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RESEARCH ARTICLE

Time to defervescence evaluation for extended- vs. standard-infusion cefepime in patients with acute leukemia and febrile neutropenia

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Abstract

Background/Objectives: Febrile neutropenia (FN) occurs in up to 80% of patients with hematologic malignancies. Evidence suggests using extended infusions (EI) of beta-lactams can improve outcomes in some populations, but there is limited clinical literature comparing cefepime standard infusion (SI) versus EI for FN. The FDA-approved regimen for FN was used at a large community teaching hospital for patients with FN until a hospital-wide EI beta-lactam protocol was introduced that allowed for EI cefepime in FN at the physicians' discretion. We sought to compare outcomes between patients with FN who received SI and EI cefepime.

Methods: Patients with acute myeloid or lymphocytic leukemia who developed FN between April 2014 and January 2021 were included in this single-center, retrospective study. The primary outcome was to compare mean time to defervescence after the initiation of cefepime SI or EI regimens. SI regimens consisted of IV cefepime 2G q8h/0.5 h, and EI regimens as IV cefepime 1G q8h/4 h. Secondary outcomes included 30-day all-cause mortality, hospital length of stay (LOS), duration of cefepime, and need to escalate therapy.

Results: Overall, 193 patients were included. Baseline characteristics were similar between groups. Time to defervescence was significantly shorter with EI compared with the SI group (median 48 h [48–100.5] vs. 70 h [48–113], $p = 0.005$). Cefepime duration of therapy was significantly shorter in the EI compared with the SI group (median 6.0 days vs. 8.0 days, $p = 0.002$). There was no difference between other secondary outcomes including LOS, mortality, and antibiotic escalation.

Conclusion: Despite reduced total daily dose of cefepime, EI cefepime administered as a 1G/0.5 h LD followed 2 h later by 1G q8h/4 h for FN acutely achieves more rapid defervescence than the FDA-approved SI regimen and ultimately attains comparable patient outcomes.

KEYWORDS
acute lymphocytic leukemia, acute myeloid leukemia, cefepime extended infusion, febrile neutropenia, time to defervescence

1 | INTRODUCTION

Febrile neutropenia (FN) is defined as an absolute neutrophil count (ANC) of <500 cells/mm^3 or an expected ANC decrease to <500 cells/mm^3 during the next 48 h, plus a temperature ≥ 38.3°C (101 °F) once or ≥ 38.0°C (100.4 °F) sustained over an hour, per Infectious Diseases Society of America (IDSA) guidelines.[1] Patients who develop profound neutropenia as defined by an ANC <100 cells/mm^3 or neutropenia lasting >7 days have a higher risk of developing fever. Up to 80% of patients with hematologic malignancies develop FN, yet pathogens are only isolated in 20–30% of patients.[1,2]

Cefepime is the only FDA-approved anti-pseudomonal beta-lactam for FN. The National Comprehensive Cancer Network (NCCN) and IDSA guidelines recommend empiric regimens consisting of an anti-pseudomonal beta-lactam such as cefepime, piperacillin-tazobactam, or a carbapenem.[1-3] Extended infusion (EI) regimens optimize the pharmacodynamics (PD) of beta-lactam antibiotics by capitalizing on their time-dependent activity. The PD target for cephalosporins is achieved when the free-drug concentration is greater than the minimum inhibitory concentration (fT > MIC) of the organism for at least 60–70% of the dosing interval.[4-6] EI cefepime improves achievability of PD targets in a variety of patient populations, but cefepime was optimized in pharmacokinetic (PK) models of critically ill patients with a diagnosis of ventilator-associated pneumonia.[7]

In April 2016, the Antimicrobial Stewardship Program (ASP) evaluated literature and implemented a facility-wide EI beta-lactam protocol utilizing a dosing strategy of cefepime 1G/0.5 h loading dose (LD) to rapidly achieve therapeutic plasma concentrations followed 2 h later by 1G q8h/4 h to target organisms with an MIC up to 8 mg/L.[8] During the first 24 h of therapy, patients in the EI group received a total of 4G of cefepime and the SI group received 6G of cefepime. Following the first 24 h of therapy, there was a 50% reduction in doses between the EI and SI group, 3G and 6G respectively. The ASP aimed to implement a standardized dosing regimen throughout the entire hospital, and 1G q8h/4 h was chosen for several reasons. Standardizing all cefepime regimens to 2G q8h/4 h would be largely unnecessary in most patients from a PK/PD perspective as it achieves concentrations to target a PK/PD breakpoint of 16 mg/L, which would treat *Pseudomonas aeruginosa* with an intermediate susceptibility.[9] Furthermore, there were safety concerns regarding drug-induced encephalopathy if this dosing strategy was utilized for all patients. Finally, though cefepime was not overly expensive when this was implemented, it was one of the primary agents used empirically for hospital-associated infections. The authors estimated that utilizing a standardized dosing regimen of 2G q8h/4 h compared with 1G Q8h/4 h would cost the institution an additional $50,000.00 annually based on cefepime cost and utilization patterns at the time.

Published literature evaluating cefepime EI dosing for FN is limited to one study that showed no difference in clinical outcomes between two groups when comparing cefepime 2G q8h/0.5 h versus 2G q8h/3 h, thus it was left to provider discretion at our institution to utilize the EI 1G q8h/4 h or SI 2G q8h/0.5 h regimen for FN.[4] Though the ASP did not have clinical literature to support standardizing cefepime EI 1G q8h/4 h for all FN patients at the time, there were concerns for SI regimens inconsistently achieving MICs to the CLSI susceptibility breakpoint of 8 mg/L for *Pseudomonas aeruginosa*; literature reports a PK/PD breakpoint range between 4 and 8 mg/L for SI 2G q8h/0.5 h regimens.[6,10] Alternatively, the EI regimen of 1G q8h/4 h consistently achieves PK/PD breakpoints of 8 mg/L in hospitalized patients.[8,11] Based on these differences in achievable PK/PD breakpoints and limited literature, this study aimed to compare the clinical outcomes for those with FN who received cefepime 2G q8h/0.5 h and cefepime 1G/0.5 h LD followed by 1G q8h/4 h.

2 | MATERIALS AND METHODS

2.1 | Study design

This single-center, retrospective, non-inferiority study was conducted at a 706-bed quaternary care community teaching hospital in Memphis, Tennessee. Patients were identified by specific FN ICD-9-CM and ICD-10-CM diagnosis codes. A review of the medical record and laboratory markers was conducted to confirm the FN diagnosis for study enrollment consideration. Patients were included if they were ≥ 18 years, had a diagnosis of acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL), had admission FN diagnosis or diagnosis during admission, and received intravenous cefepime with one of the following regimens: cefepime 2G q8h/0.5 h or cefepime 1G Q8h/4 h. Patients were excluded if they had a documented cephalosporin allergy or if they received another anti-pseudomonal beta-lactam for >24 h prior to receiving cefepime. Receipt of other antibiotic agents (e.g., vancomycin) did not disqualify the patient from inclusion. During this time, vancomycin was the standard of care agent of choice for anti-MRSA therapy initiated in FN patients admitted to this community teaching hospital. Patients were enrolled in reverse chronological order for a study period of April 2014 to January 2021. The study was approved by the local IRB, which waived the requirement for informed consent due to the retrospective nature of the study.

2.2 | Outcomes/Definitions

The primary outcome was median time to defervescence after the initiation of cefepime EI or SI regimens. Defervescence was defined as an oral temperature ≤ 100.4 °F for at least 48 h.[12] Time to defervescence was collected as time from last known febrile timepoint, which included the 48-h window. Secondary outcomes included 30-day all-cause mortality, hospital length of stay (days), duration of cefepime (days), and incidence of therapy escalation (e.g., changing to a different anti-pseudomonal agent such as piperacillin-tazobactam). Infection-related mortality was not collected due to the retrospective nature of this project design. All patients in the EI group received

a LD based on the facility's dosing protocol, but not all patients in the SI group received a LD. Patients who received a second dose within a timeframe prior to the scheduled frequency were considered to have received a LD. AKI on admission was defined as an increase in serum creatinine (SCr) 0.3 mg/dl or 1.5 times baseline SCr.[13] All patients in the EI group were candidates to receive EI cefepime based on the facility's renal dosing recommendations for cefepime in FN. Infection source was confirmed with positive cultures and documentation of the site of infection, whereas a suspected infection site was deemed such through documentation in the medical record (e.g., CT indicating pneumonia without positive cultures). The facility's microbiology laboratory utilized Vitek®2 from April 2014 to April 2016 and MALDI-TOF plus BD Phoenix™ from May 2016 through the end of the study period for culture identification and susceptibility reporting. Though there were not enough isolates to evaluate microbiology and resistance trends specifically in this patient population, these did not change at the institution-level during the study time frame. Of note, none of the hospital-specific treatment protocols for acute leukemia changed during this time including chemotherapy agents, supportive care management, antimicrobial prophylaxis, and treatment protocols for FN.

2.3 | Statistical analysis

Previously published data suggested a 22 h difference in time to defervescence when evaluating cefepime 2G q8h/0.5 h vs. 2G q8h/3 h.[4] The software R(™⟩ version 4.1.1 was used to assist in calculations and modeling. Variables were screened to evaluate assumptions of normality, homogeneity of variance, linearity, multicollinearity, and homogeneity of regression. All continuous variables violated the Shapiro–Wilk test ($p < 0.05$) indicating a deviation from normality. Mann–Whitney U tests were computed to evaluate group differences. Medians and interquartile ranges were recorded as measures of central tendency. Results did not differ after trimming outliers ±3 standard deviations from the mean; therefore, all data points were analyzed. Categorical data were analyzed using a Pearson χ^2 or Fisher's exact test. Linear regression was used to compute the relationship between the primary outcome. An a priori α value of 0.05 was identified for statistical significance.

3 | RESULTS

A total of 993 patients were reviewed and overall, 800 patients were excluded; the most common reasons for exclusion were no diagnosis of AML or ALL and alternative cefepime dosage regimen (Figure 1). The remaining 193 patients received cefepime and were separated into the SI group ($n = 95$) or EI group ($n = 98$).

Cefepime treatment group inclusion was independent of all baseline characteristics and demographics (Table 1) excluding: a greater number of patients in the EI group exhibited baseline procalcitonin abnormalities [$\chi^2(1) = 4.5$, $p < 0.05$], potassium (K) abnormalities [$\chi^2(1) = 6.8$, $p < 0.01$], and granulocyte colony-stimulating factor (GCS-F) administration [$\chi^2(1) = 8.5$, $p < 0.01$]; whereas, more patients in the SI group had reported lactate dehydrogenase (LDH) abnormalities [$\chi^2(1) = 11.5$, $p < 0.001$] and met SIRS criteria [$\chi^2(1) = 13.3$, $p < 0.001$]. Most individuals receiving the SI ($n = 81$, 77.1%) were derived from the first time period of data collection (range: 2014-April 2016), and majority of individuals receiving the EI ($n = 74$, 84.1%) were derived from the second period (range: April 2016–2021), $\chi^2(1) = 69.4$, $p < 0.001$. No statistical difference was found when analyzing patients with AKI on presentation in the SI or EI group (Table 1). There was no difference in the median baseline APACHE II scores at time of admission between the SI and EI groups (16.0 [IQR 14–18] vs. 16.0 [IQR 13–18.8], $p = 0.78$). Additionally, there was no difference in GCS-F duration, days since receipt of chemotherapy, documented administration of antibiotic prophylaxis

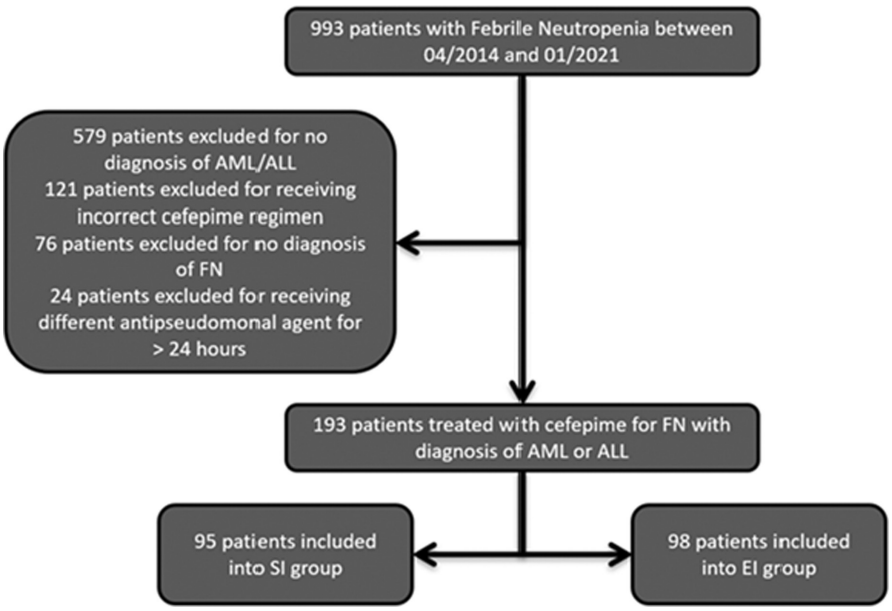

FIGURE 1 Flow diagram of study design

TABLE 1 Baseline demographics

	Standard infusion ($n = 95$)	Extended infusion ($n = 98$)	p-value
Median age, years	61.0	64.0	0.35
Male, *n* (%)	60 (63.2)	50 (51.0)	0.09
AML, *n* (%)	73 (76.8)	79 (80.6)	0.52
ALL, *n* (%)	22 (23.2)	19 (19.4)	0.52
Median weight, kg (IQR)	77.1 (65.7–91.9)	77.5 66.7–91.2)	0.81
Median baseline eGFR, ml/min (IQR)	77.6 (64.6–104.9)	83.9 (60.0–112.0)	0.98
Total patients with AKI, *n* (%)	10 (10.5)	14 (14.3)	0.43
Presented with AKI, *n* (%)	6 (6.3)	11 (11.2)	0.32
Developed AKI, *n* (%)	4 (4.2)	3 (3.1)	0.67
Mean LOS when AKI developed, days (±SD)	4.0 ± 2.2	3.7 ± 1.5	0.83
Median duration of AKI, days	7.0	3.0	0.23
Abnormal LDH at baseline, *n* (%)	53 (55.8)	31 (31.6)	<0.001
Abnormal LA at baseline, *n* (%)	30 (31.6)	24 (24.5)	0.27
Abnormal PCT at baseline, *n* (%)	12 (12.6)	24 (24.5)	0.03
Abnormal K at baseline, *n* (%)	18 (18.9)	35 (35.7)	0.009
SIRS criteria met at baseline, *n* (%)	87 (91.6)	71 (72.4)	<0.001
Median APACHE II (IQR)	16.0 (14.0–18.0)	16.0 (13.0–18.8)	0.78
Median duration of neutropenia, days (IQR)	10.0(5.0–22.0)	13.5 (6.3 to 23.8)	0.15
History of HSCT, *n* (%)	25 (26.3)	27 (27.6)	0.85
Documented prophylaxis prior to treatment, *n* (%)	54 (65.9)	52 (55.9)	0.65
Receipt of Vancomycin, *n* (%)	70 (70.7)	69 (72.6)	0.85
GCS-F			
Administration, *n* (%)	21 (23.2)	42 (42.9)	0.004
Median duration, days (IQR)	3.0(2.3–8.0)	5.0 (3.0–9.0)	0.29
Median time since most recent GCS-F administration, days (IQR)	11.5 (5.0–14.3)	7.0 (2.0–14.3)	0.30

Note: Continuous variables were analyzed using Mann–Whitney *U* tests, and categorical variables were analyzed using Pearson χ^2 or Fisher's exact test.

Abbreviations: AKI, (acute kidney injury) was defined by increase in serum creatinine (SCr) 0.3 from baseline or 1.5 times baseline SCr; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; APAHCE II, Acute Physiology and Chronic Health Evaluation scoring tool; GCS-F, granulocyte colony-stimulating factor; HSCT, hematopoietic stem cell transplant; K, baseline potassium; LA, baseline lactic acid; LDH, baseline lactate dehydrogenase; LOS, length of stay; PCT, baseline procalcitonin.

prior to starting treatment for FN, or receipt of vancomycin between the SI and EI groups.

Most patients in the SI group received cefepime 2G Q8h/0.5 h ($n = 78$, 82.1%) while a minority ($n = 17$, 17.9%) had an adjustment to 2G q12h/0.5 h or 2G q24h/0.5 h due to reduced estimated creatinine clearance (eCrCl). Similarly, the majority ($n = 93$, 94.9%) of patients in the EI group received 1G Q8h/4 h, while a small minority ($n = 6$, 5.1%) received 1G q12h/4 h for reduced eCrCl based on approved pharmacy and therapeutics committee dosing protocols.

Mann–Whitney U tests were used to examine the difference in the primary outcome after initiation of cefepime (Table 2). Median time to defervescence in the EI group (48 h, IQR = 48–100.5) was significantly more rapid than in the SI group (70 h, IQR = 48–113, $p = 0.005$).

All patients, whether they received the SI or EI treatment, defervesced within 168 h, and most patients broke fever within 144 h ($n = 80$, 84.2% in SI and $n = 86$, 87.8% in EI; Figure 2). However, at 24 h, 48 h, and 72 h a greater proportion of the patients in the EI group defervesced (Figure 2).

Kaplan–Meier analyses were performed to determine the SI and EI treatment groups' cumulative rates of defervescence. Log-rank tests showed SI and EI group rates did not differ over the full 168 h time window, $\chi^2(1) = 3.4$, $p = 0.07$ (Figure 2A). The Peto and Peto modification of the Gehan-Wilcoxon test was conducted to focus assessment to the left-side of the plot, and Kaplan–Meier curves showed significant differences between the rates of defervescence at earlier time periods, $\chi^2(1) = 8.1$, $p = 0.004$. When restricted to a 72-h time window, log-rank tests showed the rate of defervescence was greater in the EI group compared with the SI group, $\chi^2(1) = 8.6$, $p = 0.003$ (Figure 2D).

Linear regression analyses determined cefepime treatment groups ($\beta = -13.53$, $p = 0.04$) significantly predicted time to

TABLE 2 Time to defervescence and secondary outcomes

	Standard infusion ($n = 95$)	Extended infusion ($n = 98$)	p-value
Median time to defervescence, h (IQR)	70.0 (48–113.0)	48.0 (48–100.5)	0.04
Defervescence by 168 h, *n* (%)	95 (1)	98 (1)	–
Defervescence by 144 h, *n* (%)	80 (84.2)	86 (87.8)	0.62
Defervescence by 120 h, *n* (%)	74 (77.9)	78 (79.6)	0.91
Defervescence by 96 h, *n* (%)	65 (68.4)	73 (74.5)	0.44
Defervescence by 72 h, *n* (%)	49 (51.6)	67 (68.4)	0.03
Defervescence by 48 h, *n* (%)	32 (33.7)	50 (51.0)	0.02
Defervescence by 24 h, *n* (%)	1 (1.10)	21 (21.4)	<0.001
30-day all-cause mortality, *n* (%)	12 (12.6)	10 (10.2)	0.60
Median hospital length of stay, days (IQR)	19.0 (8.0–29.0)	18.0 (8.0–30.0)	0.95
Median cefepime duration, days (IQR)	8.0 (5.0–12.0)	6.0 (3.3–8.0)	0.002
Antimicrobial escalation, *n* (%)	21 (22.1)	23 (23.5)	0.82

Note: Continuous variables were analyzed using Mann–Whitney U tests, and categorical variables were analyzed using Pearson's χ^2 or Fisher's exact test.

defervescence ($R^2 = 0.02$, $F_{1,191} = 4.29$, $p = 0.04$). Using a Bonferroni-suggested p-value <0.2, other clinical variables (LDH, procalcitonin, GCS-F, SIRS, and cefepime LD) were considered for inclusion in the model. However, due to a lack of clinical relevance, only SIRS criteria were included as a control.

When controlling for SIRS criteria in the overall analysis, the model no longer predicted time to defervescence ($R^2 = 0.02$, $F_{2,189} = 2.34$, $p = 0.10$), even though cefepime treatment group was contributing to the variance explained in the model ($\beta = -14.52$, $p = 0.03$). When restricting the sample to only SIRS criteria, time to defervescence was significantly shorter with EI cefepime (M = 68.11) compared to SI (M = 86.94), $t(157) = 2.64$, $p < 0.01$. Because our Kaplan–Meier curves suggested the 24–72 h time window was relevant (Figure 2A–D), we investigated each time point while controlling for SIRS criteria. When controlling for SIRS criteria, EI vs. SI treatment groups significantly predicted time to defervescence at 24 h ($\beta = 0.21$, $p < 0.001$; $R^2 = 0.10$, $F_{2,190} = 11.05$, $p < 0.001$), 48 h ($\beta = 0.26$, $p = 0.01$; $R^2 = 0.04$, $F_{2,190} = 3.39$, $p = 0.04$), and 72 h ($\beta = 0.41$, $p = 0.01$; $R^2 = 0.04$, $F_{2,190} = 3.67$, $p = 0.03$).

Cefepime duration of therapy as a secondary outcome was significantly shorter in the EI group compared with SI [median 6.0d vs. 8.0d, $p = 0.002$]. 30-day all-cause mortality (10.2% vs 12.6%, $p = 0.60$), hospital LOS (18d vs. 19d, $p = 0.95$) and incidence of therapy escalation (23% vs. 23.5% $p = 0.82$) was not statistically different between the EI and SI regimens (Table 2).

Microbiology data were also evaluated (Tables 3, S1, and S2). More patients in the EI group ($n = 39$, 39.8%) had a confirmed or suspected site of infection compared to the SI group ($n = 22$, 23.2%), $\chi^2(1) = 6.2$, $p < 0.05$. Collection of any culture did not differ ($p = 0.62$) between EI ($n = 90$, 91.8%) and SI ($n = 89$, 93.7%) groups. Additionally, there was no difference ($p = 0.18$) in prevalence of positive cultures between EI ($n = 38$, 38.8%) and SI ($n = 46$, 48.4%) groups (Table 3).

4 | DISCUSSION

The goal of this study was to assess whether exploiting the time-dependent PK property of cefepime using an EI regimen would perform as well as the FDA-approved SI regimen in patients with FN despite the 50% dose reduction.

Of note, 10 SI patients and 10 EI patients had definitive culture growth with susceptibilities (Tables S1 and S2). Despite the small number of *Pseudomonas* isolates reported as susceptible when the PD target did not support achievement of the CLSI breakpoint MIC, we still found patients with FN who received the EI cefepime regimen defervesced more quickly. This finding provides clinical support in optimizing the beta-lactam dosing strategy to account for PK changes in patients with FN. Any patient with an infection can potentiate SIRS that can lead to sepsis. This septic picture can contribute to augmented renal clearance (ARC) that can lead to lowered $fT > MIC$ and increased risk of therapeutic failure when PD of agents, such as beta-lactams, are not optimized.[13] While literature is limited specifically in the FN population, ARC in the FN population has been associated with subtherapeutic concentrations of vancomycin and piperacillin.[15,16]

The effect of using EI cefepime dosing regimens has been evaluated in other disease states. Bauer and colleagues conducted a retrospective experimental study at a tertiary medical center that compared EI cefepime 2G q8h/4 h vs. SI cefepime 2G q8h/0.5 h in 87 patients with *Pseudomonas aeruginosa* bacteremia or pneumonia. They found a significant reduction in mortality (1 vs. 11; $p = 0.03$) and ICU length of stay (8d vs. 18.5d; $p = 0.04$) when utilizing the EI regimen.[5]

Literature evaluating EI cefepime for FN is limited to one, single-center, prospective, randomized, comparative, pilot study. Patients were randomized to receive cefepime 2G q8h/0.5 h or cefepime 2G q8h/3 h. Time to defervescence was 22 h shorter in the 3-h EI group; however, this finding did not reach statistical significance. Though no

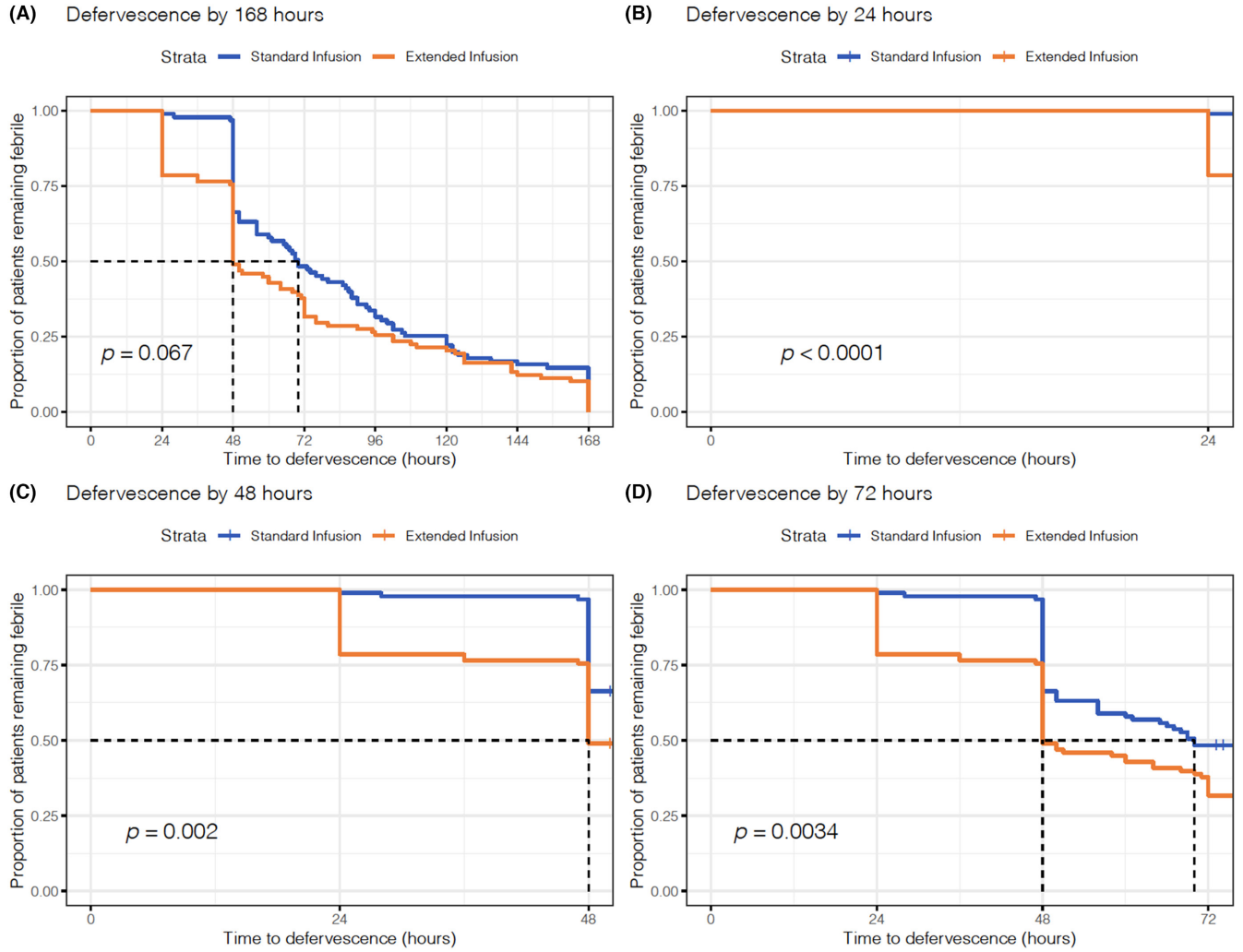

FIGURE 2 Kaplan–Meier curves and log-rank tests evaluating group differences in time to defervescence

TABLE 3 Microbiology data

	Standard infusion ($n = 95$)	Extended infusion ($n = 98$)	p-value
Any culture collected, *n* (%)	89 (93.7)	90 (91.8)	0.62
Confirmed or suspected site of infection, *n* (%)	22 (23.2)	39 (39.8)	0.01
Positive culture, *n* (%)	46 (48.4)	38 (38.8)	0.18
Growth from culture			
Blood, *n* (%)	24 (25.5)	16 (16.3)	0.12
Urine, *n* (%)	17 (17.9)	18 (18.4)	0.93
Sputum, *n* (%)	13 (13.8)	9 (9.2)	0.31
Miscellaneous, *n* (%)[a]	2 (2.1)	2 (2.0)	1.00

Note: Categorical variables were analyzed using Pearson χ^2 or Fisher's exact test.
[a]Wound, stool.

statistically significant difference in time to defervescence was observed, this could represent a clinically significant outcome in critically ill patients with FN. There was no difference between groups for 30-day mortality, hospital LOS, or incidence of antimicrobial escalation.[4]

A separate study evaluated piperacillin-tazobactam and ceftazidime EI (4 h, $n = 47$) vs. SI (0.5 h, $n = 58$) regimens in patients with FN. Significantly more patients in the EI vs SI group achieved the primary endpoint of overall clinical response (74.4% vs. 55.1%, $p = 0.044$). Significance persisted for those with a documented infection for EI and SI groups (68.4% vs. 35.7%, $p = 0.039$) and patients with a diagnosis of pneumonia for EI and SI groups ($n = 4/5$, 80% vs. $n = 0/8$, 0%, $p = 0.007$), respectively.[17] Fehér and colleagues

conducted a retrospective observational study reviewing neutropenic patients who presented with fever after having received hematopoietic stem-cell transplantation or induction chemotherapy for AML. Eighty-eight patients received meropenem 1G q8h as either an EI or SI. Treatment success was superior in the EI vs. SI group (68.4% vs. 40.9%, $p < 0.001$).[18] Finally, a randomized, multicenter, open-label, superiority clinical trial is currently enrolling hospitalized patients with hematologic malignancy meeting criteria for FN and treated with cefepime, piperacillin-tazobactam, or meropenem. Patients will be randomized 1:1 to EI and SI for each antibiotic. The primary endpoint will be clinical efficacy, defined as defervescence without modifying the antibiotic treatment within the first 5 days of therapy.[19]

From an antimicrobial stewardship perspective, these findings are significant in showing that utilizing a 50% reduced dose EI regimen provided a significantly faster time to defervescence compared with the FDA-approved SI regimen. Between the EI and the SI groups, there was a statistical difference in treatment duration (median 6.0 days vs. 8.0 days respectively, $p = 0.002$); however, these align with recommendations for duration of treatment of FN based on NCCN and IDSA guidelines which reflect a duration of treatment targeting a suspected source or empiric duration of 3–5 days if patient is afebrile with no infection identified or at least 7 days depending on ANC count recovery.[1-3]

This strategy can capitalize on the PD of cefepime and improve the likelihood of achieving the PD breakpoint while also representing a potential significant cost savings to hospitals that can reduce their cefepime spending by 50%. This dosing stratagem is not FDA-approved, so local epidemiology and patient populations should be evaluated prior to implementing a lower EI dose of cefepime for FN. Studies evaluating patients with FN have demonstrated altered PK including volume of distribution and clearance, which can lead to subtherapeutic concentrations of antimicrobials.[16,20,21] Alternative cefepime dosing regimens should be considered when patients are admitted with FN and especially when they have additional risk factors for ARC (e.g., admit directly to ICU).[14]

Dose optimizing cefepime in FN by utilizing this strategy may reduce incidence of adverse drug events as well as the development of drug resistance. Cefepime-induced neurotoxicity is thought to be associated with multiple factors including hospital LOS, prolonged antibiotic exposure, and renal insufficiency.[22] Likewise, a study reviewing exposure to cefepime, piperacillin-tazobactam, and meropenem for severe sepsis or septic shock revealed each additional day of exposure beyond the guideline-recommended duration of treatment was associated with a 4% increased risk of new resistance within 60 days of initiation.[23] In our study, we found in the EI dosing strategy a shortened time to defervescence, which resulted in overall shorter durations of treatment that might lead to fewer adverse events due to over exposure of cefepime.

In addition to evaluation of dosing strategies optimized to achieve appropriate cefepime exposure, a strength of this study is the restriction of the patient population to those with ALL and AML. By only including patients with these hematologic malignancies, confounders based on other oncology disease-specific characteristics are limited. Similar median APACHE II scores between the SI and the EI groups (16.0 [14.0–18.0] vs. 16.0 [13.0–18.8], $p = 0.78$) demonstrate another strength of this study in that clinical disease severity was similar between groups. Furthermore, exclusion of patients who received a different anti-pseudomonal beta-lactam for >24 h before starting cefepime ensures that the difference observed in the primary outcome was not due to an initial exposure of an alternative anti-pseudomonal agent.

This study is not without limitations; this is a single-center, retrospective study meaning data collection relied on accurate documentation in patients' charts. Moreover, collection of fever prior to admission involved subjective reporting of fever from outside hospitals or by patients at home. Not having access to this information could potentially influence either group if patients were afebrile on admission and remained afebrile while receiving treatment. However, the percentage of patients who had a one-time fever occurrence prior to admission did not differ between the EI and SI groups (15 vs. 15, $p = 0.93$).

The authors could not account for why more patients in the EI group received GCS-F (42.9% vs. 23.2%, $p = 0.004$); none of the hospital-specific treatment protocols for acute leukemia changed during the study timeframe. However, we do not expect this finding to impact our primary outcome as evidenced by no difference between duration of neutropenia (10.0d vs. 13.5d, $p = 0.15$). The low yield of organisms and organisms with elevated MIC data found in this study is reflective of real-world data. It does limit the ability to extrapolate these results to a patient population with frequent infections due to pathogens with high cefepime MICs.[1,2] Similarly, a continuous urine collection to accurately calculate eCrCl was not standard of care during this timeframe; thus, investigators were not able to determine how many patients may have had ARC. Though data are not currently available to estimate the PK/PD breakpoint for cefepime 1G Q8h/4 h in patients with ARC, external application of these study results should be used with caution in a patient population known to have ARC.[11]

Finally, receipt of antipyretic agents (e.g., acetaminophen) or steroids was not recorded. These agents were available to all patients through admission protocol orders and provider discretion. Though a limitation of the study, the admission protocol orders for AML, ALL, and FN did not change during the study timeframe, and receipt of these agents represents a real-world scenario in which these agents were available to all patients as needed.

5 | CONCLUSION

In conclusion, EI cefepime administered as a 1G/0.5 h LD followed 2 h later by 1G q8h/4 h for FN resulted in shorter time to defervescence compared with the FDA-approved SI dosing regimen. Using EI dosing and exploiting the time-dependent property of cefepime appears to overcome the dose reduction from 2G Q8h/0.5 h and could be considered as an empiric regimen for patients with acute leukemia with an admission or in-hospital diagnosis of FN. Future prospective studies are needed to explore whether employing this EI dosing strategy of

cefepime for FN and shortening time to defervescence reduces incidence of adverse effects associated with cefepime as well as hospital length of stay or delay in chemotherapy administration.

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CONFLICT OF INTEREST

The authors do not have any conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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