Extended Infusion Piperacillin-Tazobactam

• RATIONALE • EVIDENCE • CONCLUSIONS •

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Arkansas Association of Health-System Pharmacists — Fall Seminar, October 2012

Learning Objectives

• Differentiate between time-dependent and concentration-dependent antibiotics
• Assess the “pillars” of evidence in support of extended infusion (EI) dosing of piperacillin-tazobactam (PIP-TAZ)
• Explain the meaning of $t>T_{MIC}$ and its significance in the application of an EI dosing strategy for PIP-TAZ
• Evaluate the evidence for and against implementing an EI dosing protocol in hospital settings

Conflict of Interest Disclosure

• The speaker, Scott Kaufman, has no real or potential conflicts of interest related to the subject matter in this presentation.

Introduction & Background

EXTENDED INFUSION PIPERACILLIN-TAZOBACTAM

What Do These Hospitals Have In Common?

• Johns Hopkins University Hospital
• Stanford University Hospital
• Baylor University Medical Center
• Vanderbilt University Medical Center
• University of California San Diego Medical Center
• University of Iowa Hospitals
• Robert Wood Johnson University Hospital
• LSU Health Sciences Center
• Nebraska Medical Center
• Mercy Medical Center (Rogers, AR)

Random sampling from multiple sources (hospital websites, journal articles, other published literature, etc.)

To Extend, or Not to Extend? That is the question!
Two Trends Threatening Hospitals Today

1. alarming rise in antibiotic resistance
2. diminishing antibiotic pipeline as major drug companies withdraw from antibiotic market

Antimicrobial Resistance

- One of greatest threats to human health worldwide
- Methicillin-resistant *Staphylococcus aureus* (MRSA) *alone* kills more Americans per year than emphysema, HIV/AIDS, Parkinson’s disease, and homicide combined
- Cost to U.S. health care $21 to $34 billion/year
- Result in >8 million additional hospital days

Hospital-Acquired Infections (HAIs)

- Occur in ~2 million Americans per year
- Result in 99,000 deaths per year, mostly due to antibiotic-resistant pathogens (e.g., *Pseudomonas aeruginosa*)
- Two common HAIs—sepsis and pneumonia:
  - killed ~50,000 Americans
  - cost US health care system >$8 billion in 2006

Diminishing Antibiotic Pipeline

Potential Benefits of Dose Optimization

- Maximize efficacy (by maximizing bacterial kill)
- Impede emergence of resistance
- Preserve antibiotic efficacy
- Realize pharmacoeconomic benefits
- Become better stewards of our antimicrobial armamentarium

Infectious Diseases Society of America (IDSA) delineates two strategies for hospitals:

1. Comprehensive infection control program
2. Antimicrobial use optimization (antimicrobial stewardship)

- Dose optimization:
  - important to combat antimicrobial resistance
  - integral to antimicrobial stewardship

What Can We Do About It?
Dose Optimization

- Recently come under a great deal of scrutiny
- Extended infusions (EI) of β-lactam antibiotics proposed as an alternative dosing strategy
- Evidence suggests EI PIP-TAZ at least equivalent—and potentially superior—to standard dosing in terms of clinical efficacy

What is EI Piperacillin-Tazobactam?

- Infusion of drug over an extended (prolonged) period of time (e.g., 3 or 4 hours) instead of traditional shorter infusion time of 30 minutes
- Developed from pharmacokinetic (PK) and pharmacodynamic (PD) profiles of β-lactam antibiotics to maximize time-dependent bactericidal activity and improve probability of target attainment (PTA)

Piperacillin-Tazobactam

- Most widely studied extended infusion antibiotic
- Only one with published clinical outcomes data

Extended Infusion of β-lactams: A Novel Strategy for Dose Optimization

- Not approved by U.S. Food & Drug Administration (FDA)
- Especially beneficial in critically ill patients with difficult-to-treat infections
- Hospitals nationwide continue to adopt EI policies
- One piece of multifaceted strategy for antimicrobial stewardship

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

**Recommendation:**

“Optimization of antimicrobial dosing based on individual patient characteristics, causative organism, site of infection, and pharmacokinetic and pharmacodynamic characteristics of the drug is an important part of antimicrobial stewardship (A-II)...

*Examples of these principles in practice include prolonged or continuous infusion of β-lactams...*”

**IDSA & U.S. Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines**

<table>
<thead>
<tr>
<th>Category, grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Good evidence to support a recommendation for use</td>
</tr>
<tr>
<td>B</td>
<td>Moderate evidence to support a recommendation for use</td>
</tr>
<tr>
<td>C</td>
<td>Poor evidence to support a recommendation for use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
</tbody>
</table>

**Clin Infect Dis 2007:44:159-177.**
Pharmacodynamic Rationale

**Extended Infusion Piperacillin-Tazobactam**

Antimicrobial Pharmacodynamics:
The critical interaction between “bug and drug”

- Describes relationship between drug exposure and antimicrobial activity
- Antimicrobial PKs and PDs together determine relationship between serum drug concentrations and antimicrobial effect
- For most antimicrobials, PD target associated with maximal effect has been identified

Antimicrobial Pharmacodynamic Target Parameters Associated with Maximal Effect

<table>
<thead>
<tr>
<th>Bacterial Killing</th>
<th>Examples</th>
<th>Therapy Goal</th>
<th>PD Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration-Dependent</td>
<td>Aminoglycosides, Fluoroquinolones</td>
<td>Maximize</td>
<td>$C_{\text{max}}:\text{MIC}$</td>
</tr>
<tr>
<td>Concentration-Dependent or Time-Dependent</td>
<td>Azithromycin, Vancomycin, Clindamycin, Ketolides, Tigecycline, Linezolid</td>
<td>Maximize exposure</td>
<td>24 hr $\text{AUC:MIC}$</td>
</tr>
<tr>
<td>Time-Dependent</td>
<td>Penicillins, Cephalosporins, Carbapenems, Monobactams</td>
<td>Optimize duration of exposure $&gt;\text{MIC}$</td>
<td>$T&gt;\text{MIC}$</td>
</tr>
</tbody>
</table>

Adapted from: *Clin Infect Dis* 2007; 44:79–86

β-Lactam Pharmacodynamics

- Bactericidal activity dependent on time (T) free (non-protein-bound) drug concentration ($f$) remains above minimum inhibitory concentration (MIC) during dosing interval ($fT>\text{MIC}$)
- Optimal level of exposure varies for different agents within β-lactam class

β-Lactam Pharmacodynamics

- For penicillins, $fT>\text{MIC}$ must be:
  - $>30\%$ of dosing interval to produce bacteriostasis
  - $>50\%$ of dosing interval for optimum (maximal) bactericidal effect
- Required $\%T>\text{MIC}$ for maximal bactericidal effect:
  - ~60–70% for cephalosporins
  - ~50% for penicillins
  - ~40% for carbapenems
Beta-Lactam Pharmacodynamics

- $f/T > MIC$ is the critical factor in predicting degree of bactericidal activity for β-lactams and other antimicrobials exhibiting time-dependent PDs.
- Renewed focus on $f/T > MIC$ as best and therefore preferred PD parameter for predicting efficacy has been driving force for implementing EI dosing policies in hospitals across U.S. in recent years.

Pharmacodynamic Evidence

EXTENDED INFUSION PIPERACILLIN-TAZOBACTAM

- Objective
  - Compare conventional dosing with prolonged and continuous infusions to determine optimal dosing scheme against *P. aeruginosa*.
- Design
  - Pharmacodynamic Monte Carlo simulation model
- Data Source
  - Microbiologic data from 470 *P. aeruginosa* isolates
- Patients
  - 5000 simulated surgical patients and patients with neutropenia

Monte Carlo Simulation

- Mathematical modeling technique
  - Simulates dispersion or full spread of values (C_{max}, AUC, etc.) seen in large population after administration of specific drug dose or dosing regimen.
- Determine probability that given antimicrobial regimen will achieve PD target associated with max effect.
- Standard methodology for assessing clinical viability of both experimental and approved antimicrobial agents.

Optimal Dosing of Piperacillin-Tazobactam for Treatment of *Pseudomonas aeruginosa* Infections: Prolonged or Continuous Infusion?

- Findings
  - Prolonged- and continuous-infusions with same daily doses had similar likelihoods of bactericidal exposure.
  - Both dosing strategies improved PD profile over conventional intermittent-infusion regimens.
    - Probability of achieving 50% $f/T > MIC$ at 16 µg/mL:
      - 67.8% for intermittent regimen 3.75 g q6hr (13.5 g/day)
      - 100% for prolonged & continuous infusions (16 g/day)
    - Probability of achieving 50% $f/T > MIC$ at 32 µg/mL was:
      - 45% for high intermittent dose 4.5 g q6hr (18 g/day)
      - 90% for prolonged & continuous infusions (16 g/day)

Optimal Dosing of Piperacillin-Tazobactam for Treatment of Pseudomonas aeruginosa Infections: Prolonged or Continuous Infusion?

- Conclusions
  - Both prolonged- and continuous-infusion strategies improved PDs over traditional 30-minute intermittent-infusion regimens
  - Prolonged- and continuous infusion regimens containing same daily doses had similar likelihoods of bactericidal exposure

Piperacillin-Tazobactam for Pseudomonas aeruginosa Infection: Clinical Implications of an Extended-Infusion Dosing Strategy

- Purpose
  - Explore ways to optimize PDs of first-line antipseudomonal β-lactams to improve outcomes (patient survival, duration of hospitalization) associated with P. aeruginosa infection
- Design
  - Population PK modeling & PD Monte Carlo simulation comparing dosing schemes to assess probability of achieving 50% T>MIC vs P. aeruginosa.
  - 3.375 g as a 30-minute infusion q6hr
  - 3.375 g as a 30-minute infusion q4hr
  - 3.375 g as a 4-hour infusion q8hr

Potential Ways of Maximizing T>MIC

- Higher dose
- Increase dosing frequency
- Increase duration of infusion (prolonged)
- Increased duration of infusion (continuous)

Evaluation of T>MIC for Three Different Dosing Regimens for Piperacillin

- 2 Gm as a 30-min infusion
- 4 Gm as a 30-min infusion
- 2 Gm as a 4-hr infusion
- MIC = 10 mg/L

Interruption vs. Prolonged Infusions of Piperacillin-Tazobactam

Comparative Pharmacodynamics of Intermittent and Prolonged Infusions of Piperacillin/Tazobactam Using Monte Carlo Simulations and Steady-State Pharmacokinetic Data from Hospitalized Patients
Cumulative Fraction of Response at 50% fT>MIC for Intermittent and Prolonged Infusions of Piperacillin-Tazobactam Against Gram-Negative Pathogens

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>Escherichia coli</th>
<th>Klebsiella pneumoniae</th>
<th>Enterobacter spp.</th>
<th>Serratia marcescens</th>
<th>Citrobacter spp.</th>
<th>Pseudomonas aeruginosa</th>
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</thead>
<tbody>
<tr>
<td>Intermittent (30-min) Infusions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.5 g q6h</td>
<td>92.2</td>
<td>81.8</td>
<td>81.5</td>
<td>92.4</td>
<td>86.4</td>
<td>75.8</td>
</tr>
<tr>
<td>3.375 g q6h</td>
<td>94.5</td>
<td>84.1</td>
<td>83.1</td>
<td>94.6</td>
<td>87.7</td>
<td>76.6</td>
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<tr>
<td>4.5 g q6h</td>
<td>95.2</td>
<td>85.3</td>
<td>85.8</td>
<td>95.8</td>
<td>89.5</td>
<td>82.2</td>
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<td>3.375 g q4h</td>
<td>96.6</td>
<td>86.6</td>
<td>87.8</td>
<td>97.1</td>
<td>91.4</td>
<td>94.9</td>
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<tr>
<td>Prolonged (4-hour) Infusions</td>
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<tr>
<td>2.25 g q8h</td>
<td>95.0</td>
<td>85.6</td>
<td>82.9</td>
<td>95.2</td>
<td>87.5</td>
<td>79.9</td>
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<tr>
<td>3.375 g q8h</td>
<td>96.4</td>
<td>86.9</td>
<td>85.9</td>
<td>96.3</td>
<td>86.3</td>
<td>83.5</td>
</tr>
<tr>
<td>4.5 g q8h</td>
<td>98.0</td>
<td>87.0</td>
<td>86.6</td>
<td>100</td>
<td>91.3</td>
<td>85.9</td>
</tr>
<tr>
<td>6.75 g q8h</td>
<td>100</td>
<td>87.8</td>
<td>90.8</td>
<td>100</td>
<td>93.2</td>
<td>88.0</td>
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Comparison of Probability of Target Attainment Rates Between Intermittent and Prolonged Infusions of Piperacillin-Tazobactam According to Creatinine Clearance (CrCl) and Minimum Inhibitory Concentrations (MIC)

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
<th>CrCl (mL/min)</th>
<th>Probability of Target Attainment (50% fT&gt;MIC)</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>
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</thead>
<tbody>
<tr>
<td>Intermittent Infusion (30 min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.5 g q6h</td>
<td>100</td>
<td>81%</td>
<td>67%</td>
<td>46%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>4.5 g q6h</td>
<td>60</td>
<td>92%</td>
<td>84%</td>
<td>70%</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>3.375 g q6h</td>
<td>40</td>
<td>95%</td>
<td>90%</td>
<td>77%</td>
<td>50%</td>
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<tr>
<td>3.375 g q6h</td>
<td>20</td>
<td>98%</td>
<td>95%</td>
<td>84%</td>
<td>73%</td>
<td></td>
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<tr>
<td>Extended (Prolonged) Infusion (4 hrs)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.375 g q8h</td>
<td>100</td>
<td>99%</td>
<td>97%</td>
<td>73%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>3.375 g q8h</td>
<td>60</td>
<td>99%</td>
<td>99%</td>
<td>90%</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>3.375 g q8h</td>
<td>40</td>
<td>99%</td>
<td>99%</td>
<td>95%</td>
<td>62%</td>
<td></td>
</tr>
<tr>
<td>3.375 g q8h</td>
<td>20</td>
<td>99%</td>
<td>99%</td>
<td>97%</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>3.375 g q12h</td>
<td>40</td>
<td>99%</td>
<td>79%</td>
<td>52%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>3.375 g q12h</td>
<td>20</td>
<td>96%</td>
<td>90%</td>
<td>74%</td>
<td>40%</td>
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</table>


Nosocomial Infections

More intensive EI dosing schemes (3.375-4.5 g [3-hr infusion] q6hr) than commonly used are needed to maximize fT>MIC for MICs ≥8 mg/L

EI PIP-TAZ most effective method of administration for patients with nosocomial infections


Clinical Outcomes Evidence

EXTENDED INFUSION PIPERACILLIN-TAZOBACTAM

Piperacillin-Tazobactam for Pseudomonas aeruginosa Infection: Clinical Implications of an Extended-Infusion Dosing Strategy

- Purpose
  - Evaluate clinical implications of EI therapy in critically ill patients with P. aeruginosa infection
- Design
  - Single center, retrospective cohort study
  - Two study groups:
    - 3.375 g over 30 min q4h or q6h
    - 3.375 g over 4 hrs q8h
  - Demographics, disease severity, and microbiology data collected, and outcomes compared


Conclusion

- Prolonged infusion regimens at doses ≥3.375 g q8hr achieved excellent target attainment at 50% fT>MIC with lower daily doses compared to intermittent infusion regimens when MIC was ≤16 µg/mL.


More intensive EI dosing schemes (3.375-4.5 g [3-hr infusion] q6hr) than commonly used are needed to maximize fT>MIC for MICs ≥8 mg/L

EI PIP-TAZ most effective method of administration for patients with nosocomial infections

Piperacillin-Tazobactam for *Pseudomonas aeruginosa* Infection: Clinical Implications of an Extended-Infusion Dosing Strategy

**Inclusion** – Patients positive for *P. aeruginosa* and:
- Age ≥18 years
- Absolute neutrophil count ≥1000 cells/mm³
- *P. aeruginosa* culture result meeting CDC criteria for infection
- Received PIP-TAZ therapy within 72 hrs of onset
- Received PIP-TAX therapy for ≥48 hours

**Exclusion** – Patients meeting any of the following:
- Receipt of >1 day of intermittent infusion prior to conversion to the extended infusion protocol
- Receipt of concurrent β-lactam antibiotic with activity vs. *P. aeruginosa* within 5 days of initiation of therapy with PIP-TAZ
- *P. aeruginosa* isolate intermediate or resistant to PIP-TAZ
- Receipt of dialysis, solid-organ, or bone marrow transplant
- Diagnosis of cystic fibrosis

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**Clinical Implications of an Extended-Infusion Dosing Strategy**

**Conclusions**
- EI PIP-TAZ therapy viable alternative to traditional (30-minute infusion) dosing schemes
- Clinical benefit/improved outcomes with extended infusion PIP-TAZ particularly striking among critically ill patients infected with *P. aeruginosa* and an APACHE II score ≥17

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**Important Considerations/Shortcomings**

- Traditional infusion group received 3.375 g as 30-minute infusion q4-6 hrs
  - 3.375 g q4h = 20.25 g/day
  - 3.375 g q6h = 13.5 g/day
- Presumptive treatment of patients with nosocomial pneumonia should receive 4.5 g q6hr, totaling 18.0 g (16.0 g piperacillin/2.0 g tazobactam), plus an aminoglycoside

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**Outcomes of Extended Infusion Piperacillin-Tazobactam for Documented Gram-negative Infections**

**Design**
- Retrospective, multisite, cohort study comparing intermittent vs. extended infusion in patients with Gm-negative infection

**Inclusion**
- Age ≥18 years
- Absolute neutrophil count ≥1000 cells/mm³
- Infected with a Gram-negative pathogen
- Received PIP-TAZ therapy within 72 hrs of onset
- Received PIP-TAZ therapy for ≥48 hours

**Exclusion**
- Infected with an organism resistant to PIP-TAZ
- Receipt of dialysis, solid-organ, or bone marrow transplant
- Concurrent β-lactam within 5 days of start of PIP-TAZ
- Receipt of >1 day of traditional (30-min) infusion of PIP-TAZ
Outcomes of Extended Infusion Piperacillin-Tazobactam for Documented Gram-negative Infections

<table>
<thead>
<tr>
<th>Outcomes Overall</th>
<th>Intermittent Infusion (n=59)</th>
<th>Extended Infusion (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day mortality</td>
<td>4 (8.5%)</td>
<td>4 (5.7%)</td>
</tr>
</tbody>
</table>

Hospital LOS (median days)

- Overall 8 (5-11) 8 (5.5-15)
- MIC <8 mg/L 8 (5-11) 8 (5.5-13)
- MIC 8-16 mg/L 5 (4-9) 5 (4-10.5)
- MIC >16 mg/L 17 (17-17) NA

- No comparisons associated with a P-value <0.05

The Retrospective Cohort of Extended-Infusion Piperacillin-Tazobactam (RECEIPT) Study

Objective
- Compare efficacy of EI vs. similar spectrum, nonextended-infusion β-lactams in treatment of Gm-negative infections

Design
- Retrospective medical record review of 359 pts in 14 hospitals
- All sites used EI PIP-TAZ 3.375 g q8hr as 4-hr infusion in patients with CrCl ≥20 mL/min
- 186 EI vs. 173 nonextended-infusion comparators

Inclusion
- ≥18 years of age
- Hospitalized at least 72 hours
- Documented gram-negative infection
- Treatment with EI PIP-TAZ or nonextended cefepime, ceftazidime, imipenem-cilastatin, meropenem, doripenem, or PIP-TAZ for >48 hours
- Mixed gram-positive and gram-negative infections, as well as fungal coinfections included

Exclusion
- >24 hours effective antibiotics before initiation of EI PIP-TAZ or nonextended comparator
- Received concomitant β-lactam antibiotics
- Gm-negative infection intermediate or resistant to initial empiric therapy
- Inappropriate therapy for Gm-positive or fungal organisms

Outcomes Analysis
- Primary – Mortality rate of patients receiving EI PIP-TAZ vs. nonextended-infusion β-lactams
- Secondary – Hospital LOS, ICU LOS, and total duration of antibiotic therapy

Results
- Hospital LOS, ICU LOS, and total duration of antibiotic therapy similar between groups
- Decreased in-hospital mortality in EI PIP-TAZ group vs. comparator antibiotics (9.7% vs. 17.9%, χ²=0.02)
- EI PIP-TAZ prolonged survival by 2.77 days (p=0.01) and reduced mortality (odds ratio 0.43, p=0.05)
Comparison of mortality rates in the a priori subgroups in the RECEIPT Study

Conclusions
- PD dosing using EI PIP-TAZ decreased in-hospital mortality vs. comparative, nonextended β-lactam in patients with Gm-negative infections
- Hospital LOS, ICU LOS, and antibiotic treatment duration not significantly impacted by EI PIP-TAZ

Objective
- Clinical and pharmacoeconomic outcomes of conventional intermittent dosing of PIP-TAZ and meropenem vs. prolonged infusions in critically ill patients

Design
- Retrospective, observational study
- Comparison of two study groups (meropenem dosing not shown):
  1) Piperacillin-tazobactam 3.375 g over 30 min q6h
  2) Piperacillin-tazobactam 3.375 g over 4hrs q8h
- Demographic characteristics, disease severity, and microbiology data collected, and outcomes compared

Inclusion – Patients admitted to the med-surg ICU and:
- age 18-89 years
- ≥72 hrs therapy with PIP-TAZ or meropenem

Exclusion – Patients meeting any of the following:
- Receiving continuous renal replacement therapy (CRRT)
- Diagnosis of cystic fibrosis

Outcomes assessment
- Duration of ventilator support
- ICU length of stay (LOS)
- Hospital LOS
- In-hospital mortality

Conclusions
- Prolonged infusions of PIP-TAZ and meropenem potentially improve clinical outcomes in critically ill patient populations
- As antibiotic resistance increases in Gm-negative pathogens, β-lactam dose optimization strategies will be important for appropriate treatment
## SUMMARY OF CLINICAL OUTCOMES ACROSS STUDIES

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Design</th>
<th>N</th>
<th>Traditional Infusion</th>
<th>Prolonged/Continuous Infusion</th>
<th>Clinical Cure n/N (%)</th>
<th>Bacteriologic Cure n/N (%)</th>
<th>Mortality n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lodise (2007)</td>
<td>Retrospective cohort</td>
<td>22</td>
<td>2.5 g IV q8h over 30’ (n=8)</td>
<td>3.15 g over 4h (n=15)</td>
<td>NR</td>
<td>NR</td>
<td>14/92 (15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.15 g over 4h (n=8)</td>
<td>3.375 g over 30’ q4h (n=4)</td>
<td>NR</td>
<td>NR</td>
<td>9/102 (8.8)</td>
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<tr>
<td>Patel (2009)</td>
<td>Retrospective cohort</td>
<td>129</td>
<td>3.375-4.5 g over 30’ q6-8h (n=59)</td>
<td>3.375 g over 4h q8h (n=70)</td>
<td>NR</td>
<td>NR</td>
<td>5/59 (8.5)</td>
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<td></td>
<td>3.375 g over 4h q8h (n=102)</td>
<td>NR</td>
<td>NR</td>
<td>4/70 (5.7)</td>
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<tr>
<td>Yost (2011)</td>
<td>Retrospective cohort</td>
<td>270</td>
<td>Doses unspecified (n=84)</td>
<td>3.375 g over 4h q8h (n=186)</td>
<td>NR</td>
<td>NR</td>
<td>17/84 (20.2)</td>
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<td>3.375 g over 4h q8h (n=186)</td>
<td>NR</td>
<td>NR</td>
<td>18/186 (9.7)</td>
<td></td>
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<tr>
<td>Grant (2002)</td>
<td>Retrospective cohort</td>
<td>37</td>
<td>3.375 g over 4h q8h (n=49)</td>
<td>9 g over 24h for comm.-acquired (n=24)</td>
<td>42/51 (82)</td>
<td>44/47 (94)</td>
<td>24/33 (73)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9 g over 24h for nosocomial (n=23)</td>
<td>21/28 (89)</td>
<td>5/51 (9.8)</td>
<td>1/47 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Lorente (2009)</td>
<td>Retrospective cohort</td>
<td>48</td>
<td>4.5 g over 30’ q6h (n=46)</td>
<td>18 g over 24h (n=37)</td>
<td>24/46 (57)</td>
<td>33/37 (89)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18 g over 24h (n=37)</td>
<td>NR</td>
<td>NR</td>
<td>14/46 (30)</td>
<td></td>
</tr>
<tr>
<td>Buck (2005)</td>
<td>Prospective, randomized, open-label</td>
<td>49</td>
<td>4.5 g over 4h q8h (n=12)</td>
<td>9 g over 24h (n=12)</td>
<td>8/12 (67)</td>
<td>8/12 (67)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9 g over 24h (n=12)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Lau (2006)</td>
<td>Prospective, randomized, open-label</td>
<td>50</td>
<td>3.375 g over 30’ q6h (n=132)</td>
<td>13.5 g over 24h (n=130)</td>
<td>78/86 (88)</td>
<td>70/81 (86)</td>
<td>49/58 (85)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13.5 g over 24h (n=130)</td>
<td>NR</td>
<td>NR</td>
<td>46/56 (82)</td>
<td></td>
</tr>
</tbody>
</table>


### Pharmacoeconomic & Safety Implications

**Pharmacoeconomic Implications**

- **Lodise et al.**
  - At 651-bed facility EI dosing reduced direct drug acquisition costs by $68,750 – $137,500 per year
  - Decreased LOS in pts with APACHE-II score ≥17
  - Potential savings of $30,000/pt. receiving EI dosing

- **Grant et al.**
  - All costs directly related to antibiotic use significantly lower for continuous vs. intermittent infusion ($399.38 ± 407.22 vs. $523.49 ± $526.86, p=0.028)


**Pharmacotherapy. 2012;32(8):707-721.**

### Safety Implications

- **“Primum non nocere” (First, do no harm)**
- Safety profile appears comparable to traditional infusion PIP-TAZ
- In study by Kim et al., no adverse events were noted after multiple administrations of 6.75 or 9 g (combined total potency 6:0.75 and 8:1) q12 hrs
- More safety studies needed


**Pharmacotherapy. 2012;32(8):707-721.**

**Pharmacotherapy. 2012;32(8):707-721.**
Safety Implications: Renal Dosing

Inconsistent dosing recommendations in literature for patients with CrCl ≤20 mL/min (includes peritoneal & hemodialysis):

- 3.375 g (over 4 hrs) q12h
  - Sanford Guide, 2012; Patel et al. 2010; Nebraska Medical Center, 2010
- 3.375 g (over 30 min) q12h
  - Lodise et al., 2006

Safety Implications: Renal Dosing

Inconsistencies for renal dosing (continued):

- CrCl >40 mL/min: 4.5 g (over 4 hrs) q6h
- CrCl 20-40 mL/min: 3.375 g (over 4 hrs) q6h
- CrCl <20 mL/min or HD: Renal adjust dose (over 30 min)
  - Johns Hopkins Antimicrobial Stewardship Program
  - EI dosing in this group “...not currently supported.”
  - George et al.

Summary & Conclusions

EXTENDED INFUSION PIPERACILLIN-TAZOBACTAM

- Two 'pillars' of evidence support EI administration of PIP-TAZ:
  1. Pharmacodynamic evidence
  2. Clinical outcomes evidence
- Pharmacodynamic evidence well established
- Clinical outcomes data less robust, with need for more large-scale, prospective clinical outcomes studies

Summary & Conclusions

- Dose optimization worthy of consideration in light of recent data demonstrating approved dosage regimens incapable of achieving optimal outcomes
- Clinical studies indicate EI dosing strategies may have greatest observable impact on critically ill patients
- EI PIP-TAZ appears to be as safe as standard intermittent dosing (“Primum non nocere”)
- EI dosing appears to provide pharmacoeconomic benefits without sacrificing quality of care

To Extend, or Not to Extend? That is the question!
Summary & Conclusions

- Because near-maximal bactericidal effect observed when PIP-TAZ concentrations exceed MIC for 50% of dosing interval, EI dosing provides bactericidal exposure similar to that of continuous infusion

- Standard EI regimen of 3.375 g (over 4 hrs) q8hr likely inadequate for P. aeruginosa isolates with MICs ≥32. Instead, higher dose EI regimens of 4.5 g (over 3 or 4 hrs) q6h necessary for organisms with this MIC

Post-Test Questions

Arkansas Association of Health-System Pharmacists

Question #1

- Which of the following antimicrobial drugs has a PD profile that is time-dependent?
  
  A. Gentamicin  
  B. Levofoxacin  
  C. Daptomycin  
  D. Meropenem

Question #2

- Which of the two “pillars” of evidence supporting EI dosing of piperacillin-tazobactam is most well-established?
  
  A. Clinical outcomes evidence  
  B. Pharmacodynamic evidence

Question #3

- For piperacillin-tazobactam and other β-lactams, the PD parameter that best predicts the degree of bactericidal activity is:
  
  A. AUC:MIC  
  B. C_{max}:MIC  
  C. fT>MIC  
  D. MIC
Question #4

Clinical studies indicate the population most likely to benefit from EI dosing strategies are patients who:

A. are critically ill
B. infected with pathogens with higher MICs
C. have an APACHE-II score of ≥17
D. All of the above (A, B and C)

Question #5

Guidelines of the Infectious Diseases Society of America recommend EI dosing as one piece of a multifaceted strategy for antimicrobial stewardship in hospitals.

A. True
B. False

Answers to Post-Test Questions

1) D (Meropenem)
2) B (Pharmacodynamic evidence)
3) C (fT>MIC)
4) D (All of the above)
5) A (True)

References

References


References


References


References


References

(33) Lexi-Comp, Inc. Piperacillin and tazobactam sodium: drug information. www.uptodate.com

References


References