Extended-Infusion Piperacillin/Tazobactam (Zosyn®) Protocol for Adult Patients
9/20/2016TTO

PURPOSE

Piperacillin-Tazobactam (PTZ) is a commonly used broad-spectrum β-lactam antibiotic. Like all β-lactam antibiotics, its bactericidal activity is dependent upon the percentage of time that free drug is above the minimum inhibitory concentration (MIC) of an organism (%*f*T>MIC). In an era of increasing antimicrobial resistance and few new treatment options, it has become necessary to enhance the pharmacokinetic/pharmacodynamic (PK/PD) properties of our current antibiotics. Traditionally, PTZ has been given via a 30 minute intermittent-infusion. However, studies have shown that we can optimize the activity of PTZ to treat more resistant Gram-negative organisms, such as *Pseudomonas aeruginosa*, through the use of an extended-infusion (EI) given over 4 hours. In the case of PTZ this also results in less drug being given and subsequent cost savings.

This protocol outlines the procedures for the automatic interchange of intermittent-infusion PTZ (infused over 30 min) to EI PTZ (infused over 4 hours) for adult patients at all Aspirus acute care locations. The goals of this protocol are to:

- optimize clinical outcomes
- reduce resistance rates
- standardize Epic and Smart pump programming
- decrease drug costs.

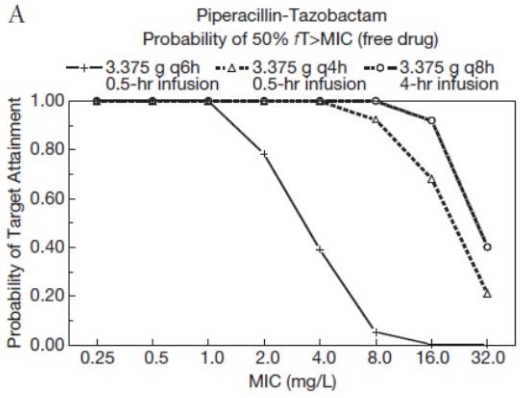
BACKGROUND

The recommended *f*T>MIC to maximize the bactericidal effects of PTZ is 50-60%.[1] The probability of attaining this target in a population of individuals is termed the probability of target attainment (PTA), and ideally is > 90%. The following are studies supporting the use of EI PTZ:

1. Lodise TP, et al. *Pharmacotherapy*. 2006;26(9):1320-1332.[2]
   Lodise TP, et al. *CID*. 2007; 44:357–363.[3]

   Lodise and colleagues utilized Monte-Carlo simulation to identify alternative ways of administering PTZ to optimize clinical outcomes.[2]
   - The standard dosing strategies using intermittent infusions did not provide high probabilities of target attainment for the treatment of *P. aeruginosa* infections with MIC > 8 mg/L.
   - The probabilities of target attainment of 50% *f*T>MIC for PTZ were as follows (**Figure 1**):
     - 3.375g q6h (30 min infusion): > 90% for MIC values ≤ 1 mg/L
     - 3.375g q4h (30 min infusion): > 90% for MIC values up to 8 mg/L
     - 3.375g q8h (4 hour infusion): >90% for MICs up to 16 mg/L
   - The extended 4 hour infusion of PTZ 3.375g IV every 8 hours achieved a PTA > 90% for an MIC < 16 mg/L, and at a lower total daily dose.

Figure 1: Probabilities of Target Attainment with Piperacillin-Tazobactam.[2]



In 2007, Lodise and colleagues published a study in which they utilized the results of this Monte-Carlo simulation to alter the use of PTZ in their clinical practice.[3] A retrospective cohort study was performed in 194 critically ill patients with *P. aeruginosa* infections to compare outcomes in those who received EI PTZ (3.375g IV every 8 hours infused over 4 hours) versus intermittent-infusion PTZ (3.375g IV q4-6h infused over 30min).

- Among the most critically ill patients (APACHE-II scores ≥17), EI PTZ resulted in significantly lower 14-day mortality (12.2% vs. 31.6%, respectively; P=0.04) and duration of hospital stay (21 days vs. 38 days; P=0.02) when compared to those who received intermittent-infusion therapy.

2. Patel GW, et al. *Diagn Microbiol Infect Dis*. 2009;64(2):236-340.[4]

   In 2009, Patel et al. published a retrospective cohort study evaluating the clinical outcomes of EI PTZ (3.375g IV q8 hours infused over 4 hours) versus intermittent-infusion PTZ (3.375-4.5g IV q6-8 hours infused over 30min) in 129 patients.[4]

   - Similar mortality and length of stay were found for both the lower-dose EI PTZ and standard-dose intermittent-infusion PTZ groups.

3. Patel N, et al. *Antimicrob Agents Chemother*. 2010; 54(1):460-465.[5]

   In 2009, Patel et al. published a study examining the effects of various levels of renal function on the PK/PD parameters of intermittent and EI PTZ utilizing population PK modeling.[5]

   - This study found improved PTA for EI PTZ when renally adjusted to be given every 12 hours in those with a CrCl ≤ 20 mL/min.

4. Yost RJ, et al. *Pharmacotherapy*. 2011; 31(8):767-775.[6]

   In 2011, The Retrospective Cohort of Extended-Infusion Piperacillin-Tazobactam (RECEIPT) study group performed a multi-center retrospective study comparing EI PTZ to that of intermittently dosed comparator β-lactams.[6]

   a. In-hospital mortality was significantly decreased for the EI PTZ group versus those receiving comparator antibiotics (9.7% vs 17.9%; P=0.02). Multivariate analysis confirmed that EI PTZ increased survival by 2.77 days (P<0.01) and reduced mortality (OR 0.43; P=0.05).

Economic Evaluation

Current costs at Aspirus Wausau Hospital:

Zosyn 2.25 gm premixed bag = $7.00
3.375 gm premixed bag = $ 9.10
4.5 gm premixed bag = $ 11.40

Table 1: Treatment cost comparisons.

Dose	Cost per day			Difference in Cost After 10 Days
	Day 1	Day 7	Day 10	
Intermittent-Infusion				
3.375g q6h	$36.40	$254.80	$364.00	$91.00
4.5g q8h	$34.20	$239.40	$342.00	$69.00
4.5g q6h	$45.60	$319.20	$456.00	$183.00
Extended-Infusion				
3.375 gm q8h over 4 hrs	$27.30	$191.10	$273.00	

Table 2: Current usage at the Aspirus hospitals from June – August 2016*

Hospital	Eligible orders	Current compliance with EI Pip/Tazo	Potential annual savings
AWH	366	92%	0
AIR	38	95%	0
AGV	28	21%	$1,500
AKH	30	0%	$2,400
Aspirus Total*	462	82%	$3,900

*Does not include ALH (no orders), AMH (1 order), ARH (not on Epic)

Interchange procedure:

1. Pharmacists will automatically interchange all adult orders for intermittent-infusion doses of PTZ to EI PTZ based on **Table 3** below, except one-time orders for the OR/PACU, ER, and ambulatory care areas. If PTZ is continued after a one-time dose is given over 30 minutes in the ER or OR/PACU, the next dose is given 6 hours after the first dose as an EI over 4 hours with subsequent EI doses given every 8 hours after that, per the standard schedule.
    a. If a provider chooses not to use an EI, they may write "Do not change to extended-infusion" on the order, and the pharmacist will verify the intermittent 30 minute infusion instead.
    b. The timing of the EI PTZ should be adjusted to avoid compatibility issues. Common Y-site incompatibilities are given in **Table 4**, and a more comprehensive list can be found through online databases.
    c. Every effort should be made to utilize the EI PTZ. However, if intravenous access becomes an issue, the pharmacist can change the order to the renally-dosed 30 minute intermittent-infusion (**Table 3**).

Table 3: PTZ Dosing Interchange Table Based on Indication and Renal Function.[3,5,7]

CrCl	**> 40 mL/min**	**20-40 mL/min**	**< 20 mL/min**	**HD/PD**	**CRRT**
Intermittent Infusion Dosing (over 30 minutes)					
General infection	3.375g IV q6h	2.25g IV q6h	2.25g IV q8h	2.25g IV q12h*	3.375g IV q6h
Nosocomial pneumonia, *Pseudomonas* infection	4.5g IV q6h	3.375g IV q6h	2.25g IV q6h	2.25g IV q8h*	
Extended-Infusion Dosing (over 4 hours)					
General infection, nosocomial pneumonia, *Pseudomonas* infection	3.375g IV q8h		3.375g IV q12h		3.375g IV q8h

*Supplemental 0.75g dose should be administered after each dialysis session.
Abbreviations: CrCl, creatinine clearance (based on Cockcroft-Gault equation); HD, hemodialysis; PD, peritoneal dialysis; CRRT, continuous renal replacement therapy (includes CVVH, CVVHD, CVVHDF).

Table 4. Common Y-site Incompatibilities.[8,9]

The standard concentration of PTZ 3.375g mini-bag with a total volume of 100 mLs = 33.75 mg/mL. More comprehensive listings of compatible and incompatible drugs may be found in drug dosing handbooks or through online databases.

Acyclovir	Droperidol	Midazolam
Amiodarone	Famotidine	Minocycline
Amphotericin B products	Ganciclovir	Phenytoin
Azithromycin	Gemcitabine	Polymyxin B
Ciprofloxacin	Haloperidol	Prochlorperazine
Diltiazem	Hydralazine	Promethazine
Dobutamine	Insulin	Tobramycin
Doxorubicin	Labetalol	Vecuronium
Doxycycline	Levofloxacin	

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