Medication Administration:
Extended-Infusion Piperacillin/Tazobactam (Zosyn®) Protocol

Related Documents: Patient Care Manual Guide: Medication Administration IV Infusion Guidelines

I. PURPOSE

Dose optimization is an essential component for clinical success in the treatment of serious infections as well as preventing the emergence of resistance. Recent literature supports prolonged/extended infusion times of beta-lactam antibiotics as a way to maximize the time-dependent bactericidal activity and improve the probability of target attainment. For beta-lactams, in vitro and animal studies have demonstrated that the best predictor of bacterial killing is the time duration which the free drug concentration exceeds the MIC of the organism (*f*T>MIC).[1] This policy is intended to improve clinical and economic benefits via hospital-wide implementation of prolonged piperacillin-tazobactam (Zosyn®) infusions for patients with suspected infections or treatment for confirmed infections caused by pathogens with high antimicrobial MICs (piperacillin-tazobactam MIC of 16 mg/L).

II. POLICY

This policy outlines the procedures for the prescribing and administration of Zosyn® at Stanford Health Care.

III. BACKGROUND

A. Supporting literature for extended-infusion piperacillin/tazobactam

Near maximal bactericidal activity for penicillins is achieved when the unbound drug exceeds the MIC for 50% of the dosing interval, thus the PK-PD target for piperacillin against gram-negative bacilli is 50% *f*T>MIC.

1. Based on the published literature examining PK/PD of Zosyn® against pseudomonas aeruginosa, the probability of achieving free piperacillin concentration in excess of the MIC for 50% (near-maximal effect) of the dosing interval (50% *f*T>MIC) for the most commonly used dosing strategy (3.375g IV q6h over 30 minutes) did not provide high probabilities of target attainment for the full range of MICs deemed to be susceptible by the CLSI. The simulation indicates that attainment of 50% *f*T>MIC for Zosyn® was best achieved with a 4-hour infusion of 3.375g IV Q8H.[2,3] (see Appendix: Figure 5).

2. In 2007, a hospital-wide substitution program where intermittently infused Zosyn® was converted to extended-infusion, patients at greatest risk for mortality (APACHE II score >17) receiving extended-infusion Zosyn® showed significantly lower 14-day mortality rates and median hospital LOS compared with patients who received intermittent infusion Zosyn®[3] (see Appendix: Figure 4).

3. In 2010, Patel, GW et al conducted a retrospective cohort study evaluated the clinical outcomes of prolonged-infusion Zosyn® and compared intermittent 30-minute infusions of 3.375–4.5 g Q 6–8H with prolonged 4-hour infusions of 3.375 g Q8H.[13] Patients with various degrees of renal impairment were included.
    a) Results indicated no significant differences in either 30-day mortality (8.5% in the intermittent-infusion group vs 5.7% in the prolonged-infusion group) or the overall hospital LOS (8 days in both groups).

4. In 2011, Yost et al. and The Retrospective Cohort of Extended-infusion Piperacillin-Tazobactam (RECEIPT) study group published a multi-institutional retrospective review of prolonged-infusion Zosyn® compared with intermittently dosed β-lactams (cefepime, ceftazidime, imipenem-cilastatin, meropenem, doripenem, and Zosyn®).[14]
    a) In-hospital mortality was significantly reduced in the extended-infusion Zosyn® group versus the group receiving comparator antibiotics, 9.7% versus 17.9%, respectively ($p = 0.02$). A multivariate analysis in this same study demonstrated prolonged survival in patients receiving extended-infusion Zosyn® (~3 days) when compared to patients on non-extended-infusion comparator antibiotics.

IV. PROCEDURES

A. Definition
1. Intermittent Infusion: infusion lasting 30-60 minutes
2. Extended-infusion: infusion lasting 4 hours

B. Physician Ordering
1. All orders will default to the extended-infusion time for Zosyn® except one-time orders in the ER, OR/PACU, and ambulatory care areas as well as those in pediatric order sets.
   a) Intermittent infusion orders will only be available to pharmacists.
      1) If a provider would like to opt-out of the extended-infusion, the applicable exception criterion (see Section V, Subsection B), must be noted on the order.
2. First doses will default to a one-time 30 minute bolus to avoid any delays in patient care. The maintenance doses will be linked to the order as extended-infusions.

C. Pharmacist Verification
1. Review each order for appropriateness based on the following parameters (not exhaustive):
   a) Indication (required from physician on order entry), allergies, site of infection, suspected pathogen(s), and drug interactions.
2. Automatically interchange intermittent infusion orders with extended-infusion as outlined in Section V unless they meet any of the exception criteria outlined in Section V, Subsection B.
3. Automatically adjust the medication dosage based on renal function (if necessary) as outlined in the Section V: Dosing Recommendations.
4. If IV access or medication timing is a problem, the pharmacist may convert the order to the equivalent intermittent dosing regimen without a physician's order.

D. Dispensing and Distribution
1. Intravenous antimicrobials are stored in the pharmacy and delivered to the dispensing cabinets (Pyxis) on a daily basis.

V. DOSING RECOMMENDATIONS

A. Pharmacists will assess, interchange and renally adjust standard doses of Zosyn® with extended-infusions as described in the adult dosing chart below.

Renal Function	CrCl > 40 ml/min	CrCl 20-40 ml/min	CrCl < 20 ml/min	IHD, PD	CRRT
Intermittent Dosing (30-min infusion)					
General	3.375 IV Q6H	2.25 gm IV Q6H	2.25 gm IV Q8H	2.25 gm IV Q12H	3.375 gm IV Q6H
Pseudomonas/ nosocomial PNA/CF	4.5 gm IV Q6H	3.375 gm IV Q6H	2.25 gm IV Q6H	2.25 gm IV Q8H	
Extended-Infusion Dosing (4-hour infusion)†					
General, Pseudomonas, nosocomial PNA,CF	3.375 gm IV Q8H (4.5g IV Q8H in select populations*)		3.375 gm IV Q12H	3.375 gm IV Q12H	3.375 gm IV Q8H*

* In select cases, higher Zosyn® dosing may be warranted, e.g. sepsis, critically ill patients with severe or deep seated infections, infections with MIC > 16 mg/L, obesity with weight > 120kg or BMI >40[15,16], CrCl > 120 ml/min, or enhanced drug clearance such as those with cystic fibrosis: consider doses of 4.5g q8h (infused over 4 hours) or q6h. (Please refer to Appendix: Figures 1, 2, 3)[10, 13]

† Orders will default to allow a 30 minute bolus first-dose followed by a maintenance dose 4 hours later (6 hours if CrCl < 20, IHD, or PD)

Abbreviations: IHD: intermittent dialysis; PD: Peritoneal dialysis; CRRT: continuous renal replacement therapy (includes CVVH, CVVHD, CVVHDF); PNA: pneumonia; CF: cystic fibrosis.

B. Exceptions
1. One-time doses for patients in the emergency department (pre-admission status only), ambulatory clinics, any emergent situations (including sepsis), or peri-op OR/PACU doses.
2. Pediatric population (less than 18 years old).
3. Medication scheduling and/or drug compatibility conflicts that cannot be resolved without placing additional lines.
4. Patients with other medical intervention (*e.g.* physical therapy) that cannot be performed adequately during the IV infusion AND administration times cannot be modified to accommodate the intervention.
5. Patients who are on a prolonged course of antibiotics (*e.g.* osteomyelitis), are clinically improving, AND the organism has an MIC ≤4.[3]
6. Note: There is no data demonstrating improved outcomes using extended-infusion in IHD/PD populations. Use of extended-infusion is optional in these patients.

VI. ADMINISTRATION AND NURSING ROLE

A. Nurse infuses Zosyn® over 4 hours piggy-backed on its own dedicated line, or run parallel with patient's maintenance IV fluid via Y-site if indicated.
B. Follow Patient Care Manual Guide: "Medication Administration IV Infusion Guidelines" under section "H. Intermittent Infusion" and section "I. Continuous Infusion."
C. Reference Lexi-comp or Micromedex for IV compatibility info. Call pharmacy with additional questions. (See appendix, Table 1)
1. Note that Zosyn® is not compatible with vancomycin >7mg/mL (i.e. concentrations used for central lines)
D. Contact pharmacist if IV line access is limited or if patients are receiving other medications concurrently.

VII. DOCUMENT INFORMATION

A. Original Author/Date
Emily Mui, PharmD, BCPS: 8/2013

B. Gatekeeper
Antimicrobial Stewardship Team and Pharmacy Department

C. Distribution
This procedure is kept in the Antimicrobial Stewardship Team and Pharmacy Policy and Procedure Manuals

D. Review and Renewal Requirement
This document will be reviewed every three years and as required by change of law or practice.

E. Revision/Review History
Lina Meng, PharmD, BCPS, Janjri Desai, PharmD, MBA, BCPS: 2/2015, 3/2015
Lina Meng, PharmD, BCPS, Emily Mui, PharmD, BCPS, 10/2015
Lina Meng, PharmD, BCPS 2/2016, 7/2016

F. Approvals
Pharmacy and Therapeutics Committee: 2/2015, 08/2016
Antimicrobial Subcommittee: 10/2015, 3/2016, 03/2016

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3. Lodise TP, Jr., Lomaestro B, Drusano GL. Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Feb 1 2007;44(3):357-363.
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APPENDIX

Table 1. Common Y-site (IV) Incompatibilities[12]

Known incompatible agents		Variable compatibility (Consult detailed reference)
Acyclovir Amiodarone HCL Amphotericin B Azithromycin Caspofungin *(EDTA formulated product only)* Chlorpromazine Dobutamine Doxycycline Droperidol Famotidine Ganciclovir	Haloperidol Hydroxyzine Minocycline Nalbuphine Pantoprazole *(EDTA formulated product only)* Prochlorperazine Promethazine Streptozocin Tobramycin *(EDTA formulated product only)*[a]	Cisatracurium Gentamicin Vancomycin ≤ 5mg/mL in D5W (≤ 7mg if in NS) is compatible [17]

[a]Avoid mixing aminoglycosides & penicillin in the same bag/infusing concurrently through same line.
For additional information or clarification, call pharmacy.

Figure 1. Kim et al, Pharmacotherapy 2007

Probability of target attainment at doubling minimum inhibitory concentration dilutions for piperacillin-tazobactam regimens containing piperacillin 16 g/day.

Note: none of the regimens below are reliable at an MIC of 64 mg/L.

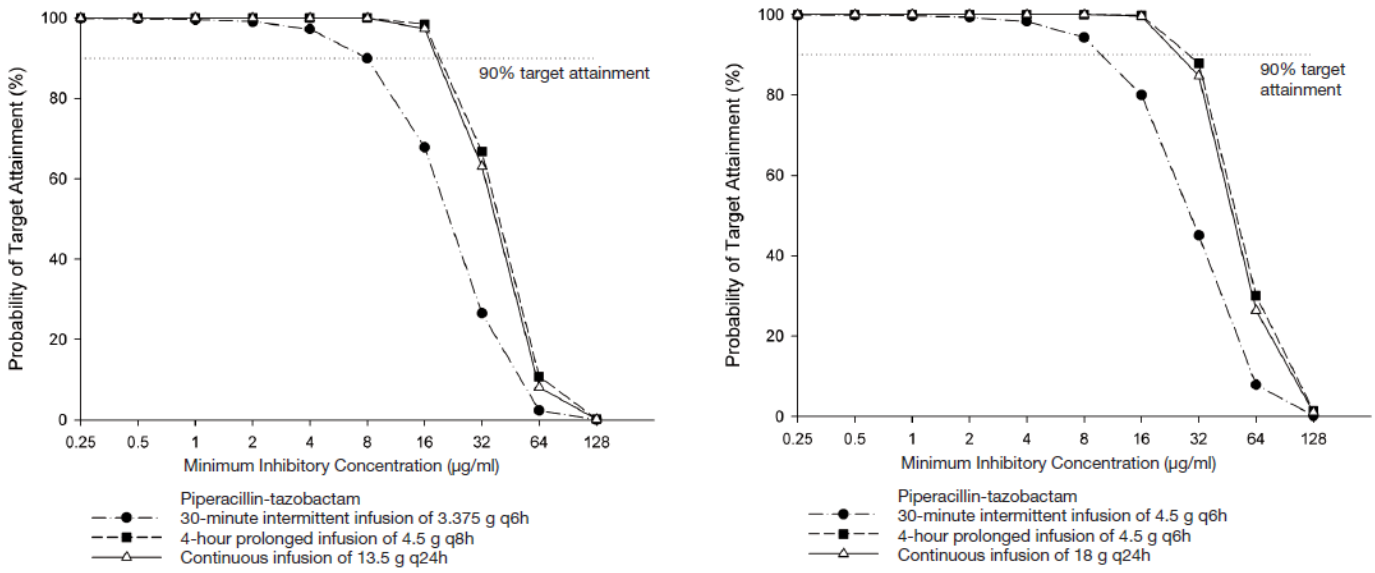


Figure 2. Kim A et al, Pharmacotherapy 2007

Note: Alternative high dose extended-infusion dosing strategies may only marginally increase the response rates depending on the MIC of Zosyn® for the pathogen. More intensive regimens are warranted for pathogens with higher MICs.

Table 3. Cumulative Fractions of Response for Various Dosages of Piperacillin-Tazobactam

	Daily Dose of Piperacillin				
Infusion Type, Dosage	9 g	12 g	16 g	18 g	20 g
Continuous (over 24 hrs)					
10.125 g	82.3%	—	—	—	—
13.5 g	—	86.5%	—	—	—
18 g	—	—	89.2%	—	—
20.25 g	—	—	—	90.0%	—
22.5 g	—	—	—	—	90.6%
Prolonged					
3.375 g over 4 hrs q8h	83.3%	—	—	—	—
4.5 g over 4 hrs q8h	—	87.1%	—	—	—
4.5 g over 3 hrs q6h	—	—	89.6%	—	—
Intermittent (over 30 min)					
3.375 g q6h	—	74.7%	—	—	—
4.5 g q6h	—	—	79.9%	—	—
3.375 g q4h	—	—	—	85.6%	—

Figure 3. Patel et al, AAC 2010

Intermittent infusion 4.5g IV Q6H (over 30 min) vs extended infusion 3.375g IV Q8h (over 4 hours), stratified by CrCl and MIC

TABLE 4. PTA of various TZP dosing regimens stratified by CL_{CR} and MIC[a]

CL_{CR} (ml/min)	Traditional regimen at TZP MIC (mg/liter):								Extended-infusion regimen at TZP MIC (mg/liter):							
	0.25	0.5	1	2	4	8	16	32	0.25	0.5	1	2	4	8	16	32
120	0.96	0.94	0.90	0.83	0.73	0.57	0.36	0.13	0.99	0.99	0.99	0.99	0.99	0.96	0.62	0.11
100	0.98	0.96	0.93	0.88	0.81	0.67	0.46	0.19	0.99	0.99	0.99	0.99	0.99	0.97	0.73	0.17
80	0.99	0.98	0.96	0.93	0.87	0.77	0.58	0.30	0.99	0.99	0.99	0.99	0.99	0.98	0.82	0.27
60	0.99	0.99	0.98	0.96	0.92	0.84	0.70	0.43	0.99	0.99	0.99	0.99	0.99	0.99	0.90	0.43
40	0.99	0.99	0.99	0.98	0.96	0.92	0.84	0.64	0.99	0.99	0.99	0.99	0.99	0.99	0.95	0.62
20	0.99	0.99	0.99	0.99	0.98	0.96	0.91	0.80	0.99	0.99	0.99	0.99	0.99	0.99	0.97	0.81

[a] Traditional regimen, 4.5 g i.v. every 6 h, 30-min infusion; extended-infusion regimen, 3.375 g i.v. every 8 h, 4-h infusion.

Figure 4. Lodise TP et al, CID 2007.

Clinical Implications of extended infusion dosing: Extended infusion 3.375g IV Q8h (over 4 hours) vs intermittent infusion 3.375g IV Q6H (over 30 min)

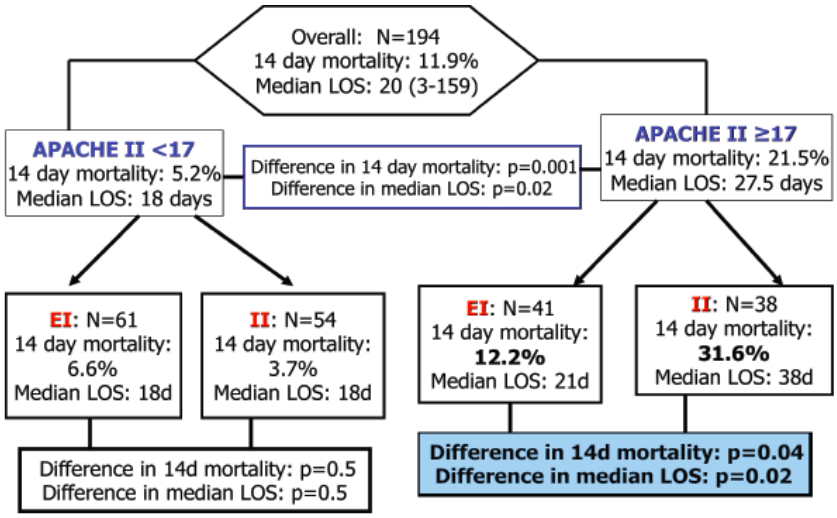
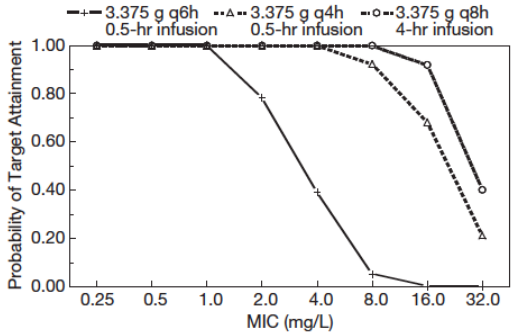


Figure 5. Lodise et al, CID 2007, Lodise et al, Pharmacotherapy 2006



Regimen	MIC for 90% PTA
3.375g IV Q6H (30-min)	< 4 mcg/mL
3.375g IV Q4H (30-min)	< 8 mcg/mL
3.375g IV Q8H (4-hr)	< 16 mcg/mL

In 2012, 91% of SHC *P aeruginosa* isolated had MICs of 16mg/L