THE NEBRASKA MEDICAL CENTER

SUPPORTING EVIDENCE FOR EXTENDED-INFUSION PIPERACILLIN/TAZOBACTAM DOSING SUBSTITUTION

BACKGROUND:

Piperacillin/tazobactam (PTZ) is a formulary agent at The Nebraska Medical Center (TNMC) approved for the treatment of susceptible pathogens in moderate-to-severe infections, including lower respiratory tract infections (community-acquired pneumonia, nosocomial pneumonia); urinary tract infections; uncomplicated and complicated skin and skin structure infections (SSSI); gynecologic infections (endometritis, pelvic inflammatory disease); bone and joint infections; intra-abdominal infections (appendicitis with rupture/abscess, peritonitis); and septicemia.[1] Tazobactam expands activity of piperacillin to encompass beta-lactamase-producing strains of *Staphylococcus aureus* [except methicillin resistant *Staphylococcus aureus* (MRSA)], *Haemophilus influenzae*, *Bacteroides spp*, and other gram-negative bacteria; but has negligible activity against extended-spectrum beta-lactamases (ESBLs), AmpC, and carbapenemases.

Table 1. The manufacturer-recommended and FDA-approved dosing of PTZ is as follows:[1,2]

	Adults and children >40kg[a]		Pediatrics >2kg and ≤40kg[abc]		
CrCl>40 ml/min or CRRT	3.375g q6hr[de]	4.5g q6hr	0-7 days; 100mg/kg q12h	8-28 days; 100mg/kg q8h	>28 days 100mg/kg q6h
Infections	Intra-abdominal infection[f] Gynecologic infection SSSI Community acquired pneumonia	Nosocomial pneumonia Pseudomonas infection	Any	Any	Any
CrCl 20-40 mL/min	2.25g q6hr	3.375g q6hr	Unknown	70% q8h	70% q6h
CrCl <20 mL/min	2.25g q8hr	2.25g q6hr	Unknown	70% q12h	70% q8h
Hemodialysis[g]	2.25g q12hr	2.25g q8hr	Unknown	Unknown	Unknown
Peritoneal dialysis	2.25g q12hr	2.25g q8h	Unknown	Unknown	Unknown

[a]duration of treatment 7-14 days; [b]data from Nelson's pocket book of pediatric antimicrobial therapy; [c]dosing based on piperacillin component; [d]alternative is 4.5 g every 8 hours since the %time>MIC is similar between the regimens for most pathogens; however should not be used for nosocomial pneumonia or if *Pseudomonas aeruginosa* is a suspected pathogen. [e] Increase to 3.375 g q4h or 4.5g q6h if *P. aeruginosa* is suspected. [f]Not recommended for mild to moderate, community-acquired intra-abdominal infections due to risk of toxicity and the development of resistant organisms. [g]0.75gm should be administered following each hemodialysis session.

Like all beta-lactams, PTZ demonstrates concentration-independent bacterial killing, with the proportion of the dosing interval that the free drug concentration remains above the minimum inhibitory concentration (MIC) (fT>MIC) being the pharmacodynamic (PD) parameter that is best correlated with optimal activity.[3,4] The PD target for PTZ against Gram-negative bacilli is 50% fT>MIC. In general, a probability of target attainment (PTA) of 90% is considered to be the threshold for achieving reliable empiric therapy. Eagye and colleagues used Monte Carlo simulation techniques to estimate the relative PTA of various antimicrobial agents against isolates of Gram-negative bacilli recovered from patients with infection in the intensive care unit (ICU).[5] PTZ MICs were determined for 74,394 Gram-negative bacilli isolates in the US between 1993 and 2004**,** and simulated doses of PTZ included 3.375 g q6h, 4.5 g q8h, and 4.5 g q6h given as 0.5hr infusions.

Table 2: Probability of Target Attainment for Various Doses of PTZ with 0.5hr Infusions Against Gram-Negative Bacilli

Dose	PTA for 50% fT>MIC			
	1996–1998	1999–2001	2002–2004	*p*-value
P. aeruginosa				
PTZ 3.375 g q6h	75.9	74	73.3	0.0024
PTZ 4.5 g q8h	70.8	69	68.4	0.0095
PTZ 4.5 g q6h	79.6	77.5	76.7	0.0004
Acinetobacter spp.				
PTZ 3.375 g q6h	56.4	51.3	43.6	<0.0001
PTZ 4.5 g q8h	51.9	47.4	40.5	<0.0001
PTZ 4.5 g q6h	61	55.3	46.6	<0.0001

The results demonstrate a significant increase in MICs of these pathogens as reflected in the steady decline in PTA for PTZ over time. Thus, more aggressive dosing is warranted in order to preserve the clinical utility of PTZ.

ALTERNATE DOSING PROPOSAL:

- Pharmacists will automatically interchange **ALL** orders for standard doses of PTZ for adults and children >40kg to the alternate doses with extended infusion (EI) as described below. PTZ doses for children > 2kg and ≤ 40kg will remain as standard doses, but the infusion time will automatically be extended to 4 hours as indicated below. Patients in the neonatal intensive care unit (NICU) are excluded from this proposal. Pharmacists will automatically adjust the dose of PTZ for renal function as indicated in the charts below. The creatinine clearance (CrCl) will be estimated using the Cockroft-Gault equation for patients ≥18 years old and the Schwartz equation for patients < 18 years old. Renal dosage adjustments will be made in accordance with the Antimicrobial Renal Dosage Adjustment policy.

Table 3. Alternate PTZ Dosing for Adult and Pediatric patients >40kg: [6-10]

Clcr(ml/min)	≥20ml/min	<20ml/min (including peritoneal or hemodialysis)	CRRT/SLED
Adults and Children >40kg	4.5g IV over 4 hours q8h	4.5g IV over 4 hours q12h	4.5g IV over 4 hours q8h

CRRT = continuous renal replacement therapy; SLED = slow extended dialysis. **Note:** Dosage substitution to 4.5g applies to **ALL** ordered doses of PTZ

Table 4. PTZ Doses for pediatric patients >2kg and ≤40kg will be substituted as follows*:

Age	**Medication Ordered**	**Interchange With**
0-7 days	Piperacillin/Tazobactam 112.5mg/kg q12hr	Piperacillin/Tazobactam 112.5mg/kg q12hr (4 hr infusion)**
8-28 days	Piperacillin/Tazobactam 112.5mg/kg q8hr	Piperacillin/Tazobactam 112.5mg/kg q8hr (4 hr infusion)**
>28 days	Piperacillin/Tazobactam 112.5mg/kg q6hr	Piperacillin/Tazobactam 112.5mg/kg q6hr (4 hr infusion)**
Doses are based on combined product. * **Extended infusion not applicable to NICU patients.** **Adjust doses for renal function based on TNMC renal adjustment protocol and infuse over 4 hours.		

Renal Dosing Adjustment for Pediatric Patients all ages <40kg:

- CrCl > 40ml/min = no adjustment
- CrCl ≤ 40ml/min = decrease original dose 30%
- CrCl ≤ 20ml/min (including peritoneal and hemodialysis) = decrease original dose 30%, infuse q12h over 4 hours
- CRRT/SLED = dose per normal renal function based on age and weight

JUSTIFICATION:

Internal MIC Surveillance

An internal study was conducted to review the MICs of PTZ against *Pseudomonas aeruginosa* isolates. A random selection of 30 blood isolates and 12 sputum isolates were evaluated, and MICs were obtained via Sensititre susceptibility plates. According to Clinical Laboratory Standards Institute (CLSI) guidelines, the breakpoint for susceptibility of Enterobacteriaceae and *Acinetobacter* spp. to PTZ is ≤ 16 mg/L, and ≤64mg/L, for *P. aeruginosa*. The results of the internal survey are illustrated below:

	PTZ
MIC_{50}	8 mg/L
MIC_{90}	>64 mg/L

The data revealed reduced susceptibility of *P. aeruginosa* isolates to PTZ and are striking for an MIC_{90} beyond the susceptibility breakpoint. As mentioned above, PTZ is a concentration-independent antibacterial, and the PD parameter that correlates to activity is %fT>MIC.[3,4] Furthermore, PTZ lacks any persistent effects [post-antibiotic effect (PAE)] 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. The necessary percent of time the concentration must remain above the MIC varies depending on the type of beta-lactam antibiotic (see table below).[3,4] The clinical implication of these findings is the potential for suboptimal dosing.

Table 5. Summary target attainments for different beta-lactam classes against different pathogens

Pathogen	Overall (%fT>MIC)	Carbapenems (%fT>MIC)	Penicillins (%fT>MIC)	Cephalosporins (%fT>MIC)
Gram-positive	20-50%	20-30%	30-40%	40-50%
Gram-negative	40-70%	40-50%	**50-60%**	60-70%

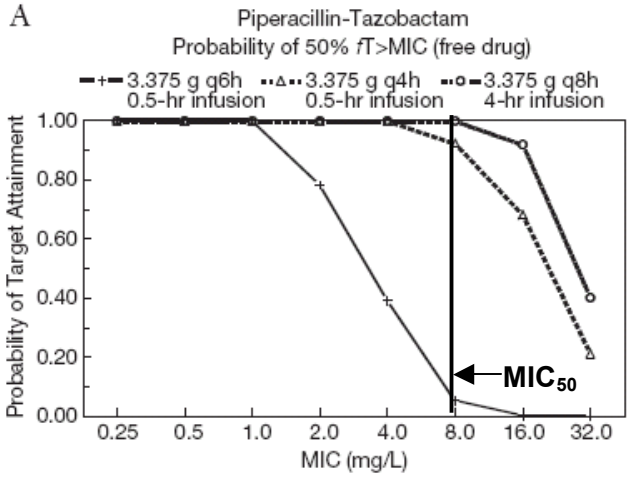
Pharmacokinetic/Pharmacodynamic (PK/PD) Simulation Studies

Several studies have explored the PK/PD parameters of PTZ with the goal of optimizing its clinical utility.[5-8,10-12] These explorations have focused on strategies to enhance the duration of drug exposure, i.e. %fT>MIC. Described below are select studies exploring EI dosing of PTZ.

Evidence 1: Monte Carlo Studies

Lodise TP, *Clin Infect Dis* 2007; 44: 357-363[6,7]

- Monte-Carlo simulation was designed to compare standard dose of PTZ with two alternative doses to delineate respective PTA against *P. aeruginosa*



- As depicted in the figure above, PTA of 50% *f*T>MIC was as follows;

- 3.375 g q6hr (0.5-hr infusion)
  - > 90% only for MIC values ≤ 1 mcg/mL
- 3.375 g q4h (0.5-hr infusion)
  - >90% for MIC values up to 8 mcg/mL
- 3.375 g q8h (4-hr infusion)
  - >90% for MICs up to 16 mcg/mL

- The result of this Monte-Carlo simulation was applied to alter the PTZ dose in clinical practice. The clinical outcomes associated with this application are described in the latter section of this document.
- Using these data in combination with data from other Monte Carlo simulations,[6-8] the following table was constructed to show the achievable PTAs for various PTZ doses and infusion times vs. *P. aeruginosa*

Table 6. Piperacillin/tazobactam target attainment (*Pseudomonas aeruginosa only)*								
Breakpoints	S	I	R					
	≤64	128	≥256					
	MIC (mcg/mL)							
Regimen/infusion	Target % fT>MIC	1	2	4	8	16	32	64
3.375g q6/0.5[6-8]	50	100	79-98	39-97	5-90	0-68	0-25	0-2
3.375g q4/0.5[6,7]	50	100	100	98-100	85-92	42-65	0-21	--
3.375g q8/4[6-8]	50	100	100	100	100	92-100	40-65	10
4.5g q6/0.5[8]	50	100	100	98	95	79	8	--
4.5g q6/4[8]	50	100	100	100	100	100	100	88

- Based on data presented in Table 5, none of the regimens are reliable at an MIC of 64mcg/ml, the susceptibility breakpoint. A dose of 3.375g q8hr infused over 4 hours provides PTA >90% for an MIC up to 16mcg/mL at a lower total daily dose than standard doses.

Evidence 2: Patel N, et al. Antimicrob Agents Chemother. 2010;54: 460-465[10]

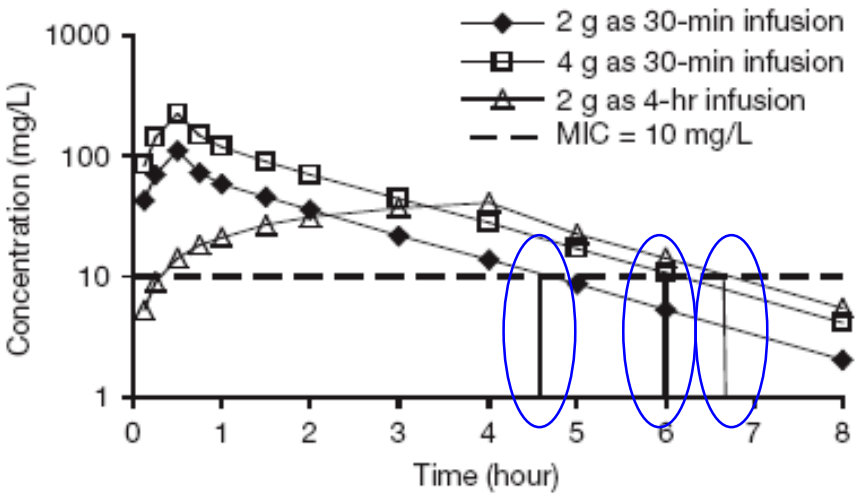
- The PTA for PTZ at a dose of 3.375 g q12hr (4 h infusion) at CrCl = 40 ml/min and CrCl = 20 ml/min was evaluated
- Attainable exposure ratios are;

Table 7. Probability of achieving 50% fT>MIC (%)						
Regimen	MIC					
	1mg/L	2mg/L	4mg/L	8mg/L	16mg/L	32mg/L
3.375g Q8hr/4hr inf (CrCl=100ml/min)	99	99	99	97	73	17
3.375g Q12hr/4hr inf (CrCl=40ml/min)	98	96	90	79	52	16
3.375g Q12hr/4hr inf (CrCl=20ml/min)	99	98	96	90	74	40

- The data presented above support the dosage adjustment recommendations for CrCl <20, although these data suggest a PTA >90% only for MICs up to 8mg/L in contrast to table 6 above.

Evidence 3: Lodise TP, et al. *Pharmacotherapy* 2006; 26: 1320-1332[6]

- This study evaluates the benefit of administering EI PTZ as opposed to intermittent infusion.
- Simulation was conducted with PTZ doses of 2.25g as 0.5hr infusion, 4.5g as 0.5hr infusion, and 2.25g as 4hr infusion.



- As shown in the graph above, EI PTZ leads to increased %fT>MIC with the same dose (2.25g over 30 mins vs. 2.25g over 4 hours). Additionally, increasing the dose to 4.5g over 30 mins provides similar %fT>MIC to that of a lower dose given via EI.

In summary:

- EI PTZ at a dose of 3.375g q8h will allow higher PTA at MICs up to 8-16 than that attainable with comparative standard doses of 3.375g q6h or 4.5g q6h over 30 minutes, while using a lower total daily dose. Furthermore, the EI dose of 3.375g q8h achieves higher PTA than the dose of 4.5g q6h given over 30 mins when the MIC is ≥4, which is common according to internal MIC data.

Clinical Outcomes Studies

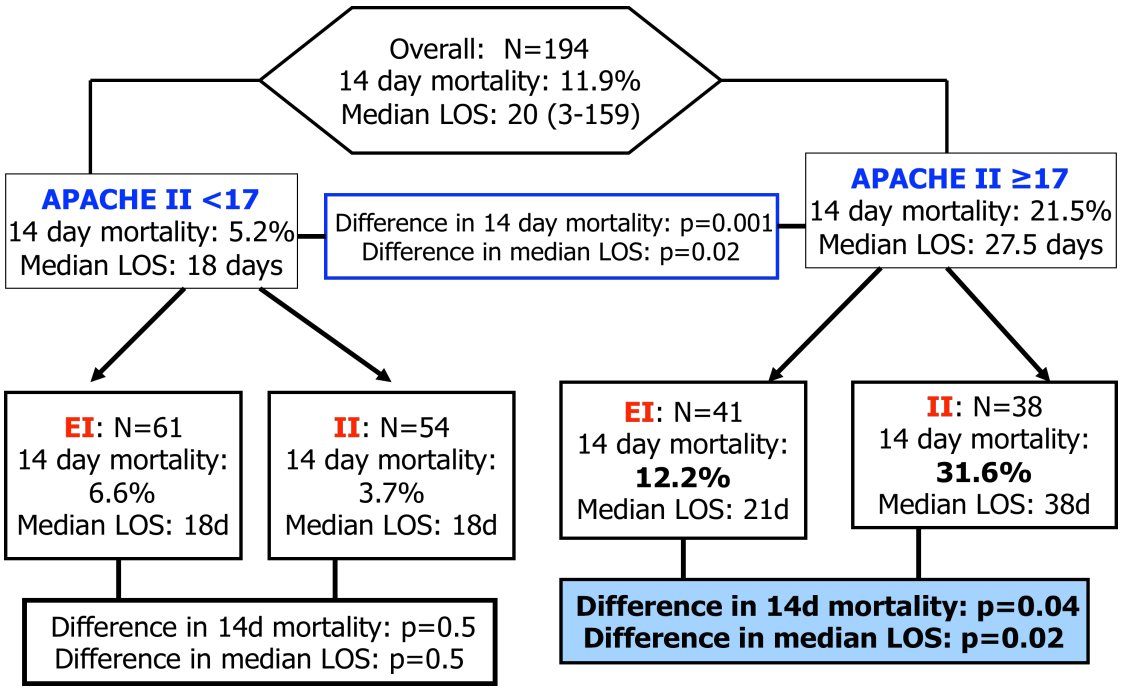
Evidence 1: Lodise TP Jr, et al. *Clin Infect Dis.* 2007;44:357-63[7]

- Design: implemented a hospital-wide substitution program where intermittently infused PTZ was automatically converted to EI in February 2002
- Primary end point: 14-day mortality, hospital length of stay (LOS) after collection of a positive *P. aeruginosa* culture

Table 8. Results:

	Extended Infusion 3.375g IV q8h over 4hr (n = 102)	**Intermittent Infusion 3.375 g IV q4 or 6 h over 0.5hr (n = 92)***	***p*-value**
Age, mean years ± SD	62.8 ± 18.3	63.9 ± 16.1	0.6
Diabetes mellitus	28 (27.5)	28 (30.4)	0.6
HIV infection	1 (1)	2 (2.2)	0.5
History of health care exposure	35 (34.3)	37 (40.2)	0.4
LOS prior to culture sample collection, median days (range)	7 (0 – 89)	6 (0 – 52)	0.5
LOS in ICU prior to onset of infection, median days (range	3.5 (0 – 30)	2 (0 – 52)	0.5
Receiving mechanical ventilation at culture sample collection	56 (54.9)	52 (56.5)	0.8
Consecutive days receiving mechanical ventilation prior to culture sample collection, median days (range)	1 (0 – 59)	1 (0 – 48)	0.8
APACHE II score at onset of infection, mean ± SD	15.3 (6.7)	16.2 (7.6)	0.3
Duration of therapy, mean days ± SD	8.4 (4.4)	8.4 (4.5)	0.9
Concomitant therapy with an aminoglycoside	21 (22.8)	26 (25.5)	0.6
Concomitant therapy with a fluoroquinolone	5 (5.9)	10 (10.9)	0.2

Primary source of culture sample			
Respiratory tract	55 (53.9)	48 (52.2)	0.8
Urinary tract	21 (20.6)	12 (13)	0.2
Skin or soft tissue	11 (10.8)	23 (25)	0.009
Intravenous catheter	3 (2.9)	0 (0)	0.1
Abdomen	4 (3.9)	1 (1.1)	0.2
Other	8 (7.8)	8 (8.7)	0.8
NOTE. Data are no. (%) or mean ± SD, as appropriate. LOS= length of stay; APACHE = Acute Physiology And Chronic Health Evaluation; ICU=intensive care unit; HIV=human immunodeficiency virus. *Only 4 (4.3%) of the patients received 3.375 g IV q4 h; the majority received infusions q6 h			



CART regression analysis to identify patients at lowest vs. greatest risk for 14-day mortality based on breakpoint APACHE II score of </≥ 17. EI= extended infusion; II= intermittent infusion; LOS= length of stay

Conclusion:

- In patients at greatest risk for mortality (APACHE II score ≥ 17), EI PTZ resulted in significantly lower 14-day mortality rates and median hospital LOS compared with patients who received II PTZ.
- EI PTZ resulted in reduction of total daily dose by 25%–50% (by 1–3 doses per day) representing a savings of $68,750–$135,750 in annual direct drug acquisition costs.

Evidence 2: Patel GW, et al. Diagn Microbiol Infect Dis. 2009 Jun;64(2):236-40[12]

- Another study evaluating clinical outcomes in patients from two medical centers treated with conventional PTZ doses vs. EI doses for Gram-negative infections did not find any significant differences in outcomes evaluated.
- Doses of PTZ studied at both institutions were : 3.375-4.5 g IV q6-8 h (30-min infusion) and 3.375 g IV every 8 h (4-h infusion)
- Organisms included: *Acinetobacter* spp. *Bacteriodes* spp. *Citrobacter* spp. *Enterobacter* spp. *E.coli*, *Haemophilus* spp, *K. pnuemoniae*, *Morganella* spp. *Proteus* spp, *Providencia* spp, *P. aeruginosa*.
- Respiratory and urinary tract were the most common sites of infection.

Table 9. Results*:

Outcome	VAMC		MCP		Overall	
	II (n = 19)	EI (n = 29)	II (n = 40)	EI (n = 41)	II (n = 59)	EI (n = 70)
MIC <8mg/L, n (%)	19 (100)	29 (100)	16 (40)	12 (29.3)	35 (59.3)	41 (58.6)
MIC 8-16mg/L, n (%)	NA	NA	23 (57.5)	29 (70.7)	23 (39)	29 (41.4)
MIC >16mg/L, n (%)	NA	NA	1 (2.5)	0 (0)	1 (1.7)	0 (0)
30 day mortality, n (%)	3 (15.8)	2 (6.9)	2 (5)	2 (4.9)	5 (8.5)	4 (5.7)
Hospital LOS, median (IQR) days	8 (5-16)	9 (6-15.5)	7 (4-11)	5 (4-11)	8 (5-11)	8 (5.5-15)
MIC <8mg/L	8 (5-16)	9 (6-15.5)	7 (5-11)	7 (3.25-13.5)	8 (5-11)	8 (5.5-15)
MIC 8-16mg/L	NA	NA	5 (4-9)	5 (4-11)	5 (4-9)	5 (4-10.5)
MIC >16mg/L	NA	NA	17 (17-17)	NA	17 (17-17)	NA
II=intermittent infusion; EI=extended infusion; VAMC=Veterans Affairs Medial Center, New York; MCP=Medical Center of Plano; IQR = interquartile range; NA = not applicable; LOS= length of stay. *None of the comparisons had a p-value <0.05						

Conclusion:

- Patient outcomes were similar between lower-dose EI PTZ and standard doses.

In summary:

- EI PTZ at a lower total daily dose has similar outcomes as II PTZ. Mortality may be reduced with EI PTZ in those at higher risk of death (i.e. APACHE ≥17).

ALARIS PUMP/INFUSION SET CONSIDERATIONS:

Infusion line dead space was identified as a potential source of piperacillin/tazobactam underdosing when administered via extended infusion.[13] To ensure patients receive a minimum of 3.375 gm over four hours as previously studied, a 4.5 gm IV dose will be utilized and dispensed in a volume of 100 mL.

PHARMACOECONOMICS:

Projected expenditures for automatic therapeutic interchange to PTZ 4.5 gm (infused over 4 hrs) q8 hrs

Drug	**Dose**	**Cost/day**	**FY09 =78.3 DDD/1000 PD x 140,927PD = 11,034.58 DDD total**
Piperacillin-tazobactam	3.375g IV q6hr	$44.25	$488,280.17
	4.5g IV q8hr	$39.93	$440,610.78
Cost Savings		$4.32	$47,669.39
FY09 = fiscal year 2009; DDD= defined daily doses (14g/day for PTZ) ; PD = patient days			

An automatic therapeutic interchange from 3.375 gm q 6 hrs (30 minute infusion) and 4.5 gm q 6 hrs (30 minute infusion) to 4.5 gm q 8 hrs (4 hr infusion) would result in a cost avoidance of approximately **$4.32/day and $13.31/day, respectively per patient.** Based on PTZ utilization data from fiscal year 2009, it is evident that a projected cost savings of $47,669.39 may be realized with a switch to EI PTZ. The cost savings are even greater if dosage comparison is made between the proposed EI dosing and the PTZ dose of 4.5g q6h.

COMPATIBILITY INFORMATION[14]:

The standard concentration of PTZ 4.5g mini-bag with a total volume of 100 mls = 45 mg/ml. More comprehensive listings of compatible and incompatible drugs may be found in drug dosing handbooks.

Compatible via Y-site:

Allopurinol	Furosemide	Ondansetron
Amikacin*	Gentamicin*	Phenylephrine
Aztreonam	Heparin	Potassium Chloride
Bivalirudin	Hydromorphone	Potassium Phosphate
Bumetanide	Linezolid	Ranitidine
Cefepime	Lorazepam	Sodium Bicarbonate
Clindamycin	Magnesium	Sulfamethoxazole/Trimethoprim
Daptomycin	Mannitol	Tigecycline
Digoxin	Methylprednisolone	Vasopressin
Diphenhydramine	Metoclopramide	Voriconazole
Dopamine	Metronidazole	
Fentanyl	Morphine	
Fluconazole	Norepinephrine	

*All available PTZ is reformulated with EDTA has been shown to be compatible in vitro for Y-site infusion with amikacin and gentamicin, but not compatible with tobramycin. PTZ should **NOT** be mixed in the same bag with aminoglycosides.

Incompatible via Y-site:

Acyclovir	Doxorubicin Lipid Formulation	Hydroxyzine
Alatrofloxacin	Doxorubicin	Micafungin
Amiodarone	Doxycycline	Minocycline
Amphotericin B products	Droperidol	Mitomycin
Azithromycin	Drotrecogin alfa	Mitoxantrone
Chlorpromazine	Famotidine	Nalbuphine
Ciprofloxacin	Ganciclovir	Prochlorperazine
Cisatracurium	Gatifloxacin	Promethazine
Cisplatin	Gemcitabine	Streptozocin
Dacarbazine	Haloperidol	Tobramycin
Daunorubicin	Idarubicin	Vancomycin*
Dobutamine	Insulin, regular	

*Variable – see note below

Variable compatibility via Y-site:

Variable compatibility has been reported for vancomycin and PTZ and is concentration-dependent. Vancomycin concentrations at or exceeding 20mg/ml are incompatible with all concentrations of PTZ. However, concentrations of 5mg/ml or lower are compatible with PTZ at concentrations of 28mg/ml or 33mg/ml via the Y-site. 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**.

CONCLUSION:

The major goals of this extended infusion protocol are to optimize patient outcomes, while curtailing resistance long-term to PTZ and reducing cost. Since isolates of *Pseudomonas aeruginosa* with higher MICs were detected during our internal MIC review, and MicroScan MIC panels do not distinguish *P.*

aeruginosa with lower versus higher MICs within the susceptible range (e.g., an organism with an MIC of 1mcg/ml and an organism with an MIC of 8mcg/ml would both be reported as MIC ≤8mcg/ml), we recommend implementing the extended infusion protocol in all patients. Due to lack of data regarding reduced dosages in pediatrics <40kg, we recommend standard doses, but at an infusion time of 4 hours rather than the standard 30 minutes in an effort to standardize PTZ infusion time for all patients and minimize errors. Optimization of the probability that drug concentrations will remain above the MIC for an appropriate period of time, a property associated with optimal activity of PTZ, is demonstrated in the studies presented above by the use of extended infusion dosing. Continuous infusion of PTZ does not offer any advantage over extended infusion, and the logistics of EI dosing are easier to accommodate.

Lastly, extended infusion dosing at TNMC is recommended in all patients with susceptible pathogens with an MIC ≤16 mcg/ml. For those with higher MICs, even though within the current susceptibility range according to CLSI, the use of an alternate agent is recommended.

REFERENCES:

1. Wyeth. Zosyn® (piperacillin sodium and tazobactam sodium) for injection prescribing information. Philadelphia, PA; 2007 Nov.
2. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. 2010; 50: 133-64
3. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis. 1998; 26: 1-10; quiz 11-2
4. 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
5. Eagye KJ, Nicolau DP, Lockhart SR, et al. A pharmacodynamic analysis of resistance trends in pathogens from patients with infection in intensive care units in the United States between 1993 and 2004. Ann Clin Microbiol Antimicrob. 2007; 6: 11
6. Lodise TP, Lomaestro BM, Drusano GL. Application of antimicrobial pharmacodynamic concepts into clinical practice: focus on beta-lactam antibiotics: insights from the Society of Infectious Diseases Pharmacists. Pharmacotherapy. 2006; 26: 1320-32
7. 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
8. 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
9. Tam VH, Gamez EA, Weston JS, et al. Outcomes of bacteremia due to *Pseudomonas aeruginosa* with reduced susceptibility to piperacillin-tazobactam: implications on the appropriateness of the resistance breakpoint. Clin Infect Dis. 2008; 46: 862-7
10. Patel N, Scheetz MH, Drusano GL, 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: 460-465
11. Eagye KJ, Kuti JL, Dowzicky M, et al. Empiric therapy for secondary peritonitis: a pharmacodynamic analysis of cefepime, ceftazidime, ceftriaxone, imipenem, levofloxacin, piperacillin/tazobactam, and tigecycline using Monte Carlo simulation. Clin Ther. 2007; 29: 889-99
12. 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: 236-240
13. Claus B, Buyle F, Robays H, Vogelaers D. Importance of infusion volume and pump characteristics in extended administration of ß-lactam antibiotics. Antimicrob Agents Chemother. 2010 Nov;54(11):4950.
14. Trissel LA. Piperacillin sodium-tazobactam sodium. *Handbook on injectable drugs* 14th ed. 2007; 13:1219-1227.

September 2011

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