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# Development and Implementation of a Piperacillin-Tazobactam Extended Infusion Guideline

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## Abstract

Administration of β-lactam antibiotics by extended infusion optimizes the pharmacodynamic properties and bactericidal activity of these agents resulting in a potential improvement in patient outcomes and reduction in drug expenditure. Consequently, a pharmacist-led piperacillin-tazobactam extended 4-hour infusion guideline was implemented hospital-wide at a 500-bed academic medical center. Each piperacillin-tazobactam infusion was prospectively monitored for 5 weeks to ensure accurate administration and identify barriers to guideline adherence. Overall, a total of 103 patients received 1215 doses of piperacillin-tazobactam by extended infusions. In all, 98% of the doses were administered at the correct extended infusion rate and 94% of the doses were given at the scheduled time. There were a total of 20 missed doses and 53 delayed doses, accounting for 2% and 4% of the total administered doses, respectively. The primary barrier to adherence was the patient not being on the unit at the time of the scheduled dose followed by the piperacillin-tazobactam dose not being available on the floor. While insufficient power prevented meaningful evaluation of clinical outcomes, we anticipate a conservative annual estimated cost savings of $108 529. Key elements contributing to our success included consistent pharmacy leadership, multidisciplinary involvement, thorough inservicing to health care professionals, hospital-wide implementation, and extensive quality assurance monitoring.

## Keywords

extended infusion, antibiotics, guideline

Gram-negative pathogens such as *Pseudomonas aeruginosa* often cause nosocomial infections associated with significant morbidity and mortality.[1-5] The treatment of Gram-negative infections can be challenging due to the potential for multiple resistance mechanisms and the emergence of strains with high minimum inhibitory concentration (MIC) values toward available antibiotics. Given the lack of novel antibiotics with Gram-negative activity in development, it is important to optimize the currently available broad-spectrum agents.[6,7] β-lactam antibiotics, such as piperacillin-tazobactam, are time-dependent antibiotics whereby the bactericidal activity is optimized when drug concentrations exceed the MIC for at least 50% of the dosing interval. Given the drug's short elimination half-life (~1 hour), traditional dosing strategies using an intermittent 30-minute piperacillin-tazobactam infusion may result in serum concentrations below the MIC for a prolonged period of time.[8] By extending the antibiotic infusion time, antibiotic levels will be sustained above the MIC of targeted organisms, which may potentially result in improved drug efficacy and clinical outcomes.[9,10]

Monte Carlo simulations have demonstrated superior bactericidal activity of piperacillin-tazobactam when administered as an extended 4-hour infusion compared to an intermittent 30-minute infusion, as the time spent above the MIC is maximized.[7,8] Furthermore, Lodise et al reported a significant decrease in 14-day mortality and duration of hospitalization among patients with an APACHE II score ≥17 after implementation of a piperacillin-tazobactam extended infusion

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**Table 1.** Piperacillin-Tazobactam Extended Infusion Guideline Regimens[a]

| Antimicrobial Agent | CrCL ≥ 20 mL/min | CrCL < 20 mL/min or ESRD | Continuous Renal Replacement Therapy |
|---|---|---|---|
| Piperacillin-tazobactam | 3.375 g Q8H | 3.375 g Q12H | 3.375 g Q8H |

Abbreviation: ESRD, end-stage renal disease
[a] Default administration times for Q8H regimen: 5 AM, 1 PM, and 9 PM; default administration times for Q12H regimen: 5 AM and 5 PM.

regimen.[11] From a larger multicenter cohort, Patel et al reported similar 30-day mortality and hospital length of stay among recipients of intermittent and extended infusion piperacillin-tazobactam for the treatment of Gram-negative infections; however, the APACHE II scores were lower, indicating a less critically ill patient population.[12] As a result, it was proposed to implement a similar hospital-wide piperacillin-tazobactam extended infusion guideline at our institution in order to optimize the pharmacodynamics and bactericidal activity of the antibiotic and subsequently improve patient outcomes.

Xamplas et al have published a description of the piperacillin-tazobactam extended infusion protocol at their medical center with an emphasis on quality assurance outcomes.[13] The authors did not include information regarding piperacillin-tazobactam dose selection, health care professional education, and the issues encountered upon implementation could be valuable to health care clinicians.[11] As a result, here we report a step-by-step guide to a pharmacist-led development and implementation of a piperacillin-tazobactam extended infusion guideline.

## Methods

Our institution is a 489-bed academic medical center including a 30-bed emergency department and 52 adult critical care beds. Overall, there are 32 categories of medical services and 24 nursing units (excluding diagnostic areas, operating rooms, and emergency department). The critical care units include: medical-surgical intensive care unit, cardiac intensive care unit, transplant intensive care unit, and neurosurgery intensive care unit. Drug distribution to these units begins with the placement of medication orders via Cerner PowerChart® (Cerner Corporation, Kansas City, Missouri), by computerized physician order entry system (CPOE). Patient-specific medications are delivered to the nursing unit from either central or a satellite pharmacy based on time of day. All nonemergent IV medications are made in the central pharmacy cleanroom. Bulk medications are stored in the nursing units and dispensed via Omnicell® (Omnicell, Mountain View, California), the automated medication dispensing system at our institution.

In the Fall of 2008, the pharmacy department developed the piperacillin-tazobactam extended infusion guideline to serve as a comprehensive reference for hospital-wide implementation. The guideline made extended infusion piperacillin-tazobactam the standard of care for all adult patients. Each piperacillin-tazobactam infusion was prospectively monitored for 5 weeks to ensure accurate administration and identify barriers to guideline adherence. The following is a step-by-step guide to the protocol development and implementation.

### *Key Elements to Piperacillin-Tazobactam Extended Infusion Guideline Development*

*Step 1: Assign pharmacy leadership with multidisciplinary contacts.* A pharmacy practice resident was the pharmacy leader for the collaborative project with assistance from the Critical Care and Infectious Diseases Clinical Pharmacists, the Associate Director of Clinical Services, and Medical Use Policy Coordinator. We sought additional input from nurses, clinical and staff pharmacists, infectious disease physicians, and hospital administration in order to tailor the protocol to our institution's needs.[9]

*Step 2: Protocol writing and considerations.* Essential protocol issues addressed included defining the patient population, piperacillin-tazobactam dose selection and preparation, administration times, and alternative regimen recommendations. The patient population included all adult patients prescribed piperacillin-tazobactam, with the exception of pediatric patients and intraoperative doses for surgical prophylaxis. Of note, piperacillin-tazobactam doses prescribed in the emergency department were administered as an extended infusion. The hospital-wide protocol was developed to minimize confusion regarding inclusion and exclusion criteria, decrease errors, and ensure that all patients received uniform care. If an extended infusion was not clinically feasible, the guideline recommended an alternative regimen of cefepime with or without metronidazole.

Prior to guideline implementation, the piperacillin-tazobactam 2.25 g, 3.375 g, and 4.5 g doses were available for use in adult patients. The piperacillin-tazobactam extended infusion guideline recommended 3.375 g dose with varying frequency based on renal function. The dosing recommendations are provided in Table 1. The decision to use the 3.375 g dose was based on the prescribing patterns and susceptibility of Gram-negative organisms such as *P aeruginosa* to piperacillin-tazobactam at our institution. While the 4.5 g dose was occasionally used for the treatment of nosocomial pneumonia, the 3.375 g dose accounted for >95% of the drug's utilization (based on normal renal function) at our institution prior to guideline implementation. The Anti-Infective Subcommittee of the Pharmacy and Therapeutics Committee reviewed antibiogram data as well as the Monte Carlo modeling by Lodise et al and decided the 3.375 g dose of piperacillin-tazobactam was sufficient for the treatment of Gram-negative infections, including *P aeruginosa*, at our

institution.[9] Default administration times were established (5 AM, 1 PM, and 9 PM for patients receiving the drug 3 times daily and 5 AM and 5 PM for patients receiving the drug 2 times daily) for ease of monitoring with the option of ordering a "NOW" dose when clinically indicated (Table 1). The times were selected to minimize interruption in concomitant drug administration and workflow. Consideration for adjustments to default dosing times was given to those patients on the rehabilitation unit on a case-by-case basis, as not to interfere with physical therapy.

*Step 3: Guideline approval.* The guideline received approval from the Anti-Infective Subcommittee of the Pharmacy and Therapeutics Committee, Pharmacy and Therapeutics Committee, and Medical Executive Committee prior to implementation.

**Table 2.** Piperacillin-Tazobactam Administration Information

| Parameter | Results N (% or Range) |
|---|---|
| Number of piperacillin-tazobactam doses | |
| Total | 1215 |
| Average Per Patient | 12 (1–58) |
| Piperacillin-tazobactam regimen | |
| Q8H | 85 (82) |
| Q12H | 14 (14) |
| One-time only | 6 (6) |
| Accuracy of administration | |
| Correct administration rate | 1193 (98) |
| Administered on schedule | 1142 (94) |
| Missed doses | 20 (2) |
| Delayed doses | 53 (4) |

## *Key Elements to Piperacillin-Tazobactam Extended Infusion Guideline Implementation*

*Step 1: Pharmacy preparation and workflow.* Staff pharmacists and pharmacy administration were consulted on modification of the piperacillin-tazobactam unit dose preparation and drug distribution with the new extended infusion regimen. Prior to guideline implementation frozen 50 mL prepacks were stored on the nursing units. With the required volume increase, it was decided to make each 100 mL dose in a patient-specific manner in central pharmacy, which was delivered to the nursing units via the pharmacy satellite. The initial patient-specific dose distribution was later converted to a bulk dose distribution due to missing piperacillin-tazobactam doses on the nursing units. The pharmacy information technology staff assisted with the creation of order sentences and incorporation of the guideline into Cerner PowerChart®. The order sentences included the default administration times and a reminder of the 4-hour extended infusion. The order sentences changed upon implementation of the extended infusion protocol to ensure a complete transition to the new guideline.

*Step 2: Health care professional education.* The guideline and implementation plans were introduced to health care professionals via a 20-minute PowerPoint® presentation during nursing and pharmacy staff and leadership meetings 1 month prior to implementation. The presentation was given by the PGY-1 pharmacy resident and detailed supporting data, protocol development process, and plans for implementation and quality assurance monitoring. This increased familiarity with the guideline, created opportunities to address questions and concerns, and aided in the development of thorough inservices prior to guideline implementation. This presentation was disseminated to all medical residents and physicians via email. Additionally, a 10-minute inservice was presented by the pharmacy resident to all pharmacy residents, nurses, and hospital pharmacists. A 1-page handout was provided with guideline highlights including: rationale, dosing, and administration instructions, clinical significance of adherence with the extended infusion regimen, and instructions for management of anticipated conflicts. These inservices were performed within 2 weeks prior to implementation. Nursing inservices were scheduled during shift change to optimize attendance. An inservice handout was placed on all Omnicell® units as a reminder.

*Step 3: Assessment of guideline adherence.* The quality assurance assessment included all patients receiving piperacillin-tazobactam per extended infusion regimen for 5 weeks following guideline implementation. The pharmacy resident performed the majority of the quality assurance monitoring in order to quickly identify barriers to adherence and take corrective action if necessary. The pharmacy resident received notification of each inpatient order for piperacillin-tazobactam placed in Cerner PowerChart®. Each order was then reviewed for accuracy in terms of order sentence selection and appropriateness related to renal function and/or type of dialysis. Each infusion was prospectively monitored at each patient's bedside to ensure the correct administration start time, piperacillin-tazobactam product, rate of infusion, and compatibility of concomitant infusions (Figure 1). The monitoring schedule was as follows: 5 AM dose was checked between 6 AM and 7 AM, 1 PM dose was checked between 2 PM and 3 PM, 5 PM dose (hemodialysis patients) was checked between 6 PM and 7 PM, and 9 PM dose was checked from 10 PM to 11 PM. Prospective quality assurance monitoring was a laborious endeavor and likely introduced bias; however, it proved essential to our success. IRB approval was obtained in anticipation of publication.

## Results and Discussion

Overall, the development and implementation of the piperacillin-tazobactam extended infusion guideline was successful, as there were relatively minimal deviations from the guideline. There were a total of 1215 piperacillin-tazobactam doses prospectively monitored in 103 patients with a mean age of 57 years (range 21-93 years). The number of patients on piperacillin-tazobactam at one time ranged from 15 to 24 during the quality assurance monitoring timeframe. Of these doses, 98% were administered at the accurate rate and 94% were administered on time (Table 2). Overall, there were 20 missed doses and 53 delayed doses, representing 2% and 4%

| MRN # | ADMISSION DATE: | | | | |
|---|---|---|---|---|---|
| PT NAME: | | | | | |
| DATE | | | | | |
| TIME | | | | | |
| LOCATION | | | | | |
| Number of IV Lines | ☐ Peripheral:__<br>☐ PICC:___<br>☐ Upper Ext C-Line:___<br>☐ Femoral: ___ | ☐ Peripheral:__<br>☐ PICC:___<br>☐ Upper Ext C-Line:___<br>☐ Femoral: ___ | ☐ Peripheral:__<br>☐ PICC:___<br>☐ Upper Ext C-Line:___<br>☐ Femoral: ___ | ☐ Peripheral:__<br>☐ PICC:___<br>☐ Upper Ext C-Line:___<br>☐ Femoral: ___ | ☐ Peripheral:__<br>☐ PICC:___<br>☐ Upper Ext C-Line:___<br>☐ Femoral: ___ |
| P/T Rate 25 ml/h | Y N NA | Y N NA | Y N NA | Y N NA | Y N NA |
| P/T Dosing Regimen<br>$CL_{Cr}$ _____ | ☐ 3.375g q8h<br>☐ 3.375g q12h<br>☐ Other | ☐ 3.375g q8h<br>☐ 3.375g q12h<br>☐ Other | ☐ 3.375g q8h<br>☐ 3.375g q12h<br>☐ Other | ☐ 3.375g q8h<br>☐ 3.375g q12h<br>☐ Other | ☐ 3.375g q8h<br>☐ 3.375g q12h<br>☐ Other |
| Administered on schedule | Y N NA | Y N NA | Y N NA | Y N NA | Y N NA |
| If no, why | | | | | |
| Concomitant Y-Site Infusion | Y N NA | Y N NA | Y N NA | Y N NA | Y N NA |
| If yes, please provide name(s) | | | | | |
| Compatible | Y N NA | Y N NA | Y N NA | Y N NA | Y N NA |

**Figure 1.** Quality assurance monitoring sheet used for prospective assessment of piperacillin-tazobactam administration.
[a] P/T = piperacillin-tazobactam

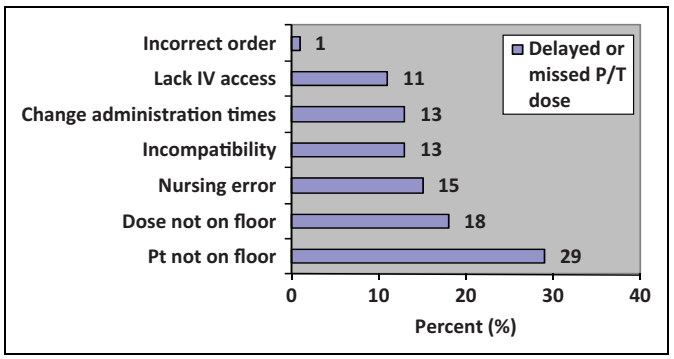


**Figure 2.** Reason for missed or delayed piperacillin-tazobactam dose[a]
[a] P/T = piperacillin-tazobactam

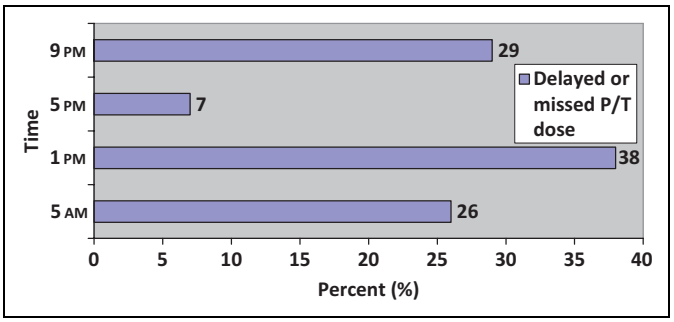


**Figure 3.** Time of missed or delayed dose[a]
[a] P/T = piperacillin-tazobactam

of the total administered doses, respectively. Delayed dose was defined as dose administration 1 hour past the scheduled time. Missed dose was defined as a scheduled dose never administered. This success is partially attributed to having 1 primary pharmacy contact person perform the quality assurance monitoring in order to quickly identify barriers to adherence and take corrective action if necessary. Additionally, the pharmacy resident became a recognizable contact for issues and concerns.

Anticipated barriers to guideline adherence included limited IV access and availability of IV pumps. Despite 52% of the patients having only a single lumen for drug and fluid administration, there were no patients switched to the recommended alternative regimen due to limited IV access or inability to perform a 4-hour infusion. The reported delayed or missed doses due to IV access were a result of loss of IV access, not a limited number of access sites or lumens. Furthermore, there were no additional IV pumps purchased for the extended infusion guideline, and lack of IV pumps was never an issue with delayed or missed piperacillin-tazobactam doses. The anticipated barriers to guideline implementation were surprisingly not significant issues.

Figure 2 illustrates a temporal pattern to protocol deviations in order to enhance identification and resolution of barriers to adherence. While a missed dose has greater clinical ramifications, both delayed and missed doses are included due to clinical significance. The primary barriers to guideline adherence included

either the patient being away from the nursing unit or the piperacillin-tazobactam dose not being available at the scheduled time of administration. The patient was typically not present in the unit due to a diagnostic procedure, medical intervention, or hemodialysis. The delayed or missed dose most frequently occurred at 1 PM, which is a common time for patients to undergo procedures and interventions (Figure 3). Per the guideline, the patient was to go to the procedure with the piperacillin-tazobactam infusion running, if possible. Otherwise, the dose was to be given as a 4-hour infusion upon return to the unit.

The issue of delayed or missed piperacillin-tazobactam doses due to lack of drug product on the nursing unit was recognized and addressed during the quality assurance monitoring. The patient-specific method of dose preparation and distribution was unable to keep up with the demand for piperacillin-tazobactam. As a result, central pharmacy converted to preparing premade batches of piperacillin-tazobactam doses, which were stored in the in refrigerators on the nursing units. There was minimal piperacillin-tazobactam waste with bulk distribution as the room temperature stability is 24 hours.

Other factors contributing to delayed or missed piperacillin-tazobactam doses included administration error and IV drug incompatibilities. Examples of administration error included a delayed or missed dose due to nursing workload, the dose present at patient's bedside but not infusing, or nurse misunderstanding. For example, there were a few instances where drug administration was unnecessarily delayed due to misconception on multiple lumen catheters. As a result, nursing inservices were performed to clarify that incompatible drugs can be given simultaneously if the patient has a multiple lumen catheter and each drug is administered through a separate lumen. The primary IV compatibility issue encountered causing delayed piperacillin-tazobactam drug administration was the unknown compatibility between piperacillin-tazobactam and vancomycin, given their concomitant empiric use in hospital-acquired infections. The protocol instructed administration of vancomycin prior to the piperacillin-tazobactam.

Additionally, we discovered it was taking longer than 4 hours to complete the piperacillin-tazobactam infusion due to a 20 mL overfill in the dosage unit, resulting in a total volume of 120 mL instead of the presumed 100 mL. Consequently, the infusion rate was increased from 25 mL/h to 30 mL/h to accommodate overfill. The education and precautions necessary to implement this guideline change were expedited with assistance from staff pharmacists, nurse coordinators, and information technology staff. This demonstrates the importance of developing working relationships and obtaining input from various perspectives during the guideline development process.

Piperacillin-tazobactam was most commonly discontinued due to narrowing the spectrum of antibiotic or switching to an oral alternative based on culture results. Other reasons for drug discontinuation included completion of a full antibiotic treatment course, infection ruled out, isolation of a resistant pathogen, and adverse effects. Although the total cumulative daily dose is reduced with the extended infusion regimen, there is greater antibiotic exposure. Consequently, we monitored for adverse events and noted 2 potential adverse effects reported over 5 weeks: thrombocytopenia and presumed drug fever. Piperacillin-tazobactam was never proven to be the culprit of these adverse effects; however in both instances, the agent was converted to alternative therapy as a precautionary measure. The inconvenience of or inability to complete a 4-hour infusion was never a reason for piperacillin-tazobactam discontinuation.

Furthermore, important outcomes of the extended infusion guideline included optimal pharmacodyamic attainment, which may lead to decreased mortality, reduced hospital length of stay, and cost minimization. Unfortunately, our data were insufficiently powered to meaningfully evaluate clinical outcomes; however, the cost reduction with the extended infusion was calculated. Most institutions are challenged by budget restrictions with pressure to decrease pharmacy costs. A cost savings of $9217 was observed over 5 weeks, with a projected annual savings of $108 529; however, this value is strictly limited to drug expenditure and does not reflect a complete cost analysis. This value may be conservative, as it is based on the utilization of piperacillin-tazobactam between December and January when the hospital census is generally decreased. The implementation of the protocol required a significant investment of time and labor; however, hiring additional employees was not required.

## Conclusion

Overall, the piperacillin-tazobactam extended infusion guideline implementation was successful, as there were relatively minimal deviations from the guideline. Key elements contributing to our success included: consistent pharmacy leadership, multidisciplinary involvement, thorough inservicing to all health care professionals, hospital-wide implementation, and extensive quality assurance monitoring. Challenges addressed during the implementation included pharmacy drug distribution, administration error, and patients being away from the unit. Surprisingly, IV access and pump availability were not barriers to protocol implementation. Our experience can serve as an example of a pharmacist-led extended infusion guideline development and implementation for other institutions.

### Declaration of Conflicting Interests

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