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Extended Infusion of Beta-Lactams Is Associated With Improved Outcomes in Pediatric Patients

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OBJECTIVE The pharmacokinetics of beta-lactam antibiotics favor administration via an extended infusion. Although literature supporting extended infusion beta-lactams exists in adults, few data are available to guide the practice in pediatrics. The purpose of this study was to compare clinical outcomes between extended and standard infusions in children.

METHODS This retrospective chart analysis included hospitalized patients 0 to 18 years old who received at least 72 hours of cefepime, piperacillin-tazobactam, or meropenem between October 1, 2017, and March 31, 2019. Clinical outcomes of care included hospital length of stay, readmission within 30 days, and all-cause mortality.

RESULTS A total of 551 patients (258 extended infusion, 293 standard infusion) met criteria for evaluation. Clinical outcomes among the entire population were similar. A subanalysis of select populations demonstrated decreased mortality in critical care patients (2.1% vs 19.6%, p = 0.006) and decreased 30-day readmission rates in bone marrow transplant patients (0% vs 50%, p = 0.012) who received the extended infusion compared with a standard infusion.

CONCLUSIONS Outcomes were similar between extended and standard infusions in children. Subgroup analyses suggest a possible mortality benefit in the critically ill and decreased readmission rate in bone marrow transplant patients.

ABBREVIATIONS BMT, bone marrow transplant; ECMO, extracorporeal membrane oxygenation; *f*T>MIC, free time above minimum inhibitory concentration; ICU, intensive care unit; IV, intravenous; MIC, minimum inhibitory concentration; PICU, pediatric intensive care unit; PRISM, pediatric risk of mortality

KEYWORDS beta-lactam; extended infusion; outcomes; pediatrics; pharmacokinetics

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Introduction

Beta-lactam antimicrobials have long been a cornerstone for treatment of pediatric infections. At clinically relevant concentrations, beta-lactam antimicrobials exhibit time-dependent microbiological effects.[1] Optimal efficacy for beta-lactams is achieved when free drug concentrations exceed the minimum inhibitory concentration (*f*T>MIC) for a specific portion of the dosing interval, which varies by disease and type of beta-lactam.[1] In general, penicillins require at least 50% *f*T>MIC, cephalosporins require at least 50% to 70% *f*T>MIC, and carbapenems require at least 30% to 40% *f*T>MIC for optimal bacterial killing.[1–3] In adults, extending the duration of infusion (i.e., over 3–4 hours) of beta-lactam antibiotics has been shown to increase the probability of attaining these *f*T>MIC targets.[4]

Outcome studies comparing standard and extended infusion beta-lactam antibiotics in adults are conflicting. Studies with positive benefits suggest increasing the infusion time to 3 to 4 hours improves clinical outcomes (e.g., lower mortality, decreased length of stay, decreased ventilator days, and/or decreased time to defervescence).[5–8] Others have reported no difference, though acknowledged differences in study design and/or patient population may have affected the ability to detect treatment effects.[9,10] Two meta-analyses of adult patients receiving extended infusions of beta-lactam antibiotics have also revealed a significant reduction in mortality compared with standard infusion times.[11,12]

Currently, few data are available to guide the practice of extending the infusion duration of beta-lactam antibiotics in the pediatric population. One pediatric institution has published on the feasibility of using extended infusion piperacillin-tazobactam and extended infusion cefepime in children with encouraging results.[13,14] This same institution then reported on a subset of the feasibility study population who had documented Gram-negative infection and were treated with extended infusion piperacillin-tazobactam.[15] The authors concluded that a majority of patients achieved a 21-day clinical cure. However, there was no comparator. A systematic review of the available literature on the

use of extended or continuous infusion of beta-lactam antibiotics by Walker et al[16] identified only 1 randomized controlled trial in children; the remainder were pharmacokinetic or pharmacodynamic studies, case series, or case reports.[16] The single randomized controlled trial studied continuous infusion ceftazidime and failed to demonstrate clinical benefit over traditional dosing. To date, no pediatric studies have been published comparing clinical outcomes of standard-length infusions to extended infusions of multiple beta-lactam antibiotics. The purpose of this study was to evaluate if extending the duration of the infusion leads to improved clinical outcomes in a pediatric population.

Methods

Beginning July 1, 2018, our hospital implemented a system-wide protocol extending the infusion duration for cefepime, meropenem, and piperacillin-tazobactam as the standard of care for hospitalized pediatric patients. Education was completed with pharmacy, nursing, and medical staff prior to the change in practice. Updates were made to the electronic health record to default the infusion time to the extended infusion upon order entry. Smart pumps (Alaris; Becton, Dickinson and Company; Franklin Lakes, NJ) were updated to include the new, longer infusion durations. Extended infusion piperacillin-tazobactam was given as 100 mg/kg (maximum 4000 mg piperacillin/dose) IV every 8 hours with each dose given over 4 hours. Extended infusion cefepime was given as 50 mg/kg (maximum 2000 mg/dose) IV every 8 hours with each dose given over 4 hours. Meropenem was administered as 20 to 40 mg/kg (maximum 2000 mg/dose) IV every 8 hours with each dose given over 3 hours. Doses for standard infusions were the same. Standard infusions for all 3 antibiotics were delivered over 15 to 30 minutes. Doses were adjusted for renal impairment. Per hospital protocol, patients requiring continuous renal replacement therapy and those weighing < 3.5 kg were excluded from receiving extended infusions. The weight cutoff served as a surrogate to exclude neonates, as exclusion based on age was not possible in our current electronic health record.

As part of a quality improvement project, we performed a retrospective chart analysis to compare clinical outcomes between patients who received extended vs standard infusion cefepime, meropenem, or piperacillin-tazobactam. Indication for antibiotic therapy and duration of therapy were not assessed. Patients < 18 years of age who received at least 72 hours of cefepime, meropenem, or piperacillin-tazobactam between October 1, 2017, and March 31, 2019, were included in the study. Outcome analyses were limited to the first course of antibiotics per patient. Patients who received both standard and extended infusions during a single course were excluded.

Demographic data including age, sex, weight at the time of initial antibiotic order, and select severity markers including the need for mechanical ventilation, epinephrine and/or norepinephrine (vasopressors), or extracorporeal membrane oxygenation were collected. Pediatric risk of mortality scores were recorded for patients in the PICU using the pediatric risk of mortality-3 scoring system.[17] Outcomes of care were recorded including hospital length of stay, time to blood culture clearance in patients with a Gram-negative bacteremia, hospital readmission within 30 days, and all-cause mortality within 30 days of antibiotic completion. Blood culture time to clearance was limited to Gram-negative organisms where the subject antibiotic was known to have activity. Readmission rates within 30 days were limited to patients discharged within 14 days of completing antibiotic therapy. A manual chart review of all deaths was performed to review documented cause of death. Adverse reactions were not measured.

Multiple subanalyses were performed to identify populations who may especially benefit from extended infusions. Subspecialties with high prescribing rates for cefepime, meropenem, or piperacillin-tazobactam were selected a priori for the subanalyses. Outcome data limited to oncology, bone marrow transplant (BMT), critical care, and general surgery patients receiving extended vs standard infusions were compared. Patients were included in these subanalyses based on assigned medical service on the last day of antibiotic therapy.

Proportions of patients with various demographic or medical characteristics who received extended vs standard infusion were compared using χ^2 tests or Fisher exact tests. Continuous/numeric variables (e.g., age and length of stay) were compared by type of infusion using Kruskal-Wallis or Mann-Whitney tests. Non-parametric tests were used due to the skewed distribution of many of the variables. Logistic regression was performed to evaluate the OR for mortality after adjusting for risk of mortality in critical care patients. P values were not adjusted for the fact that multiple tests were performed due to the exploratory nature of this study. Statistical analysis was performed using R version 3.3.1 (R Core Team, 2016) and IBM SPSS Statistics version 20.0.

Results

A total of 609 patients received cefepime, meropenem, or piperacillin-tazobactam for at least 72 hours between October 1, 2017, and March 31, 2019. Of those, 58 patients received both extended and standard infusion during their course of therapy and were excluded from the outcome's analysis. Of the remaining 551 patients, 258 received extended infusions and 293 received standard infusions. Following implementation of the extended infusion protocol, greater than 90% of all eligible patients completed therapy using the extended infusion method. Baseline demographics were similar between the 2 groups (Table 1). Markers of disease severity, including need for mechanical ventila-

Table 1. Comparison of Demographic and Clinical Characteristics of Hospitalized Patients Receiving Extended or Standard Infusion of Cefepime, Meropenem, or Piperacillin-Tazobactam

Characteristics	Extended Infusion (n = 258)	Standard Infusion (n = 293)	p value
Sex, n (%), male	147 (57)	180 (61.4)	0.288
Age, median (IQR), yr	7.2 (2.8–13.7)	8.3 (3.1–13.0)	0.597
Duration of antibiotics, median (IQR), days	5.9 (4.2–9.2)	5.9 (4–8.8)	0.91
Dosing weight, median (IQR), kg	23.6 (13–46.6)	27.4 (14.5–50.1)	0.105
Received mechanical ventilation, n (%)	52 (20.2)	46 (15.7)	0.172
Received vasopressors, n (%)	43 (16.7)	33 (11.3)	0.066
Received ECMO support, n (%)	12 (4.7)	13 (4.4)	0.904
PRISM-3 Probability of death,[19] median (IQR)*	1.6 (0.6–5.1)	1.3 (0.5–4.6)	0.374

ECMO, extracorporeal membrane oxygenation; PRISM-3, pediatric risk of mortality-3

* Limited to patients in the PICU, extended (n = 48) and standard (n = 51).

tion, vasopressor support, or need for extracorporeal membrane oxygenation were also similar (Table 1). Among critical care patients, probability of death was similar between patients receiving either extended or standard infusion.

Clinical outcomes comparing extended vs standard infusions among the entire study population are described in Table 2. The median length of stay was similar for patients who received extended vs standard infusion (median, 9.8 vs 9.7 days; p = 0.981). Likewise, all-cause mortality within 30 days of antibiotic completion was not statistically significant between the extended and standard infusion groups (1.2% vs 3.8%; p = 0.054). Additionally, there were no statistically significant differences in readmissions within 30 days. There were 11 and 10 patients in the extended and standard groups, respectively, with Gram-negative bacteremia in the evaluation period. There were no detectable differences in time to blood culture clearance between the extended and standard infusion groups (median, 3.9 vs 2.8 days; p = 1).

A subanalysis of outcomes in oncology, BMT, critical care, and general surgery patients was also performed (Table 3). No statistically significant differences were observed between the 2 infusion groups for oncology or general surgery patients. Among BMT patients, there were fewer readmissions in patients who received extended infusions vs standard infusions (0% vs 50%; p = 0.012). Of those patients who were readmitted, 1 was for new onset bacteremia (patient was not previously bacteremic), 2 were for a potential infectious etiology (but no positive cultures were identified), and the remainder were not infection related. Among critical care patients, all-cause mortality within 30 days of antibiotic completion was lower in patients who received extended compared with standard infusions (2.1% vs 19.6%; p = 0.006). The odds of mortality within 30 days remained significantly lower for the extended group after adjusting for the probability of death (OR, 0.074; 95% CI, 0.008–0.670). Of note, all deaths in the standard infusion group occurred before implementation of extended infusions as a standard practice.

Discussion

At our institution, cefepime, meropenem, and piperacillin-tazobactam are the most frequently used beta-lactams where literature supporting an extended infusion exists. In July 2018, we implemented a protocol for these 3 beta-lactam antibiotics to be administered via extended infusion as the standard of care, regardless of indication, based on many studies supporting this method in the adult population. Nichols et al[13,14] previously demonstrated the feasibility of implementing an extended infusion dosing strategy for piperacillin-tazobactam and cefepime as the standard of care in children. Like Nichols et al,[13,14] we achieved greater than 90% adherence to the new practice, even among critically ill patients requiring vasopressors and multiple other IV medications.

Many studies report on the benefits of extended infusions in adults. Dow et al[6] compared outcomes among 121 adult patients who received at least 72 hours of piperacillin-tazobactam or meropenem via extended or standard infusion in a medical and surgical ICU at an academic medical center. Patients receiving extended infusions demonstrated a decrease in ventilator days, ICU length of stay, and hospital length of stay compared with the standard infusion group. Additionally, risk of mortality was nearly 50% lower in the extended group. A meta-analysis including 1876 adult patients comparing extended vs standard infusions of antipseudomonal beta-lactams for the treatment of sepsis also demonstrated improved mortality rates among patients receiving extended compared with standard infusions.[5] Likewise, our study observed a decrease in all-cause mortality within 30 days of completing the antibiotic course among critically ill patients who received extended infusions. Critically ill patients have higher

Table 2. Comparison of Clinical Outcomes of All Hospitalized Patients Receiving Extended or Standard Infusion of Cefepime, Meropenem, or Piperacillin-Tazobactam

Clinical Outcomes	Extended Infusion (n = 258)	Standard Infusion (n = 293)	p value
Hospital length of stay, median (IQR), days	9.8 (5.7–21.3)	9.7 (5.7–24.2)	0.981
Readmission within 30 days, n (%)	57 (22.1)	81 (27.6)	0.133
All-cause mortality within 30 days, n (%)	3 (1.2)	11 (3.8)	0.054

volumes of distribution, altered renal clearance, and hypoalbuminemia that may alter the pharmacokinetics compared with other hospitalized patients.[6] Furthermore, patients in the ICU are more likely to be receiving several medications creating the increased potential for drug interactions altering pharmacokinetic parameters of an individual patient. These alterations might lead to the inability to achieve antibiotic concentrations above the minimum inhibitory concentration (MIC) of the organism for a sustained period of time.[18–20] As such, it is especially important to optimize delivery of antibiotics to critically ill patients, perhaps even irrespective of a susceptible drug MIC.

Additionally, adult studies have reported on decreased mortality with the use of extended infusions among patients with Gram-negative infections. Bauer et al[8] evaluated clinical outcomes associated with extended infusion cefepime for the treatment of *Pseudomonas aeruginosa* infections among 592 adult patients at a large tertiary care facility. Overall mortality was lower (3% vs 20%; p = 0.03) in the extended infusion group compared with standard infusion cefepime. Another study, an individual patient data meta-analysis, identified randomized controlled trials comparing continuous vs intermittent infusion of beta-lactam antibiotics in critically ill patients with Gram-negative sepsis.[21] The rate of hospital mortality (RR, 0.74; 95% CI, 0.56–1.0) was lower in the continuous infusion group and the rate of clinical cure (RR, 1.2; 95% CI, 1.03–1.4) was improved in the continuous infusion group. We evaluated a subset of patients with Gram-negative bacteremia. Unfortunately, there were not many positive cultures within our data set. Nevertheless, of the positive blood cultures with Gram-negative organisms against which the included beta-lactams would be expected to have activity, none of these organisms showed resistance to the antibiotic selected for treatment. Furthermore, our institutional antibiogram does not reflect a pattern of high-level resistance, with susceptibility rates from 90% to 100% for the majority of Gram-negative organisms to the included beta-lactams. Thus, clinical benefits observed in the extended infusion group would likely not be due to improved coverage of more resistant organisms, but rather improved pharmacokinetics and pharmacodynamics. Pharmacokinetics/pharmacodynamics factors have been shown to be particularly important in critically ill patients, which may be 1 reason we did not observe clinical differences in the other populations we studied.[19,20] Additionally, the non-critically ill patients in general have a very low mortality rate, shorter length of stay, and low readmission rate. Thus, alternative outcome measures or larger patient population might be required to observe a potential benefit.

Extended infusions have also been associated with a reduction in hospital readmissions. Winstead et al[22] evaluated 30-day all cause hospital readmissions among patients receiving extended vs standard infusion piperacillin-tazobactam for the treatment of Gram-negative infections. The authors report a significant decrease in readmissions in the extended infusion arm (1.2% vs 13.7%; p = 0.002). We also observed decreased readmission rates among BMT patients receiving extended compared with standard infusions. In fact, all readmissions among BMT patients occurred in the standard infusion group. However, because p values were not adjusted for the fact that multiple subgroups were examined, our finding regarding decreased readmissions in the BMT population should be treated with caution.

Extended infusions have been associated with improved time to defervescence. Przybylski and Reeves[7] evaluated 166 adult patients receiving cefepime via extended or standard infusion for febrile neutropenia at a community teaching hospital. Defervescence at 24 hours was achieved more frequently in the extended infusion group compared with the standard infusion group (82% vs 51%; p = 0.002) and median time to defervescence was decreased by 14 hours (10 vs 24 hours; p = 0.02). Unfortunately, due to the methods and retrospective nature of our study, we were unable to reliably demonstrate if there was a difference in time to defervescence in our population.

Although data exist in adults to guide the practice of administering extended infusion beta-lactams, there is only 1 pediatric study comparing outcomes and this was limited to meropenem only. Shabaan et al[23] evaluated 102 infants in Egypt with Gram-negative late-onset sepsis who received meropenem over 4 hours (extended infusion) or 30 minutes (standard infusion). Patients receiving extended infusions had a lower mortality rate (14% vs 31%; p = 0.03), improved microbiologic eradication at 7 days (82% vs 56.8%; p = 0.009), and higher rates of clinical improvement at the end of therapy (61% vs 33%; p = 0.009).[20] Our study showed improved clinical outcomes associated with 3 different beta-lactam antimicrobials administered as

Table 3. Comparison of Clinical Outcomes Among Subspecialty Patients Receiving Extended or Standard Infusion of Cefepime, Meropenem, or Piperacillin-Tazobactam

Clinical Outcomes	Extended	Standard	p value
Oncology*			
Number of patients	51	84	—
Length of stay, median (IQR), days	6.8 (5.2–12.8)	7.1 (5.2–13.4)	0.635
Readmission within 30 days, n (%)	20 (39.2)	33 (39.3)	0.994
All-cause mortality within 30 days, n (%)	2 (3.9)	1 (1.2)	0.297
Bone marrow transplant*			
Number of patients	9	24	—
Length of stay, median (IQR), days	35.2 (11–36.3)	28.7 (8.4–48.9)	0.968
Readmission within 30 days, n (%)	0	12 (50)	0.012
All-cause mortality within 30 days, n (%)	0	0	NA
Critical care*			
Number of patients	48	51	—
Length of stay, median (IQR), days	39.7 (17.5–67.4)	44.7 (22.8–122.9)	0.378
Readmission within 30 days, n (%)	16 (33.3)	13 (25.5)	0.391
All-cause mortality within 30 days, n (%)	1 (2.1)	10 (19.6)	0.006
General surgery*			
Number of patients	83	76	—
Length of stay, median (IQR), days	6.6 (4.6–9.9)	5.8 (4.1–9.3)	0.258
Readmission within 30 days, n (%)	13 (15.7)	13 (17.1)	0.806
All-cause mortality within 30 days, n (%)	0	0	NA

NA, not available

* No statistically significant differences in demographic characteristics (including pediatric risk of mortality-3 probability of death score for critical care patients).

extended infusions in children though, because of the limited number of positive blood cultures, we did not limit our study to bacteremic patients.

Although most of the published data showing benefits of extended infusion beta-lactams are in critically ill adults, our pediatric hospital continues to use extended infusion as the default infusion time for all patients where it is feasible. Reasons for this include the benefit of a standardized institutional approach that is consistent for all nurses and pharmacists (particularly for those that work on different units from day to day). Additionally, a more universal approach helps to ensure that most patients who may benefit from extended infusion receive this method. This would potentially include patients who may not be initially recognized as critically ill but then clinically decompensate.

Strengths of our study include a large sample size with a very high uptake of the new practice, which helped to limit selection bias. Additionally, we performed a manual review of the patients who died during the study period. All deaths that occurred in the standard infusion group happened before the extended infusion protocol went into effect. Therefore, we presume the reason these patients did not receive extended infusions was not due to concerns for vascular access or other limitation, but rather because the practice was not yet the standard.

There are limitations to our study. First, this was a retrospective cohort study at a single center, with transition to extended infusions during the study period. Indications for modifying antibiotic therapy among the 3 included antibiotics were not assessed. Likewise, we did not evaluate patient receipt of concomitant antibiotics. Additionally, we relied on the medication administration record in the electronic medical record to categorize patients as receiving extended or standard beta-lactam infusions. Furthermore, we were unable to evaluate infection-related mortality, and instead evaluated only all-cause mortality. Generalizability to other institutions may not be applicable. Additional markers of clinical improvement such as time to defervescence and time to normalization of inflammatory markers (i.e., white blood cell count, procalcitonin, and C-reactive protein), which may have helped to corroborate our findings, were unable to be accurately assessed due to limitations with the data set. Multiple subgroup

analyses were performed, which increase the risk for type 1 errors. Caution should be exercised with the subgroup results. Future prospective studies may be able to overcome these limitations.

Conclusion

Outcomes were similar between extended and standard infusions in children. Subgroup analyses suggest a possible mortality benefit in the critically ill and decreased readmission rate in BMT patients. These findings should be further explored in future studies.

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