Optimization of Beta-lactam Antibiotic Therapy for Gram Negative Bacterial Infections

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Infectious Disease Pharmacist
Billings Clinic

Learner Objectives

• Discuss the reasons for needing to optimize antimicrobial therapy.
• Describe the pharmacokinetic and pharmacodynamic rationale for using extended or continuous infusion beta-lactams.
• Explain the limitations and difficulties of implementing alternative infusion methods.

State of Resistance

STATEMENT OF THE INFECTIOUS DISEASES SOCIETY OF AMERICA BEFORE THE FOOD AND DRUG ADMINISTRATION
PART 15 HEARING PANEL ON ANTIMICROBIAL RESISTANCE

APRIL 28, 2008

"a mounting public health concern"

"unresolved scientific issues regarding clinical development in the antibacterial drug arena, which has been identified as a serious impediment to new antibacterial development"
IDSA Statement

- Lack of resources allocated to fight growing problem
- Organisms of concern
  - E. Coli
  - Acinetobacter spp.
  - Klebsiella spp.
  - Enterobacter spp.
  - Pseudomonas aeruginosa
- Lack of new drug development

Drug development

![Drug development graph](image)

Figure 1. Number of New Molecular Entity (NME) Systemic Antibiotics Approved by the US FDA Per Five-year Period, Through 3/31.

Drugs in Pipeline

<table>
<thead>
<tr>
<th>Company</th>
<th>Stage</th>
<th>Indication</th>
<th>Target</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company A</td>
<td>Phase 1</td>
<td>Infectious Disease</td>
<td>bacteria</td>
<td>Clinical trial</td>
</tr>
<tr>
<td>Company B</td>
<td>Phase 2a</td>
<td>Infectious Disease</td>
<td>bacteria</td>
<td>Phase 2 complete</td>
</tr>
<tr>
<td>Company C</td>
<td>Phase 3</td>
<td>Infectious Disease</td>
<td>bacteria</td>
<td>Enrollment complete</td>
</tr>
</tbody>
</table>

*Health Care, Education and Research*
CLSI Breakpoint Updated 2010

<table>
<thead>
<tr>
<th>Drug (mg/dl)</th>
<th>S</th>
<th>I</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
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<td>1</td>
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<td>Ceftriaxone</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Resistance Mechanisms Growing in Numbers

- ESBL associated resistance genes
  - OXA
  - CTX
  - SHV
  - NDM

Economic Impact of MDRO’s

- Studies have shown increased LOS and health care costs associated with MDRO vs. Non-MDRO
  - HAI total hospital cost increases 29.3%
  - Average LOS increases 23.8%
- Annual cost to US health care system $21-34 Billion
- Greater than 8 million additional hospital days
**Beta-lactam PK/PD**

- Targeted T>MIC
  - PCN: 50-60% of dosing interval
  - Cephalosporins: 60-70% of dosing interval
  - Carbapenems: 20-40%
  - Monobactams: 50-60%

**Antibiotic Pharmacodynamics**

- %fT>MIC
  - Vary among β-lactam sub-classes & organisms

**EXTENDED INFUSION (EI) BETA-LACTAMS**
Health Care, Education and Research


1953: Gerber et al. “Impact of dosing intervals on activity of gentamicin and ticarcillin against Pseudomonas aeruginosa in granulocytopenic mice” J Infect Dis

1990: Leggett et al. “Comparative dose-effect relations at several dosing intervals for beta-lactam, amino-glycoside and quinolone antibiotics against gram-negative bacilli in murine thigh infection and pneumonia models” Scand J Infect Dis

2007: Lodise et al. “Piperacillin/tazobactam for Pseudomonas aeruginosa infections: clinical implications of an extended infusion dosing strategy” CID

2013: Falgas et al. “Clinical Outcomes With Extended or Continuous Versus Short-term Intermittent Infusion of Carbapenems and Piperacillin-Tazobactam: A Systematic Review and Meta-analysis” CID

EI Rationale

• Provide maximal kill
• Utilization of optimal amount of drug
• Prolong utility of drug in clinical practice
• Overcome elevated MIC’s

<table>
<thead>
<tr>
<th>Dosing Regimen (infusion time)</th>
<th>Clearance (relative)</th>
<th>MIC 4 μg/mL</th>
<th>MIC 8 μg/mL</th>
<th>MIC 16 μg/mL</th>
<th>MIC 32 μg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 h. I.V.</td>
<td>100</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>3.175 g. q.h.i.</td>
<td>90</td>
<td>90%</td>
<td>90%</td>
<td>90%</td>
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</tr>
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<td>3.175 g. q.h.i.</td>
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<td>90%</td>
<td>90%</td>
</tr>
</tbody>
</table>

Note: MIC = minimum inhibitory concentration. Values reflect the percentage of the dosing interval that reduced drug concentrations remained above the MIC.

Clinical Outcomes With Extended or Continuous Versus Short-term Intravenous Infusion of Carbapenems and Piperacillin-Tazobactam: A Systematic Review and Meta-analysis


<table>
<thead>
<tr>
<th>Antibiotic Regimen</th>
<th>SSA</th>
<th>ECO</th>
<th>ECO-IA</th>
<th>ECO-EA</th>
<th>ECO-EI</th>
<th>ECO-IE</th>
<th>ECO-DT</th>
<th>ECO-PI</th>
<th>ECO-AM</th>
<th>ECO-AM (inclusion)</th>
<th>ECO-AM (exclusion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime 1 g q6h</td>
<td>94.7</td>
<td>92.6</td>
<td>88.9</td>
<td>90.9</td>
<td>90.9</td>
<td>90.9</td>
<td>90.9</td>
<td>90.9</td>
<td>90.9</td>
<td>90.9</td>
<td>90.9</td>
</tr>
<tr>
<td>Ceftazidime 2 g q6h</td>
<td>98.0</td>
<td>98.0</td>
<td>98.0</td>
<td>98.0</td>
<td>98.0</td>
<td>98.0</td>
<td>98.0</td>
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<td>98.0</td>
<td>98.0</td>
</tr>
<tr>
<td>Ceftazidime 1 g q6h (inclusion)</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
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</tr>
<tr>
<td>Ceftazidime 2 g q6h (inclusion)</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
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<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Note: Table 11 refers to Table 11 in the original article, which is linked to the citation.
Falgas et al.\textsuperscript{11}

• Meta-analysis of studies reporting outcomes of extended or continuous infusion vs. intermittent infusion
  – Divided patients into 2 groups
    • Extended or Continuous Infusion
    • Short-term Infusion

• Exclusions
  – Case reports and case series including <10 patients

Falgas et al.\textsuperscript{11}

• Primary outcome
  – All-cause mortality
  – Clinical cure

• Secondary
  – Adverse events
  – Emergence of resistance during therapy

Falgas et al.\textsuperscript{11}

• Results
  – 7282 articles identified (PubMed 1319, Scopus 5963) + 1 abstract from ICAAC
  • 14 studies met eligibility
    – 8 retrospective, 3 prospective, 3 RCT
      » Carbapenem 6 studies (N= 302)
      » PIP/Tazo 7 studies (N= 806)
      » 1 study assessing both classes of abx
• Conclusions
  – Mortality lower with extended or continuous infusion vs. short term
    • (RR 0.59; 95% 0.41-0.83)
      – Extended to pneumonia subset (RR 0.50; 95% CI, 0.26-0.96)
  – Clinical cure trended towards favoring extended or continuous
    • (RR 1.13; 95% CI, 0.99-1.28)
Clinical Outcomes of Studies\(^9\)

- Lodise et al. 2007
  - Single center, retrospective COHORT
  - Two study groups compared for pip/tazo
    - Pip/tazo 3.375gm IV q8h infused over 4 hours (N=102)
    - Pip/tazo 3.375gm IV q4h infused over 30 min (N=92)
Clinical Outcomes Studies

- Inclusion
  - 18 yrs or older
  - ANC 1,000 or greater
  - P. aeruginosa culture meeting CDC criteria for infection
  - Pip/tazo administered within 72h of onset infection
  - Receipt of piperacillin for at least 48h

- Exclusion
  - Receipt of >1 d of intermittent infusion
  - Receipt of a concurrent abx with pseudomonal activity within 5 d of initiation of therapy (excludes cipro or AG)
  - Dialysis
  - Transplant
  - Cystic fibrosis

Clinical Outcomes Studies

- Pip/tazo EI Results

<table>
<thead>
<tr>
<th>Dose</th>
<th>Mortality (APACHE II ≥ 17)</th>
<th>P value</th>
<th>Length of stay</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.375 gm q4h or q6h infused over 30 mins</td>
<td>31.6%</td>
<td>0.04</td>
<td>38 days</td>
<td>0.02</td>
</tr>
<tr>
<td>3.375 gm q8h infused over 4 hours</td>
<td>12.2%</td>
<td></td>
<td>21 days</td>
<td></td>
</tr>
</tbody>
</table>

- Limitations
  - Not RCT
  - Single center
Clinical Outcomes of Studies\textsuperscript{10}

- Piperacillin-tazobactam

<table>
<thead>
<tr>
<th>Dose</th>
<th>Mortality</th>
<th>P value</th>
<th>Prolonged survival (days)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.375 gm IV q4h infused over 35 mins</td>
<td>17.9%</td>
<td>0.02</td>
<td>2.77</td>
<td>0.01</td>
</tr>
<tr>
<td>3.375 gm IV q8h infused over 4 hours</td>
<td>9.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EI PROTOCOL EXAMPLE

Inclusion Criteria

- Patients admitted to Billings Clinic receiving:
  - Piperacillin-tazobactam
  - Meropenem
  - Ceftazidime
- Hemodialysis/peritoneal dialysis patients
- Cystic fibrosis patients ≥13 y/o
## Exclusion Criteria

- Neonates and infants 0-1 y/o
- Pediatrics (non-cystic fibrosis) age ≤16 y/o
- Cystic fibrosis pediatric patients ≤12 y/o
- First doses:
  - In ED prior to admission
  - As procedural prophylaxis

## Extended-infusion Protocol

### Table 1. Extended-Infusion Therapeutic Interventions and Branial Dosing

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Initial Dose</th>
<th>Time/Volume</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone (Fortum)</td>
<td>1 g IV q24h over 40 min</td>
<td></td>
<td>Ceftriaxone 2 g IV q24h inflow over 4 hours</td>
</tr>
<tr>
<td></td>
<td>1 g IV q24h over 40 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 g IV q24h over 40 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 g IV q24h over 40 min</td>
<td></td>
</tr>
<tr>
<td>Meropenem (Merrem)</td>
<td>1 g IV q6h over 3 h</td>
<td>500 mg IV q6h over 3 h</td>
<td>Meropenem 1 g IV q6h inflow over 4 hours</td>
</tr>
<tr>
<td></td>
<td>2 g IV q6h over 40 min</td>
<td></td>
<td>Meropenem 2 g IV q6h inflow over 4 hours</td>
</tr>
</tbody>
</table>

*Only indicated for monotherapy, cystic fibrosis, and microorganisms with a meropenem/bropan 8IC of 4 mg/L.*

### Table 2. Extended-infusion Protocol

<table>
<thead>
<tr>
<th>Piperacillin/Tazobactam (Zosep)</th>
<th>CIC ≥20 mL/min or CRRT</th>
<th>CIC &lt;20 mL/min, hemodiagnosis or peritoneal dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5 g IV q6h over 30 min</td>
<td></td>
<td>Piperacillin/Tazobactam 3.25 g IV q12h inflow over 4 hours</td>
</tr>
<tr>
<td>3.25 g IV q6h over 30 min</td>
<td></td>
<td>Pipercillin/Tazobactam 3.25 g IV q12h inflow over 4 hours</td>
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</tbody>
</table>
Gaps in Research

- Follow up studies using RCT
  - Most studies reporting EI are retrospective

- Questions regarding outcomes in special populations
  - Obesity
  - Pediatrics
  - Febrile neutropenia
Conclusions

- Gram-negative bacterial resistance is increasing
- Lack of drug development
  - Recent legislation passed that give drug companies incentives to develop abx may help
- Extended infusion beta-lactams
  - Reduces resistance
  - Improves patient outcomes of both clinical cure and mortality
  - Data is strong enough to recommend implementation
- Antimicrobial stewardship needed to help combat growing problem

References
