Justification and Protocol for Extended-Infusion Piperacillin/Tazobactam in Adult Patients
version 2/5/13 [DRAFT]

EXECUTIVE SUMMARY

1. Use of extended infusions (EI) of piperacillin-tazobactam (PTZ) optimizes the probability that drug concentrations will remain above the minimum inhibitory concentration (MIC) for an appropriate period of time.
2. The goals of the extended infusion PTZ protocol are to optimize treatment outcomes, while curtailing resistance to PTZ and reducing cost.
3. **We recommend implementing the extended infusion protocol in all adult patients** to realize both clinical and economic advantages. It was noted that a number of *Pseudomonas aeruginosa* isolates at <<HOSPITAL>> have MICs > 8 mcg/mL and the extended infusion protocol would offer an advantage in the treatment of these cases.

BACKGROUND

Piperacillin/tazobactam is a β-lactam/ β-lactamase inhibitor combination formulary antibiotic frequently used at XXX Hospital for the treatment of moderate-to-severe infections, including sepsis, lower respiratory tract, urinary tract, complicated skin and skin structure, gynecologic, bone and joint, and intra-abdominal infections. Overall, PTZ is one of the most commonly used antibiotics at <<HOSPITAL>>.

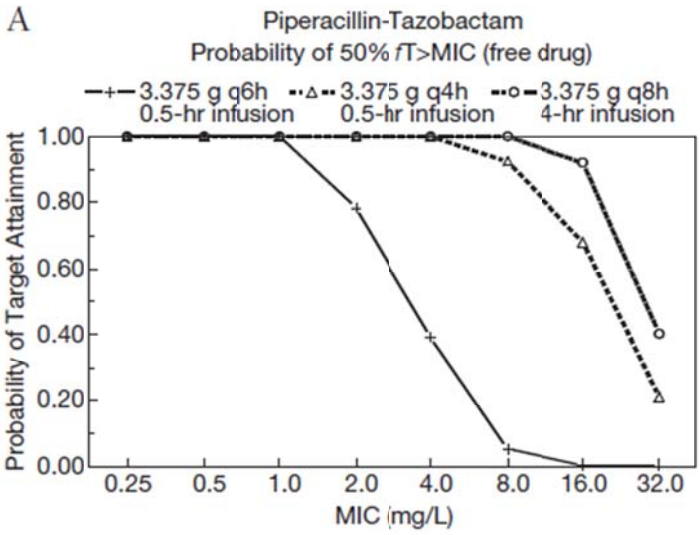
Increasing antimicrobial resistance and the resulting increased mortality has led to the reevaluation of the optimal method to administer antibiotics. Studies have shown that for β-lactams (including PTZ), the best predictor of bacterial killing is the time during which the free drug concentration exceeds the minimum inhibitory concentration of the organism (%fT>MIC). Specifically, maximal bactericidal effect is achieved when free drug concentration exceeds the MIC by approximately four-fold for 40% to 60% of the dosing interval.[1,2]

JUSTIFICATION

Pharmacodynamic studies. Several studies have explored the PK/PD parameters of PTZ with the goal of optimizing its clinical utility. These studies have focused on strategies to enhance the duration of drug exposure. In one such study (illustrated in Figure 1), the probabilities of target attainment of 50% fT>MIC for PTZ were as follows:

- 3.375g q6hr (0.5-hr infusion): > 90% for MIC values ≤ 1 mg/L
- 3.375g q4hr (0.5-hr infusion): > 90% for MIC values up to 8 mg/L
- 3.375 g q8h (4-hr infusion): >90% for MICs up to 16 mg/L

Figure 1: Probabilities of target attainment with PTZ [4]



MIC = minimum inhibitory concentration

As illustrated above, traditional dosing of PTZ (up to four times daily) failed to provide adequate time above the MIC for organisms with an MIC > 8 mg/L.[3,4] None of the regimens were reliable at an MIC of 64 mg/L (the susceptibility breakpoint). Alternatively, a dose of 3.375g q8hr infused over 4 hours provides a probability of target attainment >90% for an MIC up to 16 mg/L at a lower total daily dose than standard doses. Furthermore, PTZ lacks any persistent effects (post-antibiotic effect) that last after antimicrobial exposure to most organisms, such that once the free drug concentrations fall below the MIC, bacterial re-growth is almost instantaneous. Extending the administration time takes advantage of the pharmacodynamic properties of this extended spectrum β-lactam/β-lactamase inhibitor combination.

An internal review of the MICs of PTZ against *P. aeruginosa* isolates was conducted with <<HOSPITAL>> microbiology data from January 2011 to December 2011. According to the Clinical Laboratory Standards Institute (CLSI) guidelines, the breakpoint for susceptibility of *P. aeruginosa* is ≤64 mg/L. Results of the internal survey are illustrated in Table 1 and 2 below:

Table 1: Combined ICU: *P. aeruginosa* PTZ MIC; 2011

	Susceptible				Intermediate/ Resistant	
MIC	≤ 8	16	32	64	> 64	Total
# isolates	82	**11**	**3**	**7**	21	124

Table 2: All hospital isolates: *P. aeruginosa* PTZ MIC; 2011

	Susceptible				Intermediate/ Resistant	
MIC	≤ 8	16	32	64	> 64	Total
# isolates	348	**48**	**10**	**38**	65	509

These data reveal that 22% (n=96) of isolates hospital-wide may potentially be sub-optimally treated by traditional administration of PTZ. Continuing with the current practice could result in a negative outcome for a number of patients per year cared for at <<HOSPITAL>>. Both ICU and non-ICU settings are affected by impaired drug susceptibility, with several patients affected on the non-ICU general wards.

Clinical studies. The clinical relevance of these findings has also been investigated. In one such study, outcomes were examined in patients before and after implementation of a hospital-wide substitution

program where intermittently infused PTZ was automatically converted to EI.[5] In patients at greatest risk for mortality (APACHE II score ≥ 17) EI PTZ resulted in significantly lower 14-day mortality rates (12.2% vs. 31.6%, *p*=0.04) and median hospital length of stay (LOS) (21 days vs. 38 days, *p*=0.02) compared with patients who received intermittent infusion PTZ.

Furthermore, in a recent meta-analysis, the authors noted a reduced mortality among patients receiving β-lactam agents administered by EI compared to those receiving intermittent infusions.[6]

Economic evaluation. In the previous study, EI PTZ resulted in reduction of total daily dose by 25%-50% representing considerable savings in annual direct drug acquisition costs.[5]

Projected expenditures for automatic therapeutic interchange to PTZ 3.375g (infused over 4 hrs) q8h at <<HOSPITAL>> are summarized in Table 3. Based on PTZ utilization data from fiscal year 2012, a projected cost savings of approximately $150,000 may be realized with a switch to extended infusion PTZ.

Table 3. Projected Financial Impact of PTZ Prolonged Infusion at <<HOSPITAL>> in FY2013

	PTZ Dose	**Cost/day/patient**	**FY13 Total**
	3.375g IV q6h	$44	$602,250
	3.375g IV q8h	$ 33	$ 451,688
Difference		$ 11	$ 150,562

ALTERNATE DOSING PROPOSAL:

Patient populations impacted: Adult patients hospitalized at <<HOSPITAL>> on adult wards
Procedure: Orders for standard doses/administration of PTZ for adults will be interchanged with extended-infusion as described in Table 4. Pharmacists will assist providers in adjusting the dose of PTZ for renal function as indicated in the chart below:

Table 4. Adjustment of EI Piperacillin/tazobactam Dosing Based on Renal Function[4,7]

Clcr(mL/min)	Over 20 mL/min	≤20 mL/min (including peritoneal or hemodialysis)	Continuous Renal Replacement Therapy (CRRT)
Pip/Tazo Dose	3.375g IV over 4 hours q8h	3.375g IV over 4 hours q12h	3.375g IV over 4 hours q8h

Exceptions to the Policy

Dose adjustments: Certain populations with enhanced drug clearance, such as critically ill patients with severe infections or patients with cystic fibrosis, may benefit from more intensive PTZ dosing to maximize %fT>MIC. However, dose intensification studies in these populations are limited and require further elucidation. It is not recommended to increase the dose beyond 3.375g q8h without careful consideration of patient-specific factors including severity of illness and MIC of the organism.

Emergency Department (pre-admission status only), OR and PACU areas, and ambulatory clinics: Patients with orders for PTZ from these areas for which 4-hour infusion times may not be practical may receive a traditional standard 30-minute infusion at the discretion of the physician and/or nursing staff. Subsequent extended-infusion doses should be administered 6-8 hours after the intermittent dose.

Medication scheduling and/or drug compatibility conflicts: Clinical pharmacists will also be available to assist nursing to help resolve medication scheduling and compatibility issues (see Appendix A). If shifting medication administration times does not alleviate the problem, nursing may request standard 30-min

infusions after consulting with the pharmacist and physician. Placing new lines to accommodate extended-infusion PTZ is discouraged, and should only be done upon the discretion of the attending physician or Infectious Diseases Consult Team in which the benefits are believed to outweigh any risks.

IMPLEMENTATION TIMELINE:

Extended-Infusion PTZ Implementation Component	Suggested Time
EI PTZ Protocol ASET review	February 2013
EI PTZ Protocol P&T review	March 2013
Pharmacist education Nursing/physician education (allow 4-6 weeks prior to implementation for pharmacist-lead inservice presentations and distribution of educational handouts)	March 2013 – April 2013
E-browser CPOE/HMM implementation	April 15, 2013
EPIC implementation	June 22, 2013
6 month audit and feedback data collection	Sept 2013

REFERENCES:

1. Craig WA, Ebert SC. Continuous infusion of beta-lactam antibiotics. *Antimicrob Agents Chemother* 1992; 36:2577-2583.
2. Grant E, Nicolau DP, Nightingale CH, Quintiliani R. Continuous infusion of beta-lactam antibiotics. *Conn Med* 1999; 63: 275-277.
3. Lodise TP, Lomaestro B, Rodvold K, Danziger L, Drusano G. Pharmacodynamic profiling of piperacillin in the presence of tazobactam in patients through the use of population pharmacokinetic models and Monte Carlo simulation. *Antimicrob Agents Chemother* 2004; 48(12):4718-24.
4. Lodise TP, Lomaestro B, Drusano G. Application of antimicrobial pharmacodynamic concepts into clinical practice: focus on β-lactam antibiotics. *Pharmacotherapy* 2006; 26(9): 1320-1332.
5. Lodise TP, Lomaestro B, Drusano G. Piperacillin-tazobactam for *Pseudomonas aeruginosa* infection: clinical implications of an extended-infusion dosing strategy. *Clin Infect Dis* 2007; 44(3):357-63.
6. Falagas ME, Tansarli GS, Ikawa K, Vardakas KZ. Clinical outcomes with continuous or extended versus short-term intravenous infusion carbapenems and piperacillin/tazobactam: a systematic review and meta-analysis. *Clin Infect Dis* 2013; 56(2):272-82.
7. Patel N, Scheetz MH, Drusano GL, Lodise TP. Identification of optimal renal dosage adjustments for traditional and extended-infusion piperacillin/tazobactam dosing regimens in hospitalized patients. *Antimicrob Agents Chemother* 2010; 54(1): 460-65.
8. Trissel LA. Piperacillin sodium-tazobactam sodium. Handbook on Injectable Drugs 16th ed. 2011:1279-1287.

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Appendix A. Compatibility of Select Drugs with PTZ administered by intermittent or continuous infusion[8]

The standard concentration of PTZ 3.375g mini-bag with a total volume of 100 mL = 33 mg/mL. More comprehensive listings of compatible and incompatible drugs may be found in drug-dosing handbooks.

Y-site compatible [Can be Y-sited together with these intermittent or continuous IV meds]

Antibiotics	Anticoagulants	GI/Reflux	Other
Amikacin	Bivalirudin	Pantoprazole	Allopurinol
Aztreonam	Heparin	Metoclopramide	Digoxin
Cefepime		Ranitidine	Diphenhydramine
Clindamycin	Diuretics		Magnesium sulfate
Metronidazole	Bumetanide	Pressors	Mannitol
TMP/SMX (Bactrim®)	Furosemide	Dopamine	Methylprednisolone
Tigecycline		Norepinephrine	Potassium Chloride
	Drips	Phenylepherine	Potassium phosphate
Antifungals	Fentanyl	Vasopressin	
Amphotericin B liposomal (Ambisome®)	Lorazepam		
Amphotericin B lipid complex (Abelcet®)	Morphine		
Fluconazole	Sodium Bicarbonate		
Voriconazole			

NOT-COMPATIBLE-[Do Not Piggyback Together]

Antibiotics	Antivirals	Other	Other
Azithromycin	Acyclovir	Chlorpromazine	Haloperidol
Ciprofloxacin		Diltiazem	Insulin, regular
Doxycycline	Antifungals	Dobutamine	Promethazine
Gentamicin	Micafungin	Famotidine	Nalbuphine
Levofloxacin			Midazolam
Moxifloxacin			Propofol
Tobramycin			
Vancomycin**			

****Variable compatibility via Y-site**:

Variable compatibility has been reported for vancomycin and PTZ and is concentration-dependent. Vancomycin concentrations at or exceeding 20 mg/mL are incompatible with all concentrations of PTZ. PTZ concentrations of 45 mg/mL are compatible with vancomycin concentrations of <=2 mg/mL but this concentration of vancomycin is not typically used. **Thus, vancomycin and PTZ should be considered incompatible**.