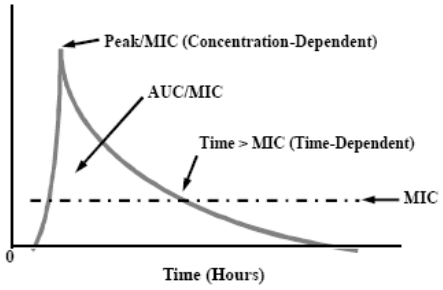
I. PURPOSE:

Dose optimization is an essential component for clinical success in the treatment of serious infections as well as preventing the emergence of resistance. 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 minimum inhibitory concentration (MIC) of the organism (fT>MIC).[1] This policy is intended to optimize the antibacterial activity of beta-lactams based on their pharmacokinetic and pharmacodynamic properties through a hospital-wide implementation of prolonged beta-lactam infusions.



II. POLICY:

This policy outlines the procedures at Stanford Health Care (SHC) for the prescribing and administration of the following antimicrobials:

A. Cefepime (Maxipime®)
B. Meropenem (Merrem®)
C. Piperacillin/tazobactam (Zosyn®)

Please see Appendix A for additional supporting information.

III. DEFINITIONS:

A. Intermittent/standard Infusion – infusion lasting 30-60 minutes
B. Extended/prolonged Infusion – infusion lasting 3-4 hours

IV. PROCEDURE:

A. Physician Ordering
   1. All orders will default to extended infusion except one-time orders in the Emergency Department, OR/PACU, and ambulatory care areas as well as those in pediatric order sets.
      a. Intermittent infusion orders will only be available to pharmacists.

   b. 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. The first dose 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.

B. 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 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.

C. Dispensing and Distribution
1. Intravenous antimicrobials are stored in the pharmacy and made on a patient-specific basis. The pharmacist must first verify and authorize the clinical appropriateness of the antibiotic, pharmacy technician prepares the medication.

D. Administration and Nursing Role
1. Nurse infuses the medication (see below for administration time based on drug) piggy-backed on its own dedicated line, or run parallel with patient's maintenance IV fluid via Y-site if indicated.
   a. Cefepime: 4 hours
   b. Meropenem: 3 hours
   c. Piperacillin/tazobactam: 4 hours
2. Follow: "Medication Administration - IV Guidelines"
3. Reference Lexi-comp or Micromedex for IV compatibility info. Call pharmacy with additional questions.
4. Contact pharmacist if IV line access is limited or if patients are receiving other medications concurrently.
5. E. Maintenance dose to start based on the following:

Drug	Loading (Bolus) Dose*^	Maintenance Dose
Cefepime	Given over 30 minutes	Maintenance to start based on order frequency • E.g. cefepime 1g x1 (over 30 minutes), then 1g q8h (over 4 hours) starting 8 hours after bolus
Meropenem	Given over 30 minutes	Maintenance to start based on order frequency • E.g. meropenem 1g x1 (over 30 minutes), then 1g q8h (over 3 hours) starting 8 hours after bolus
Piperacillin/ Tazobactam	Given over 30 minutes	Maintenance to start 4 hours after bolus • Exception: maintenance to start 6 hours after bolus for CrCl < 20, IHD, or PD
*If patient already received a bolus dose, time subsequent doses accordingly (not necessary to re-bolus) ^Some areas may opt to use IV push for initial administration of antibiotics (if applicable), for which the suggested loading dose administration time may differ from this table		

V. DOSING & MONITORING GUIDELINES

A. Pharmacists will follow the SHC Antimicrobial Dosing Guide in conjunction with clinical discretion to optimize dosing and minimize toxicity

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.

VI. COMPLIANCE: (These are requirements and are not to be changed)

A. All workforce members including employees, contracted staff, students, volunteers, credentialed medical staff, and individuals representing or engaging in the practice at Stanford Health Care (SHC) are responsible for ensuring that individuals comply with this policy.

B. Violations of this policy will be reported to the Department Manager and any other appropriate Department as determined by the Department Manager or in accordance with SHC policy. Violations will be investigated to determine the nature, extent, and potential risk to SHC. Workforce members who violate this policy will be subject to the appropriate disciplinary action up to and including termination.

VII. REFERENCES:

A. Drusano GL. Antimicrobial pharmacodynamics: critical interactions of "bug and drug." Nat Rev Microbiol. 2004;2(4):289-300. doi:10.1038/nrmicro862

B. Lodise TP, Lomaestro BM, Drusano GL. Application of Antimicrobial Pharmacodynamic Concepts into Clinical Practice: Focus on β-Lactam Antibiotics. Pharmacother J Hum Pharmacol Drug Ther. 2006;26(9):1320-1332. doi:10.1592/phco.26.9.1320

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D. Roos JF, Bulitta J, Lipman J, Kirkpatrick CMJ. Pharmacokinetic-pharmacodynamic rationale for cefepime dosing regimens in intensive care units. J Antimicrob Chemother. 2006;58(5):987-993. doi:10.1093/jac/dkl349

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M. Lodise TP, Lomaestro B, Drusano GL. Piperacillin-Tazobactam for Pseudomonas aeruginosa Infection: Clinical Implications of an Extended-Infusion Dosing Strategy. Clin Infect Dis. 2007;44(3):357-363. doi:10.1086/510590

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P. Rhodes NJ, Liu J, O'Donnell JN, et al. Prolonged Infusion Piperacillin-Tazobactam Decreases Mortality and Improves Outcomes in Severely Ill Patients: Results of a Systematic Review and Meta-Analysis*. Crit Care Med. 2018;46(2):236-243. doi:10.1097/CCM.0000000000002836

VIII. RELATED DOCUMENTS/PROCEDURES:

A. SHC Antimicrobial Dosing Guide
B. Medication Administration – IV Guidelines

IX. DOCUMENT INFORMATION:

A. Legal References/Regulatory Requirements:
   1. CA State Board of Pharmacy Lawbook BP&C 4051.2(a)(2), BP&C 4051.2(a)(4)
B. Original Document
   1. 11/2022, Brian Lu, PharmD
   2. 08/2013, Emily Mui, PharmD
   3. Stored in: Pharmacy Manual
C. Review and Renewal Requirements:
   1. This policy will be reviewed and/or revised every three years or as required by change of law or practice.

D. Review and Revision History:
   1. Cefepime Extended Infusion Protocol
      a) Last reviewed: 10/2019 Emily Mui, PharmD; Lina Meng, PharmD; Will Alegria, PharmD; David Ha
   2. Meropenem Extended Infusion Protocol
      a) Last reviewed: 02/2016 Emily Mui, PharmD; Lina Meng, PharmD
   3. Piperacillin/tazobactam Extended Infusion Protocol
      a) Last reviewed: 07/2016 Lina Meng, PharmD
   4. Extended Infusion Beta-Lactam Protocol
      a) 11/2022 Brian Lu, PharmD; Emily Mui, PharmD; Lina Meng, PharmD

E. Approvals:
   1. Cefepime Extended Infusion Protocol
      a) Last approved: 03/2016 Pharmacy & Therapeutics Committee
   2. Meropenem Extended Infusion Protocol
      a) Last approved: 08/2016 Pharmacy & Therapeutics Committee
   3. Piperacillin/tazobactam Extended Infusion Protocol
      a) Last approved: 08/2016 Pharmacy & Therapeutics Committee
   4. Extended Infusion Beta-Lactam Protocol
      a) 12/2022 Antibiotic Subcommittee

Stanford MEDICINE | Health Care

APPENDIX A: Supporting Literature

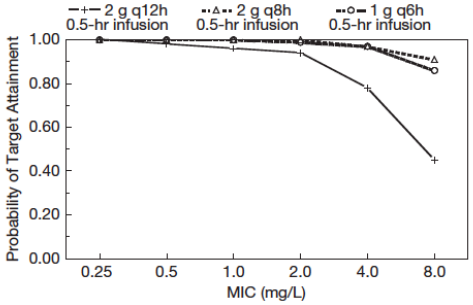
A. SHC *Pseudomonas aeruginosa* breakpoint distribution 2021 (one per patient, first isolate only)

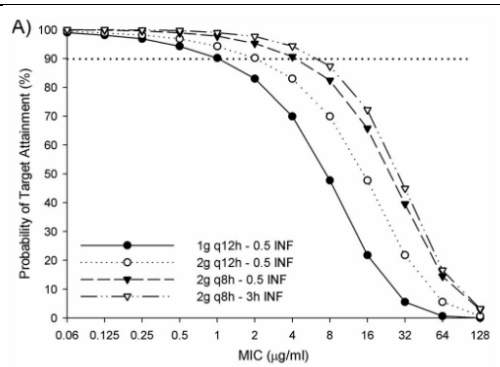
	# Isolates	Breakpoint	S%	MICs (% distribution)									
				0.25	0.5	1	2	4	8	16	32	64	128
Cefepime	578	8 mg/L	92%			16	54	12	10	4	3		
Meropenem	578	2 mg/L	94%	21	7	63	2	2	1	2			
Piperacillin/ Tazobactam	559	16 mg/L	95%					16	72	7	2	1	2

B. Goal target attainments by beta-lactam class

Pathogen	Carbapenems	Cephalosporins	Penicillins
Gram-positive	20-30% *f*T>MIC	40-50% *f*T>MIC	30-40% *f*T>MIC
Gram-negative	40-50% *f*T>MIC	60-70% *f*T>MIC	50-60% *f*T>MIC

C. Supporting literature for extended infusion and alternative dosing

Drug	Supporting Literature
Cefepime	Cefepime displays a time-dependent bactericidal activity, and its efficacy is optimized when the free drug concentration exceeds the MIC (fT>MIC) for at least 60-70% of the dosing interval for treatment of Gram-negative bacteria. Prolonging the infusion time for cefepime has been shown to achieve greater probability of target attainment (PTA) for many Gram-negative organisms, including *Pseudomonas aeruginosa*. Some studies have also observed improvements in clinical outcomes with extended infusion cefepime as compared to standard dosing. 1. Monte Carlo simulations using 67% fT>MIC as the pharmacodynamic target showed that cefepime 1g IV q6h as a 30-minute infusion had similar probability of target attainment profile as maximal cefepime dosing (2g IV q8h as a 30-minute infusion).[2]  2. A Monte Carlo analysis evaluated cefepime exposures in patients infected with *P. aeruginosa* to identify the pharmacodynamic relationship of microbiologic response. Microbiological failure was associated with an fT>MIC of <60% (77.8% failed cefepime therapy when fT>MIC was <60%, whereas 36.2% failed cefepime therapy when fT>MIC was >60%; P = 0.013). Cefepime doses of at least 2g q8h are required to achieve this target against CLSI-defined susceptible *P. aeruginosa* organisms in patients with normal renal function.[3]



3. In a pharmacokinetic analysis utilizing population kinetics, the expected probabilities of target attainment were obtained for the various MIC distributions for common ICU pathogens (*E.coli*, *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii*).[4] Prolonging the infusion provides greater probability of target attainment compared to intermittent infusion for regimens with the same total daily dose.

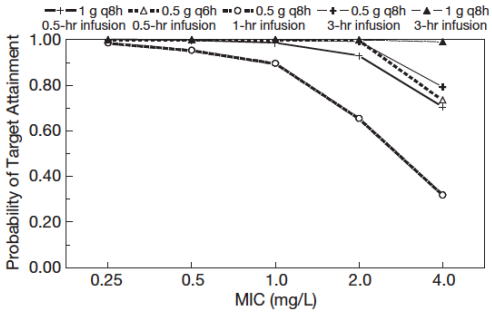
Dosing Regimens	**PTA expectation values (%)**			
	E. coli	***K. pneumoniae***	***P. aeruginosa***	***A. baumannii***
Intermittent				
1g q4h (6g/day)	95.3	95.3	82.6	57.9
2g q8h (6g/day)	95.8	95.8	84.9	61.1
1g q6h (4g/day)	91.9	91.9	69.5	41.5
2g q12h (4g/day)	78.9	78.9	53.6	28.2
1g q12h (2g/day)	66.1	66.1	35.5	11.6
Continuous infusion with loading dose of 0.5g				
2g/day	95.2	95.2	81.3	56.3
4g/day	96.9	96.9	91.7	68.5
6g/day	97.9	97.9	94.8	74.6

4. In a single centered study comparing inpatients who received cefepime for bacteremia and/or pneumonia to those receiving the same dose but extended infusion over 4 hours, the overall mortality was significantly lower in the group that received extended-infusion treatment (20% versus 3%; p=0.03). The mean length of stay was 3.5 days less for patients who received extended infusion (p=0.36), and for patients admitted to the ICU, the length of stay was significantly less than in the extended infusion arm (p=0.04).[5]

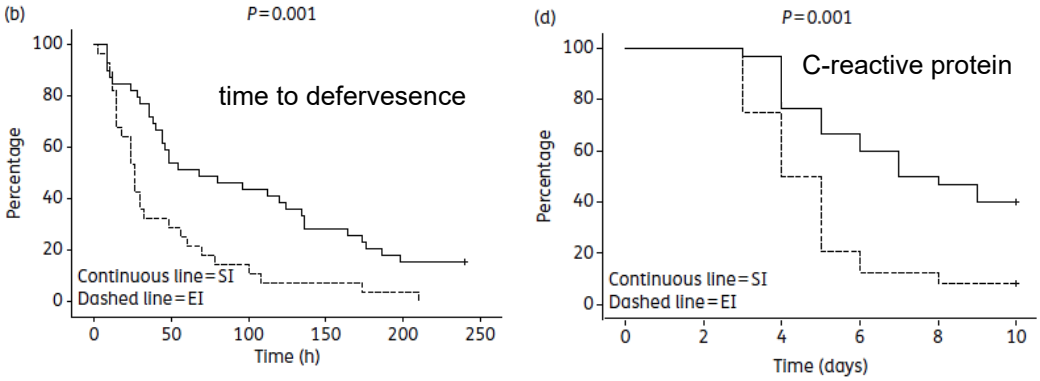
5. An evaluation of clinical outcomes in patients stratified by antimicrobial MICs to cefepime suggested that there are increased odds of mortality with higher cefepime MICs. A multivariate logistic regression revealed increased odds of mortality at a cefepime MIC of 4 mg/L (adjusted odds ratio [aOR] 6.47; 95% CI 1.25–33.4) and 64 mg/L (aOR 6.54, 95% CI 1.03-41.4). There was not enough data to analyze patients at a cefepime MIC of 8, 16, or 32 mg/L. However, among those who survived, patients with cefepime MICs ≥4 mg/L experienced a longer median ICU LOS of 16 days compared to 2 days (p = 0.026).[6]

6. In 2018, Wrenn et al. conducted a prospective, randomized, comparative pilot study that compared standard infusion and extended infusion cefepime as empiric treatment of febrile neutropenia. There was no difference observed for the primary outcome of defervescence by 72

<table>
<tr><td></td><td>hours, but there was a nonsignificant difference in rates of defervescence by 24 hours favoring the extended infusion arm (53% vs 36%, p=0.07). No other outcomes were considered statistically significant and there were no practical or safety concerns identified with use of extended infusion in this population.[7]</td></tr>
<tr><td>Meropenem</td><td>The PK/PD goal of meropenem is to achieve free drug concentration exceeding the MIC for at least 40% of the dosing interval when treating Gram-negative bacteria. Extended infusions of meropenem have been shown to provide more robust PTA for various nosocomial pathogens, such as P. aeruginosa and Acinetobacter spp. Extended infusion meropenem has been associated with improved clinical outcomes in several populations, such as critically ill patients and those with febrile neutropenia.

1. Monte Carlos simulations using PK data from healthy volunteers show that extended-infusion meropenem provides more robust probabilities of target attainment than convention meropenem dosing regimens. Using the global Meropenem Yearly Susceptibility Testing Information Collection (MYSTIC) surveillance data as the measure of MIC distribution and frequency, the overall probability of target attainment for various nosocomial pathogens (for both 1-hour and 3-hour infusions) were covered except for P. aeruginosa and Acinetobacter spp. For these pathogens, meropenem 1g IV q8h administered over 3 hours provided higher probabilities of target attainment.[2,8]
<table>
<tr><th>Organism</th><th>Meropenem 500mg q8h (1-hour infusion)</th><th>Meropenem 500mg q8h (3-hour infusion)</th><th>Meropenem 1g q8h (3-hour infusion)</th></tr>
<tr><td>Staphylococcus aureus</td><td>95%</td><td>98.4%</td><td>98.8%</td></tr>
<tr><td>Klebsiella spp</td><td>97.5%</td><td>99.5%</td><td>99.6%</td></tr>
<tr><td>Enterobacter spp</td><td>97.3%</td><td>99.5%</td><td>99.8%</td></tr>
<tr><td>Serratia spp</td><td>96.2%</td><td>99.4%</td><td>99.6%</td></tr>
<tr><td>Acinetobacter spp</td><td>76.4%</td><td>77.1%</td><td>83.0%</td></tr>
<tr><td>P. aeruginosa</td><td>76%</td><td>79.3%</td><td>86.4%</td></tr>
</table>
2. Several published Monte Carlo simulations reveal that meropenem 500mg q6h and meropenem 1g q8h achieve similar percentages of fT>MIC.[9] Using data from neutropenic patients, another research group observed similar T>MIC between meropenem 500mg q6h and meropenem 1,000mg q8h. For MICs greater than 2mg/L, the probably of target attainment was near 99% with 1g q8h infused over 3 hours.[2,10]
 

3. A retrospective observational study demonstrated that meropenem 1g IV q8h given via extended infusion (4 hours) compared to standard infusion (30 mins) led to favorable clinical outcomes in febrile neutropenia patients. The subgroup analysis revealed that patients treated with meropenem alone experienced significantly shorter times to defervescence and decreased C-reactive protein values. In addition, patients who received meropenem monotherapy had treatment success on day 5 of antibiotic therapy (OR: 5.59, 95% CI: 1.83-16.99). However, there was no difference in hospital length of stay or 100-day mortality rate.[11]</td></tr>
</table>

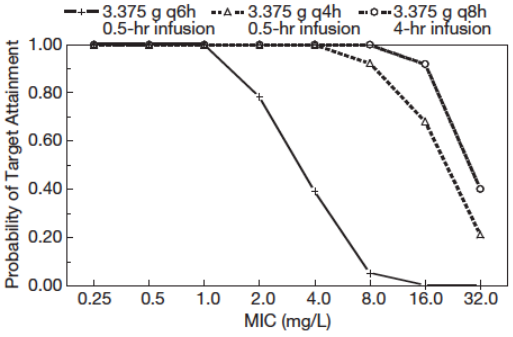


4. In a post-hoc analysis of a prospective multicenter study of critically ill patients from 68 ICUs across 10 countries, patients receiving beta-lactams via prolonged infusion demonstrated significantly better 30-day survival when compared with intermittent-bolus patients [86.2% (25/29) versus 56.7% (17/30); P=0.012]. Additionally, in patients with a SOFA score of ≥9, administration by prolonged infusion compared with intermittent-bolus dosing demonstrated significantly better clinical cure [73.3% (11/15) versus 35.0% (7/20); P=0.035] and survival rates [73.3% (11/15) versus 25.0% (5/20); P=0.025].[12]

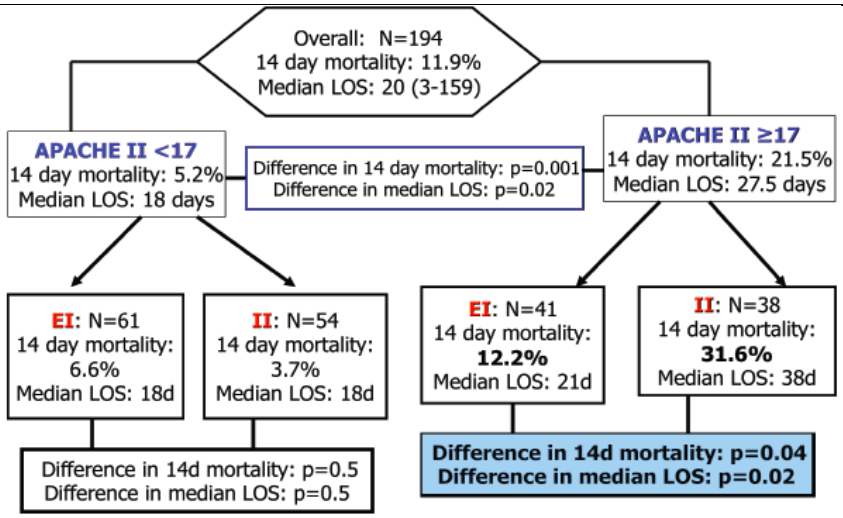
Piperacillin/ Tazobactam

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% fT>MIC. PK/PD literature suggests that a 4-hour infusion of piperacillin/tazobactam was more likely to achieve 50% *f*T>MIC than standard infusion when used for *P. aeruginosa*. Some retrospective data suggest potential clinical benefits with the use of extended infusion piperacillin/tazobactam.

1. Based on the published literature examining PK/PD of piperacillin/tazobactam against *P. aeruginosa* and a target of 50% *f*T>MIC, 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 indicated that attainment of 50% *f*T>MIC for piperacillin/tazobactam was best achieved with a 4-hour infusion of 3.375g IV q8h.[2,13]



2. In 2007, a hospital-wide substitution program where intermittently infused piperacillin/tazobactam was converted to extended-infusion, patients at greatest risk for mortality (APACHE II score >17) receiving extended-infusion piperacillin/tazobactam showed significantly lower 14-day mortality rates and median hospital LOS compared with patients who received intermittent infusion piperacillin/tazobactam.[13]



3. In 2010, Patel et al conducted a retrospective cohort study that evaluated the clinical outcomes associated with prolonged-infusion (3.375–4.5g q6–8h with prolonged 4-hour infusions) and intermittent infusion piperacillin/tazobactam (3.375g q8h with intermittent 30-minute infusions). Patients with various degrees of renal impairment were included.[14] 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 piperacillin/tazobactam compared with intermittently dosed beta-lactams (cefepime, ceftazidime, imipenem/cilastatin, meropenem, doripenem, and piperacillin/tazobactam).[15] In-hospital mortality was significantly reduced in the extended-infusion piperacillin/tazobactam 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 piperacillin/tazobactam (~3 days) when compared to patients on non-extended-infusion comparator antibiotics.

5. A systematic review/meta-analysis from 2018 evaluated 18 studies (3,401 patients) in which critically ill patients were treated with piperacillin/tazobactam.[16] Prolonged infusion of piperacillin/tazobactam was associated with a pooled 1.46-fold lower odds of mortality (95% CI, 1.20-1.77) as compared to intermittent infusion. These results were similar when studies were restricted to those showing an average mortality probability of ≥20% (OR 0.69, 95% CI 0.55-0.86) and <20% (OR 0.69, 95% CI 0.46-1.03). There was also more clinical cure (OR 1.77, 95% CI 1.24-2.54) and microbiological cure (OR 1.22, 95% CI 0.84-1.77) associated with prolonged infusion.