potential decrease in length of hospital stay

• Possible decreased length of ICU stay and hospital stay with other beta-lactams
  – No decrease in total daily drug dosage

Review Question 4

• Which of the following is an area where pharmacists can make an impact on proper use of extended infusion beta-lactams?
  A. Administration technique of extended infusion beta-lactams
  B. IV incompatibility surveillance
  C. Diagnosis of an infectious disease process
  D. All the above
Steps Toward Implementation
Nursing

- Education on benefit and purpose of extended infusion therapy
- Maintain cleanliness of line sites to prevent infections
- PT / OT issues with IV administration of medications
Pharmacy

• Configuration of smart pumps and CPOE entries

• Selection of appropriate patient

• Considerations:
  – IV incompatibilities
  – Line access
Summary

• Time-dependent properties allows extended-infusions

• Piperacillin-tazobactam has the most evidence for use

• Extended infusion beta-lactams should be used in:
  – Critically ill patients
  – Pulmonary infections

• Patient outcomes are improved when used appropriately

• Multidisciplinary implementation is required for successful extended-infusion beta lactams
Acknowledgement

• Kane Hosmer, PharmD, BCOP
Combating Antimicrobial Resistance with Extended Infusion Beta-lactams

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