Extended Infusion Piperacillin-Tazobactam

• RATIONALE • EVIDENCE • CONCLUSIONS •

Scott Eric Kaufman, RN, PharmD

Assistant Professor
UAMS College of Pharmacy
Northwest Campus
Fayetteville, Arkansas

Clinical Specialist
Department of Pharmacy
Mercy Medical Center
Rogers, Arkansas

UAMS COLLEGE OF PHARMACY

Conflict of Interest Disclosure

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

Learning Objectives

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- 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 *f*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

Introduction & Background

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EXTENDED INFUSION PIPERACILLIN-TAZOBACTAM

What Do These Hospitals Have In Common?

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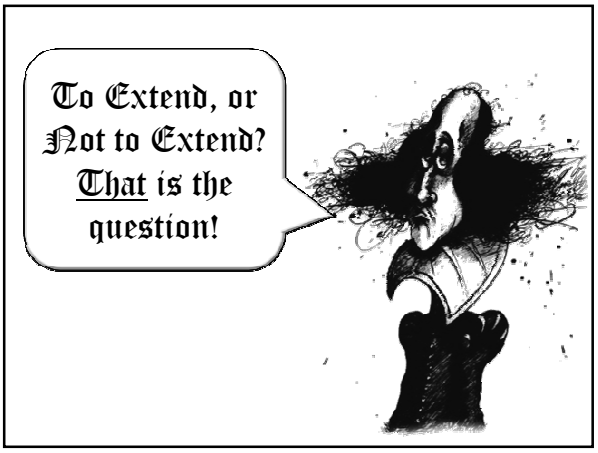
- Johns Hopkins University Hospital
- Stanford University Hospital
- Baylor University Medical Center
- Vanderbilt University Medical Center
- University of California San Diego Medical Center
- University of Iowa Hospitals
- Robert Wood Johnson University Hospital
- LSU Health Sciences Center
- Nebraska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

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



Two Trends Threatening Hospitals Today

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(1) alarming rise in antibiotic resistance

(2) diminishing antibiotic pipeline as major drug companies withdraw from antibiotic market

Clin Infect Dis 2011;52(S5):S397–S428.
Pharmacotherapy 2012; 32(8):707-721.

Antimicrobial Resistance

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- 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

Clin Infect Dis 2011;52(S5):S397–S428.
JAMA 2007; 298:1763–71.

Hospital-Acquired Infections (HAIs)

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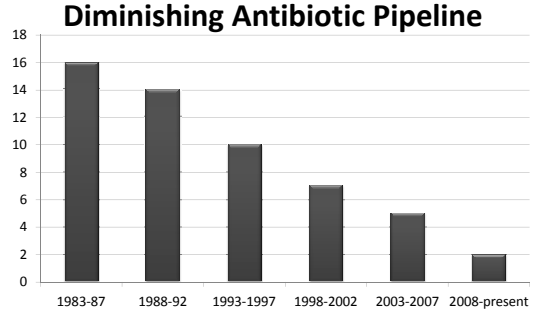
- Occur in ~2 million Americans per year
- Result in 99,000 deaths per year, mostly due to antibiotic-resistant pathogens (e.g., *Pseudomonas aeruginosa*)
- Two common HAIs—sepsis and pneumonia:
  - killed ~50,000 Americans
  - cost US health care system >$8 billion in 2006

Clin Infect Dis 2011;52(S5):S397–S428.
Arch Intern Med 2010; 170:347–53.

Diminishing Antibiotic Pipeline



New Molecular Entity Systemic Antibiotics Approved in the U.S.
(1983-Present, per 5-Year Period)

Adapted from: *Clin Infect Dis* 2011;52(S5):S397–S428, and IDSA Policy Statement, March 8, 2012

What Can We Do About It?

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- 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

Clin Infect Dis 2007;44:159-177.
Pharmacotherapy 2012; 32(8):707-721.

Potential Benefits of Dose Optimization

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

Infect Dis Clin Pract 2011;19:413-417
Pharmacotherapy 2006;26(9):1320-1332
Pharmacotherapy 2012; 32(8):707-721.

Dose Optimization

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- 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

Pharmacotherapy 2012; 32(8):707-721.
Am J Health-Syst Pharm. 2011; 68(16):1521-1526.

What is EI Piperacillin-Tazobactam?

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- 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)

Am J Health-Syst Pharm. 2011; 68(16):1521-1526.
Zosyn® (piperacillin and tazobactam for injection) package insert.
Pharmacotherapy 2012; 32(8):707-721.

Piperacillin-Tazobactam

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

Pharmacotherapy 2012; 32(8):707-721.
Clin Infect Dis 2007; 44:357–63.

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

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- 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

Clin Infect Dis 2007;44:159-177.
Pharmacotherapy 2012; 32(8):707-721.

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…"

Clin Infect Dis 2007;44:159-177.

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

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for use
Quality of evidence	
I	Evidence from ≥1 properly randomized, controlled trial
II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Clin Infect Dis 2007;44:159-177.

Pharmacodynamic Rationale

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EXTENDED INFUSION PIPERACILLIN-TAZOBACTAM

Antimicrobial Pharmacodynamics: The critical interaction between "bug and drug"

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- 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

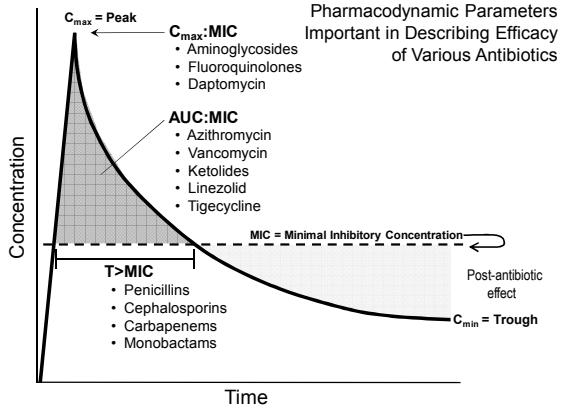
Pharmacotherapy 2006;26(9):1320-1332
Am J Health-Syst Pharm 2011;68:1521-1526

Antimicrobial Pharmacodynamic Target Parameters Associated with Maximal Effect

Bacterial Killing	Examples	Therapy Goal	PD Parameter
Concentration-Dependent	Aminoglycosides Fluoroquinolones Metronidazole Daptomycin	Maximize exposure	C_{max}:MIC 24-hr AUC:MIC
Concentration-Dependent or Time-Dependent	Azithromycin Vancomycin Clindamycin Ketolides Tigecycline Linezolid	Maximize exposure	24-hr AUC:MIC
Time-dependent	β-lactams: Penicillins Cephalosporins Carbapenems Monobactams	Optimize duration of exposure >MIC	*f*T>MIC

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

Pharmacodynamic Parameters Important in Describing Efficacy of Various Antibiotics



Adapted from: *Am J Med* 2006;119(6A):S37–S44, and *Clin Infect Dis* 2007; 44:79–86

β-Lactam Pharmacodynamics

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

Clin Infect Dis 2007;44:357-363.
Clin Infect Dis 2003;36(suppl 1):S42-50.

β-Lactam Pharmacodynamics

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- For penicillins, *f*T>MIC must be:
  - >30% of dosing interval to produce bacteriostasis
  - ≥50% of dosing interval for optimum (maximal) bactericidal effect
- Required %T>MIC for maximal bactericidal effect:
  - ~60-70% for cephalosporins
  - ~50% for penicillins
  - ~40% for carbapenems

Clin Infect Dis 2007;44:357-363.
Clin Infect Dis 2003;36(suppl 1):S42-50.

Beta-Lactam Pharmacodynamics

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- *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 implementating EI dosing policies in hospitals across U.S. in recent years

Diagn Microbiol Infect Dis. 2009; 64:236-40.
Clin Infect Dis. 2007; 44:79-86. [Erratum, *Clin Infect Dis.* 2007; 44:624.]
Am J Health-Syst Pharm. 2009; 66(suppl 4):S23-30.
Pharmacotherapy 2006;26(9):1320-1332
Am J Health-Syst Pharm 2011;68:1521-1526

Available online at www.sciencedirect.com
ScienceDirect
Diagnostic Microbiology and Infectious Disease 64 (2009) 236–240
DIAGNOSTIC MICROBIOLOGY AND INFECTIOUS DISEASE
www.elsevier.com/locate/diagmicrobio

Outcomes of extended infusion piperacillin/tazobactam for documented Gram-negative infections☆

Gita Wasan Patel[a], Nimish Patel[b], Asma Lat[a], Kristen Trombley[b], Sam Enbawe[b], Kelli Manor[d], Raymond Smith[d], Thomas P. Lodise Jr.[b,c,*]

- "Optimizing the pharmacokinetics and pharmacodynamics of antimicrobial agents is critical for successfully treating infectious diseases…"
- "Traditional dosing of piperacillin-tazobactam does not provide adequate *f*T>MIC for organisms with an MIC greater than 8 mg/L. ***Thus, it is imperative to find alternative dosing regimens that maximize fT>MIC.***"

Diagn Microbiol Infect Dis. 2009;64:236-40.

Pharmacodynamic Evidence

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EXTENDED INFUSION PIPERACILLIN-TAZOBACTAM

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

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- 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

Kim *et al. Pharmacotherapy* 2007;27(11):1490–1497

Monte Carlo Simulation

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- 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

Clin Infect Dis 2007;44:79-86.
Pharmacotherapy 2006;26(9):1320-1332.
Nat Rev Microbiol. 2004; 2:289-300.

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

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- 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 3.375 g q6hr (13.5 g/day)
      - 100% for prolonged- & continuous-infusions (12 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)

Kim *et al. Pharmacotherapy* 2007;27(11):1490–1497

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

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- 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

Kim *et al. Pharmacotherapy* 2007;27(11):1490–1497

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

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- 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% *f*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

Clin Infect Dis 2007;44:357-363.
Pharmacotherapy 2006;26(9):1320-1332.

Potential Ways of Maximizing T>MIC

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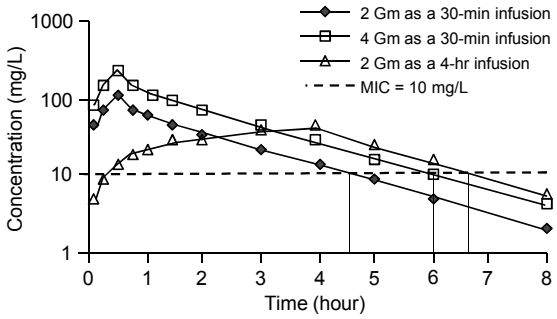
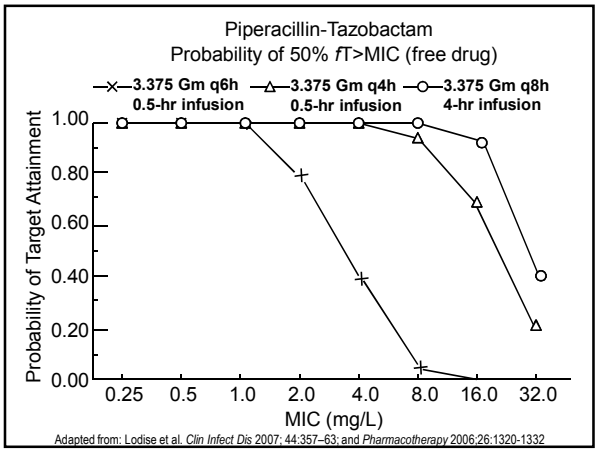
- Higher dose
- Increase dosing frequency
- Increase duration of infusion (prolonged)
- Increased duration of infusion (continuous)

Adapted from: Lodise TP. Module: Applied Antimicrobial Pharmacodynamics. *Society of Infectious Disease Pharmacists Antimicrobial Stewardship Certification Program* 2010.

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



Pharmacotherapy 2006;26(9):1320-1332.



Adapted from: Lodise et al. *Clin Infect Dis* 2007; 44:357–63; and *Pharmacotherapy* 2006;26:1320-1332

Intermittent vs. Prolonged Infusions of Piperacillin-Tazobactam

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RESEARCH REPORTS

Infectious Diseases

Comparative Pharmacodynamics of Intermittent and Prolonged Infusions of Piperacillin/Tazobactam Using Monte Carlo Simulations and Steady-State Pharmacokinetic Data from Hospitalized Patients

Ann Pharmacother. 2009; 43:1747-1754.

Cumulative Fraction of Response at 50% *f*T>MIC for Intermittent and Prolonged Infusions of Piperacillin-Tazobactam Against Gram-Negative Pathogens

REGIMEN	*Escherichia coli*	*Klebsiella pneumoniae*	*Enterobacter spp.*	*Serratia marcescens*	*Citrobacter spp.*	*Pseudomonas aeruginosa*
Intermittent (30-minute) Infusions						
4.5 g q8h	92.2	81.8	81.5	92.4	85.4	75.8
3.375 g q6h	94.5	84.1	83.1	94.5	87.7	78.5
4.5 g q6h	95.2	85.3	85.8	95.8	89.5	82.2
3.375 g q4h	96.8	86.6	87.8	97.1	91.4	84.9
Prolonged (4-hour) Infusions						
2.25 g q8h	96.0	85.6	82.9	95.2	87.5	79.9
3.375 g q8h	96.4	86.9	85.9	96.3	90.3	83.5
4.5 g q8h	98.0	87.0	88.6	100	91.3	85.5
6.75 g q8h	100	87.8	90.8	100	93.2	88.0

Ann Pharmacother. 2009; 43:1747-1754.

Intermittent vs. Prolonged Infusions of Piperacillin-Tazobactam

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

Ann Pharmacother. 2009; 43:1747-1754.

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)

Dosing Regimen	CrCl (mL/min)	Probability of Target Attainment (50% *f*T>MIC) MIC 4 μg/ml	MIC 8 μg/ml	MIC 16 μg/ml	MIC 32 μg/ml
Intermittent Infusion (30 min)					
4.5 g q6h	100	81%	67%	46%	19%
4.5 g q6h	60	92%	84%	70%	43%
3.375 g q6h	40	95%	90%	77%	50%
3.375 g q6h	20	98%	95%	88%	73%
Extended (Prolonged) Infusion (4 hrs)					
3.375 g q8h	100	99%	97%	73%	17%
3.375 g q8h	60	99%	99%	90%	43%
3.375 g q8h	40	99%	99%	95%	62%
3.375 g q8h	20	99%	99%	97%	81%
3.375 g q12h	40	90%	79%	52%	16%
3.375 g q12h	20	96%	90%	74%	40%

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

Nosocomial Infections

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Population Pharmacokinetics of Extended-Infusion Piperacillin-Tazobactam in Hospitalized Patients with Nosocomial Infections

T. W. Felton,[a] W. W. Hope,[a] S. M. Lomaestro,[b] J. M. Butterfield,[c] A. L. Kwa,[d] G. L. Drusano,[e] and T. P. Lodise[c]

- More intensive EI dosing schemes (3.375-4.5 g [3-hr infusion] q6hr) than commonly used are needed to maximize *f*T>MIC for MICs ≥8 mg/L
- EI PIP-TAZ most effective method of administration for patients with nosocomial infections

Antimicrob Agents Chemother 2012 Aug; 56(8):4087-4094.

Clinical Outcomes Evidence

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EXTENDED INFUSION PIPERACILLIN-TAZOBACTAM

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

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- 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

Clin Infect Dis 2007; 44:357–63)

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

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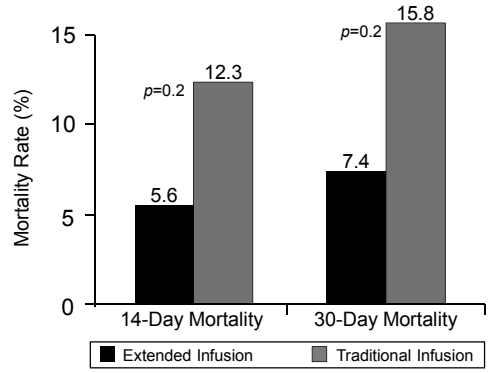
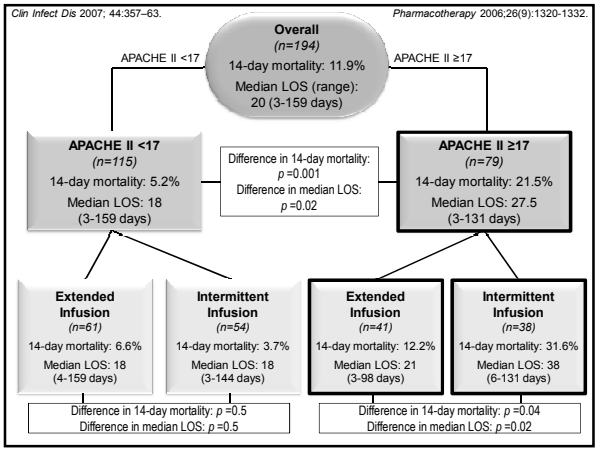
- Inclusion – Patients positive for *P. aeruginosa and:*
  - Age ≥18 years
  - Absolute neutrophil count ≥1000 cells/mm3
  - *P. aeruginosa* culture result meeting CDC criteria for infection
  - Received PIP-TAZ therapy within 72 hrs of onset
  - Received PIP-TAX therapy for ≥48 hours
- Exclusion – Patients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

Clin Infect Dis 2007; 44:357–63)



Clin Infect Dis 2007; 44:357–63. *Pharmacotherapy* 2006;26(9):1320-1332.



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

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- 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

Clin Infect Dis 2007; 44:357–63.

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

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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

Clin Infect Dis 2007; 44:357–63.
Am J Health-Syst Pharm. 2011; 68(16):1521-1526.
Zosyn® (piperacillin and tazobactam for injection) package insert.

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

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- 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

Diagn Microbiol Infect Dis. 2009; 64:236-40.

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

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Outcomes Overall	Intermittent Infusion (n=59)	Extended Infusion (n=70)
30-day mortality	5 (8.5%)	4 (5.7%)
Hospital LOS (median days)		
Overall	8 (5-11)	8 (5.5-15)
MIC <8 mg/L	8 (5-11)	8 (5.5-15)
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

Diagn Microbiol Infect Dis. 2009; 64:236-40.

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

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Important Considerations/Shortcomings

- Most MICs <8 mg/L, and PIP-TAZ administered by traditional infusion achieves an adequate *f*T>MIC in that range
- Higher dosing (4.5 g) often used in traditional infusion group, whereas EI group limited to 3.375 g
- Low disease severity in most patients
- Small sample size: >1300 patients required in each group to detect 30-day mortality difference

Diagn Microbiol Infect Dis. 2009; 64:236-40.
Am J Health-Syst Pharm. 2011; 68(16):1521-1526.

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

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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

Pharmacotherapy 2011;31(8):767–775.

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

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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

Pharmacotherapy 2011;31(8):767–775.

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

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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

Pharmacotherapy 2011;31(8):767–775.

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

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Outcomes Analysis

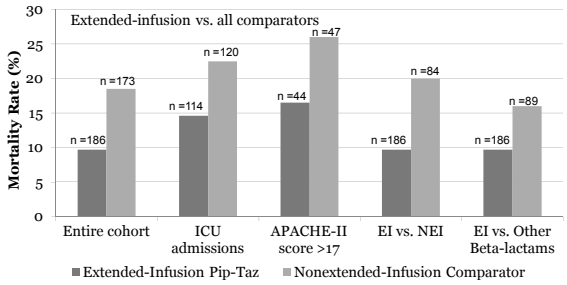
- Primary – Mortality rate of patients receiving EI PIP-TAZ vs. nonextended-infusion β-lactams
- Secondary – Hospital LOS, ICU LOS, and total duration of antibiotic therapy

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%, p=0.02)
- EI PIP-TAZ prolonged survival by 2.77 days (p=0.01) and reduced mortality (odds ratio 0.43, p=0.05)

Pharmacotherapy 2011;31(8):767–775.

Comparison of mortality rates in the *a priori* subgroups in the RECEIPT Study



Pharmacotherapy 2011;31(8):767–775.

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

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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

Pharmacotherapy 2011;31(8):767–775.

Retrospective Study of Prolonged Versus Intermittent Infusion Piperacillin-Tazobactam and Meropenem in ICU Patients

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- 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

Infect Dis Clin Pract 2011;19:413-417.

Retrospective Study of Prolonged Versus Intermittent Infusion Piperacillin-Tazobactam and Meropenem in ICU Patients

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- 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

Infect Dis Clin Pract 2011;19:413-417.

Retrospective Study of Prolonged Versus Intermittent Infusion Piperacillin-Tazobactam and Meropenem in ICU Patients

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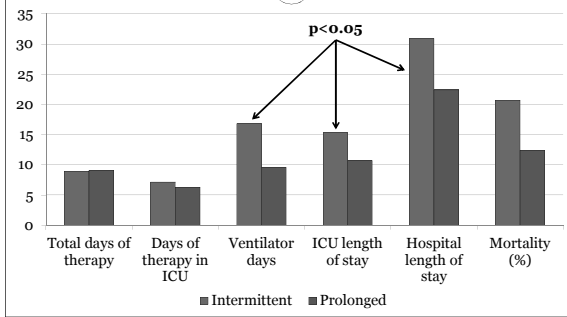

Infect Dis Clin Pract 2011;19:413-417.

Retrospective Study of Prolonged Versus Intermittent Infusion Piperacillin-Tazobactam and Meropenem in ICU Patients

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- 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

Infect Dis Clin Pract 2011;19:413-417.

SUMMARY OF CLINICAL OUTCOMES ACROSS STUDIES

Ref.	Design	N	Traditional Infusion	Prolonged/ Continuous Infusion	Clinical Cure n/N (%)		Bacteriologic Cure n/N (%)		Mortality n/N (%)	
					TI	PI/C	TI	PI/C	TI	PI/C
Lodise (2007)[22]	Retrospective cohort	194	3.375 g over 30" q4h (n=4) 3.375 g over 30" q4h (n=88)	3.375 g over 4h q8h (n=102)	NR	NR	NR	NR	14/92 (15)	9/102 (8.8)
Patel (2009)[18]	Retrospective cohort	129	3.375-4.5 g over 30" q6-8h (n=59)	3.375 g over 4h q8h (n=70)	NR	NR	NR	NR	5/59 (8.5)	4/70 (5.7)
Yost (2011)[24]	Retrospective cohort	270	Doses unspecified (n=84)	3.375 g over 4h q8h (n=186)	NR	NR	NR	NR	17/84 (20.2)	18/186 (9.7)
Grant (2002)[37]	Retrospective cohort	98	3.375 q6h (n=2) 4.5 q8h (n=49)	9 g q24h for comm.-acquired (n=24) 13.5 g q24h for nosocomial (n=23)	42/51 (82)	44/47 (94)	24/33 (73)	21/28 (89)	5/51 (9.8)	1/47 (2.1)
Lorente (2009)[48]	Retrospective cohort	83	4.5 over 30" q6h (n=46)	18 g q24h (n=37)	24/46 (57)	33/37 (89)	NR	NR	14/46 (30)	8/37 (22)
Buck (2005)[49]	Prospective, randomized, open-label	24	4.5 q8h (n=12)	9 g q24h (n=12)	8/12 (67)	8/12 (67)	NR	NR	NR	NR
Lau (2006)[50]	Prospective, randomized, open-label	262	3.375 g over 30" q6h (n=132)	13.5 g q24h (n=130)	78/86 (88)	70/81 (86)	49/58 (85)	46/56 (82)	3/132 (2.3)	1/130 (0.8)

Adapted from: *Ann Pharmacother* 2012;46:265-275.

Pharmacoeconomic & Safety Implications

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EXTENDED INFUSION PIPERACILLIN-TAZOBACTAM

Pharmacoeconomic Implications

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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)

Clin Infect Dis 2007;44:357-363.
Pharmacotherapy 2006;26(9):1320-1332.
Pharmacotherapy 2012;32(8):707-721.
Pharmacotherapy. 2002; 22:471-83.

Pharmacoeconomic Implications

64

Xamplas et al.

- Changing to EI dosing resulted in significant (p=0.001) reduction in mean doses/1000 pt. days
- 24% reduction in total grams PIP-TAZ per year during study period
- Reduction in total doses and grams of drug translated to cost savings of $107,592/year

Heinrich et al.

- Estimated annual cost savings of >$100,000 at their 489 bed academic medical center

Am J Health-Syst Pharm. 2010; 67:622-8.
J Pharm Pract 2011;00:1–6.
Pharmacotherapy 2012;32(8):707-721.

Pharmacoeconomic Implications

65

- Successful Antimicrobial Stewardship Program (ASP) provides a strategy to optimize antibiotic therapy while minimizing over-/underutilization of antibiotics
- EI dosing economically favored since lower total daily doses used, yet are shown to have similar or greater likelihood of achieving PK/PD targets

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

Safety Implications

66

- "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

Am J Health-Syst Pharm. 68(16):1521-1526, August 15, 2011.
J Antimicrob Chemother. 2001; 48:259-67.
Pharmacotherapy 2012;32(8):707-721.

Safety Implications: Renal Dosing

67

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

The Sanford Guide to Antimicrobial Therapy 2012, 42nd ed. Sperryville, VA; 2012
Patel et al. *Antimicrob Agents Chemother* 2010;54(1):460-465.
Njoku et al. Nebraska Medical Center, 2010 (See Reference 54)
Lodise et al. *Pharmacotherapy* 2006;26(9):1320-1332.

Safety Implications: Renal Dosing

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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.

Johns Hopkins Antimicrobial Stewardship Program. (See Reference 53).
Pharmacotherapy 2012;32(8):707-721.

Summary & Conclusions

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EXTENDED INFUSION PIPERACILLIN-TAZOBACTAM

Summary & Conclusions

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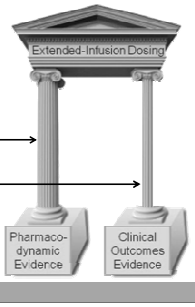
- Two 'pillars' of evidence support EI administration of PIP-TAZ:
  (1) Pharmacodynamic evidence
  (2) Clinical outcomes evidence
- Pharmacodynamic evidence well established
- Clinical outcomes data less robust, with need for more large-scale, prospective clinical outcomes studies



Summary & Conclusions

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- 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

Summary & Conclusions

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- 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

Summary & Conclusions

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- IDSA guideline recommend EI dosing as one piece of a multifaceted approach to antimicrobial stewardship (A-II graded recommendation)
- Overall, available evidence from PK-PD, clinical outcomes, and pharmacoeconomic studies consistently suggest that EI administration of PIP-TAZ is a safe, efficacious, cost-effective, and potentially superior strategy compared with traditional 30-minute infusions

Post-Test Questions

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Arkansas Association of Health-System Pharmacists

Question #1

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

Question #2

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- 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

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- 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. *f*T>MIC
  - D. MIC

Question #4

79

- 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

80

- 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

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1) D (Meropenem)

2) B (Pharmacodynamic evidence)

3) C (*f*T>MIC)

4) D (All of the above)

5) A (True)

Questions?

Arkansas Association of Health-System Pharmacists

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References

83

(1) Infectious Diseases Society of America (IDSA). Combating antimicrobial resistance: Policy recommendations to save lives. *Clin Infect Dis* 2011;52(S5):S397–S428.

(2) George JM, Towne TG, Rodvold KA. Prolonged infusions of β-lactam antibiotics: Implication for antimicrobial stewardship. *Pharmacotherapy* 2012;32(8):707-721.

(3) Klevens RM, Morrison MA, Nadle J, et al. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. *JAMA* 2007; 298:1763–71.

(4) Eber MR, Laxminarayan R, Perencevich EN, Malani A. Clinical and economic outcomes attributable to health care-associated sepsis and pneumonia. *Arch Intern Med* 2010; 170:347–53.

References

84

(5) IDSA. IDSA Policy Statement: Promoting Anti-Infective Development and Antimicrobial Stewardship through the U.S. Food and Drug Administration Prescription Drug User Fee Act (PDUFA) Reauthorization. March 8, 2012. Accessed August 7, 2012 at: http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Advancing_Product_Research_and_Development/Bad_Bugs_No_Drugs/Statements/IDSA%20PDUFA%20GAIN%20Testimony%20030812%20FINAL.pdf

(6) IDSA. "Principles & Strategies Intended To Limit The Impact of Antimicrobial Resistance" Retrieved from: http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Advancing_Product_Research_and_Development/STAAR_Act/Statements/Principles%20and%20Strategies%20to%20Limit%20the%20Impact%20of%20Antimicrobial%20Resistance.pdf#search=%22principles strategies%22

References

85

(7) Dellit et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship. *Clin Infect Dis* 2007;44:159-177.

(8) Kaufman SE, Donnell RW, Hickey WS. Rationale and evidence for extended infusion of piperacillin-tazobactam. *Am J Health-Syst Pharm*. 68(16):1521-1526, August 15, 2011.

(9) Zosyn® (piperacillin and tazobactam for injection) package insert. Philadelphia:Wyeth Pharmaceuticals; Revised May 2012.

(10) Lodise TP, Lomaestro BM, Drusano GL. Application of antimicrobial pharmacodynamic concepts into clinical practice: focus on β–lactam antibiotics. *Pharmacotherapy* 2006;26(9):1320-1332.

(11) Craig, W. A. Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. *Infect Dis Clin North Am* 2003; 17:479-501.

References

86

(12) Ambrose PG, Bhavnani SM, Rubino CM, et al. Pharmacokinetics-Pharmacodynamics of Antimicrobial Therapy: It's Not Just for Mice Anymore. *Clin Infect Dis* 2007;44:79-86. [Erratum, *Clin Infect Dis*. 2007; 44:624.]

(13) Drusano GL, Craig WA. Relevance of pharmacokinetics and pharmacodynamics in the selection of antibiotics for respiratory tract infections. *J Chemother* 1997;9:38-44.

(14) Drusano G, Labro MT, Cars O, et al. 1998. Pharmacokinetics and pharmacodynamics of fluoroquinolones. *Clin Microbiol Infect* 1998; 4(Suppl. 2):S27-S41.

(15) Gilbert DN, Moellering RC Jr, Eliopoulos GM, Chambers HF, Saag MS, eds. *The Sanford Guide to Antimicrobial Therapy 2012*, 42nd ed. Sperryville, VA: Antimicrobial Therapy; 2012

References

87

(16) Rybak MJ. Pharmacodynamics: Relation to Antimicrobial Resistance. *Am J Med* 2006;119(61):S37-S44.

(17) Owens RC, Shorr AF. Rational dosing of antimicrobial agents: pharmacokinetic and pharmacodynamic strategies. *Am J Health-Syst Pharm*. 2009; 66(suppl 4):S23-30.

(18) Patel GW, Patel N, Lat A et al. Outcomes of extended infusion piperacillin/tazobactam for documented Gram-negative infections. *Diagn Microbiol Infect Dis*. 2009; 64:236-40.

(19) Lodise TP. Module: Applied Antimicrobial Pharmacodynamics. *Society of Infectious Disease Pharmacists Antimicrobial Stewardship Certification Program* 2010. Accessed at: http://www.sidp.org/index.php?module=pagesetter&func=viewpub&tid=6&pid=91

References

88

(20) Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug.' *Nat Rev Microbiol.* 2004; 2:289-300.

(21) Kim A, Sutherland CA, Kuti JL et al. Optimal dosing of piperacillin-tazobactam for the treatment of *Pseudomonas aeruginosa* infections: prolonged or continuous infusion? *Pharmacotherapy*. 2007;27:1490-7.

(22) Lodise TP Jr, Lomaestro B, Drusano GL. Piperacillin-tazobactam for *Pseudomonas aeruginosa* infection: clinical implications of an extended-infusion dosing strategy. *Clin Infect Dis*. 2007; 44:357-63.

(23) Shea KM, Cheatham SC, Smith DW et al. Comparative pharmacodynamics of intermittent and prolonged infusions of piperacillin/tazobactam using Monte Carlo simulations and steady-state pharpharmacokinetic data from hospitalized patients. *Ann Pharmacother*. 2009; 43:1747-1754.

References

89

(24) Yost RJ, Cappelletty DM, and the RECEIPT Study Group. The Retrospective Cohort of Extended-Infusion Piperacillin-Tazobactam (RECEIPT) Study: A Multicenter Study. *Pharmacotherapy* 2011;31(8):767–775.

(25) Kim MK, Xuan D, Quintiliani R et al. Pharmacokinetic and pharmacodynamic profile of high dose extended interval piperacillin-tazobactam. *J Antimicrob Chemother*. 2001; 48:259-67.

(26) Mah GT, Mabasa VH, Chow I, Ensom MHH. Evaluating outcomes associated with alternative dosing strategies for piperacillin/tazobactam: a qualitative systematic review. *Ann Pharmacother* 2012;46:265-275.

(27) Arnold A et al. Empiric therapy for gram-negative pathogens in nosocomial and health careassociated pneumonia: starting with the end in mind. *J Intensive Care Med. 2010;*25:259-70.

References

90

(28) DiPiro JT, Spruill WJ, Wade WE et al. *Concepts in clinical pharmacokinetics*. 5th ed. Bethesda, MD: American Society of Health-System Pharmacists; 2010:1.

(29) Craig WA . Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis*. 1998; 26:1-10.

(30) Rodvold KA. Pharmacodynamics of antiinfective therapy: taking what we know to the patient's bedside. *Pharmacotherapy*. 2001; 21(11, suppl):319S-330S.

(31) Lacy MK, Nicolau DP, Nightingale CH et al. The pharmacodynamics of aminoglycosides. *Clin Infect Dis 1998; 27:23-7.*

(32) Lode H, Borner K, Koeppe P. Pharmacodynamics of fluoroquinolones. *Clin Infect Dis. 1998; 27:33-9.*

References

91

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

(34) Ambrose PG, Owens RC Jr, Garvey MJ et al. Pharmacodynamic considerations in the treatment of moderate to severe pseudomonal infections with cefepime. *J Antimicrob Chemother*. 2002; 49:445-53.

(35) Pier GB, Ramphal R. *Pseudomonas aeruginosa.* In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and practice of infectious diseases*. 7th ed. Philadelphia:Churchill Livingstone Elsevier; 2010:2835-60.

(36) Piperacillin/tazobactam. *Medical Letter*. 1994; 36(914):7-9.

(37) Grant EM, Kuti JL, Nicolau DP et al. Clinical efficacy and pharmacoeconomics of a continuous-infusion piperacillin-tazobactam program in a large community teaching hospital. *Pharmacotherapy*. 2002; 22:471-83.

References

92

(38) Albany Medical Center. About us. (accessed 2012 August 18) at: www.amc.edu/About%20Us/index.html

(39) American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Resp Crit Care Med.* 2005; 171:388-416.

(40) Abbo L. Antimicrobial stewardship activities for the Jackson Memorial Hospital/University of Miami. www.cdc.gov/getsmart/healthcare/improve-efforts/stories.html (accessed 2011 May 2).

(41) Xamplas RC, Itokazu GS, Glowacki RC et al. Implementation of an extended infusion piperacillin-tazobactam program at an urban teaching hospital. *Am J Health-Syst Pharm*. 2010; 67:622-8.

References

93

(42) Sarubi C. Implementation of a new extended-infusion piperacillin-tazobactam protocol at UCSD Medical Center. http://www.sdshp.cshp.org/uploads/informulary/Informulary_Vol_2_Issue%206.pdf (accessed 2012 August 18).

(43) Dow RJ, Rose WE, Fox BC, et al. Retrospective Study of Prolonged Versus Intermittent Infusion Piperacillin-Tazobactam and Meropenem in Intensive Care Unit Patients at an Academic Medical Center. *Infect Dis Clin Pract* 2011;19:413-417.

(44) Mattoes HM, Kuti JL, Drusano GL, et al. Optimizing antimicrobial pharmacodynamics: dosage strategies for meropenem. *Clin Ther* 2004;26:1187-1198.

(45) Lodise TP, Lomaestro B, Rodvold KA, et al. Pharmacodynamic profiling of piperacillin in the presence of tazobactam in patients through the use of population pharmacokinetic models and Monte Carlo simulation. *Antimicrob Agents and Chemotherapy* 2004;48(12):4718-4724.

References

94

(46) Roberts JA, Kirkpatrick CMJ, Roberts MS, et al. First-dose and steady-state population pharmacokinetics and pharmacodynamics of piperacillin by continuous or intermittent dosing in critically ill patients with sepsis. *Int J Antimicrob Agents* 2010;35:156-163.

(47) Zelenitsky SA, Ariano RE, Zhanel GG. Pharmacodynamics of empirical antibiotic monotherapies for an intensive care unit (ICU) population based on Canadian surveillance data. *J Antimicrob Chemother* 2011;66:343-349.

(48) Lorente L, Jimenez A, Martin MM, et al. Clinical cure of ventilator-associated pneumonia treated with piperacillin/tazobactam administered by continuous or intermittent infusion. *Int J Antimicrob Agents* 2009;33:464-468.

(49) Buck C, Bertram N, Ackermann T, et al. Pharmacokinetics of piperacillin-tazobactam: intermittent dosing versus continuous infusion. *Int J Antimicrob Agents* 2005;25:62-67.

References

95

(50) Lau WK, Mercer D, Itani KM, et al. Randomized, open label, comparative study of piperacillin-tazobactam administered by continuous infusion versus intermittent infusion for treatment of hospitalized patients with complicated intra-abdominal infection. Antimicrob Agents Chemother 2006;50:3556-3561.

(51) Heinrich LS, Tokumaru, Clark NM, et al. Development and implementation of a pipiercillin/tazobactam extended infusion guideline. J Pharm Pract 2011;00:1–6.

(52) Patel N, et al. Identification of Optimal Renal Dosage Adjustments for Traditional and Extended-Infusion Piperacillin-Tazobactam Dosing Regimens in Hospitalized Patients. Antimicrob Agents Chemother 2010;54(1):460-465.

References

96

(53) Johns Hopkins Antimicrobial Stewardship Program. Continuous and Extended Infusion Beta-lactams. Accessed 08.24.2012 at: http://www.hopkinsmedicine.org/amp/includes/Continuous_and_Extended_Infusion_Beta_lactams.pdf

(54) Njoku JC, Hermsen ED, Schooneveld TV. Supporting evidence for extended-infusion piperacillin/tazobactam dosing substitution (updated September 2011). Accessed 08.24.2012 at: http://www.nebraskamed.com/app_files/pdf/careers/education-programs/asp/pip-tazoei_protocol_detail-final.pdf

(55) Felton TW, Hope WW, Lomaestro BM, et al. Population pharmacokinetics of extended-infusion piperacillin-tazobactam in hospitalized patients with nosocomial infections. *Antimicrob Agents Chemother* 2012 Aug; 56(8):4087-4094.