

# A Randomized Clinical Trial of Bayesian-Guided Beta-Lactam Infusion Strategy and Associated Bacterial Resistance and Clinical Outcomes in Patients With Severe Pneumonia

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**Background:** Antimicrobial resistance is a growing health concern worldwide. The objective of this study was to evaluate the effect of

beta-lactam infusion on the emergence of bacterial resistance in patients with severe pneumonia in the intensive care unit.

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N. Maranchick was the study coordinator, who performed data analysis and collection and wrote the manuscript. C. Trillo-Alvarez reviewed the trial candidates daily and facilitated the clinical aspects of the trial. V. Kariyawasam reviewed the candidates for study outcomes and facilitated data collection for study outcomes. V. Venugopalan reviewed the potential candidates daily, helped facilitate the clinical aspects of the trial, and assisted with data collection. A. Kwara secured the study funding and contributed to the study design. Kenneth Rand was involved in the study design. C.A. Peloquin was involved in securing the study funding, study design, and overseeing therapeutic drug monitoring of beta-lactams. M.H. Alshaer was involved in all aspects of the study, including securing funding, study design, data collection and analysis, and assistance with manuscript writing. All the authors reviewed the manuscript.

The Institutional Review Board at the University of Florida (Ref # IRB202101979) reviewed and approved the study. Participants or their families/designated healthcare surrogates provided written informed consent in accordance with UF IRB policy.

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**Methods:** Adult intensive care patients receiving cefepime, meropenem, or piperacillin–tazobactam for severe pneumonia caused by Gram-negative bacteria were randomized to receive beta-lactams as an intermittent (30 minutes) or continuous (24 hours) infusion. Respiratory samples for culture and susceptibility testing, with minimum inhibitory concentrations (MIC), were collected once a week for up to 4 weeks. Beta-lactam plasma concentrations were measured and therapeutic drug monitoring was performed using Bayesian software as the standard of care.

**Results:** The study was terminated early owing to slow enrollment. Thirty-five patients were enrolled in this study. Cefepime ( $n = 22$ ) was the most commonly prescribed drug at randomization, followed by piperacillin ( $n = 8$ ) and meropenem ( $n = 5$ ). Nineteen patients were randomized into the continuous infusion arm and 16 into the intermittent infusion arm. *Pseudomonas aeruginosa* was the most common respiratory isolate ( $n = 19$ ). Eighteen patients were included in the final analyses. No differences in bacterial resistance were observed between arms ( $P = 0.67$ ). No significant differences in superinfection ( $P = 1$ ), microbiological cure ( $P = 0.85$ ), clinical cure at day 7 ( $P = 0.1$ ), clinical cure at end of therapy ( $P = 0.56$ ), mortality ( $P = 1$ ), intensive care unit length of stay ( $P = 0.37$ ), or hospital length of stay ( $P = 0.83$ ) were observed. Achieving 100%  $fT > MIC$  ( $P = 0.04$ ) and  $fT > 4 \times MIC$  ( $P = 0.02$ ) increased likelihood of clinical cure at day 7 of therapy.

**Conclusions:** No differences in the emergence of bacterial resistance or clinical outcomes were observed between intermittent and continuous infusions. Pharmacokinetic/pharmacodynamic target attainment may be associated with a clinical cure on day 7.

**Key Words:** beta-lactams, resistance, Gram-negative bacteria, pneumonia

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## BACKGROUND

Antimicrobial resistance puts millions of lives at risk.<sup>1</sup> In the United States, antibiotic-resistant bacteria and fungi contribute to more than 35,000 deaths annually. The Centers for Disease Control and Prevention have specified that certain bacteria pose a greater threat because of their resistance pattern and high mortality rates, including carbapenem-resistant and

extended-spectrum beta-lactamase-producing *Enterobacteriaceae* and multidrug-resistant *Pseudomonas aeruginosa*.<sup>2</sup> Judicious use of antibiotics is warranted to minimize resistance, because bacteria are highly adaptable to antimicrobials through rapid replication, mutation, and exchange of genetic material within and between species.<sup>3</sup> Because of the slow development of novel antibiotics, additional strategies to optimize treatment and minimize the development of bacterial resistance are warranted.

Pneumonia, including ventilator-associated pneumonia, is one of the most commonly encountered bacterial infections in intensive care units (ICUs) and is associated with prolonged mechanical ventilation, increased length of ICU stay, and a high mortality rate.<sup>4</sup> Clinical trials have demonstrated that 10%–50% of patients with hospital- and ventilator-associated pneumonia because of *P. aeruginosa* treated with beta-lactams, developed resistance.<sup>5,6</sup> In addition, early and adequate antibiotic pharmacodynamic target attainment has been demonstrated to significantly affect pneumonia outcomes, including the suppression of new bacterial resistance.<sup>7,8</sup>

Beta-lactams are commonly prescribed antibiotics in ICUs, and their bacterial killing is dependent on the amount of time that free drug concentrations remain above the minimum inhibitory concentration (MIC) of the bacteria.<sup>8</sup> Package insert dosing may be inadequate to treat serious infections, such as pneumonia, especially in critically ill patients with high variability in pharmacokinetics.<sup>9</sup> Currently, there are no published prospective clinical trials that have evaluated the impact of the beta-lactam infusion type with Bayesian-guided therapeutic drug monitoring (TDM) on the emergence of Gram-negative bacterial resistance in patients with severe pneumonia. Therefore, the primary objective of this study was to compare the incidence of Gram-negative bacterial resistance between participants receiving intermittent and continuous Bayesian-guided infusions of beta-lactams for severe pneumonia.

## METHODS

This was a prospective, randomized, open-label study of participants admitted to the University of Florida (UF) Health Shands Hospital in Gainesville, FL, between September 2021 and February 2023. Participants were screened for the following inclusion criteria (revised in March of 2022 to improve the rate of enrollment, see **Table S1, Supplemental Digital Content 1**, <http://links.lww.com/TDM/A689>): age  $\geq 18$  years, admission to the ICU with severe pneumonia defined per IDSA/ATS 2019 definition,<sup>10</sup> positive respiratory culture for Gram-negative bacteria, and received within the past 72 hours or will receive meropenem, cefepime, or piperacillin (in combination with tazobactam). Participants were excluded if they were pregnant, prisoners, had an allergy to beta-lactams in the study, received renal replacement therapy, had negative baseline respiratory cultures or baseline resistance to the study drugs, or were COVID-positive and were enrolled in other research trials. Participants randomized to the continuous infusion arm who were then started on renal replacement therapy were allowed to switch to the intermittent infusion arm. This study was reviewed and approved by the institutional review board at the University of Florida (IRB202101979). Participants or their families/

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designated health care surrogates provided written informed consent in accordance with the UF IRB policy.

The participants were randomized in a 1:1 ratio to receive beta-lactam as an intermittent (30 minutes) or a continuous (over 24 hours) infusion. Randomization was stratified according to the beta-lactam regimen. Table 1 shows the initial beta-lactam regimen based on creatinine clearance. The beta-lactam regimen and duration of therapy were determined by the treatment team. If the participants' therapy was changed to a nonstudy beta-lactam during the first 72 hours, they were withdrawn from the study. If it was changed to a nonstudy antibiotic after 72 hours, the patients remained enrolled. Participants who switched between beta-lactams in the study (ie, cefepime, meropenem, and piperacillin) would remain enrolled. Patients may have received concomitant antibiotics; however, beta-lactams were the drugs of interest.

According to the standard of care at the UF Health Shands, all participants had beta-lactam plasma concentrations measured for TDM.<sup>11</sup> For the intermittent infusion arm, a peak was ordered 1 hour after the end of infusion and a trough was ordered before the next dose. For continuous infusion, 2 samples at least 3 hours apart were drawn at any time after the start of infusion. Total beta-lactam concentrations were quantified at the Infectious Disease Pharmacokinetics Laboratory at UF using validated liquid chromatography with tandem mass spectrometry assays. The detection was 2–100 mg/L, and the interday and intraday precision and accuracy were  $<10\%$ . Pharmacokinetic/Pharmacodynamic (PK/PD) target attainment and beta-lactam dose recommendations were determined using BestDose software (LAPKB, University of Southern CA) and previously published models.<sup>12–14</sup> Beta-lactam doses administered, beta-lactam concentrations, weight, age, and renal function were inputted into BestDose to determine therapy adjustments (to the same infusion arm) to achieve  $100\% \text{ fT} > 4 \times \text{MIC}$ . All patients underwent TDM within the first day of randomization, and TDM was repeated if patients had an onset of acute kidney injury (per the KDIGO definition) or were at risk for neurotoxicity. Protein binding was assumed to be 20% for cefepime, 2% for meropenem, and 30% for piperacillin.<sup>15–17</sup>

Respiratory samples [sputum, endotracheal, or bronchoalveolar lavage (BAL)] were collected from participants and sent initially for pneumonia panel screening, culture, and susceptibility testing (with MICs) in the UF Health Shands lab. The FilmArray Pneumonia panel (BioFire Diagnostics, Salt Lake City, UT), a multiplex PCR-based diagnostic test, could also be performed initially. If positive, respiratory samples were collected once weekly for up to 4 weeks to track bacterial growth and MIC values. Bacteria were identified and had susceptibility tested using VITEK and Vitek II (bioMérieux, Durham, NC) or Etest. The Etest was used for the following bacteria (beta-lactams): *Burkholderia cepacia* complex (meropenem), *Acinetobacter* spp. (cefepime, meropenem, and piperacillin–tazobactam), and Gram-negative nonfermenters (cefepime, meropenem, and piperacillin–tazobactam).

New resistance was defined as new numeric increases ( $\geq 2$ -fold) in the bacterial MIC during the follow-up period compared with the baseline when starting beta-lactam therapy. Superinfection was defined as the growth of resistant

**TABLE 1.** Initial Beta-Lactam Doses per Infusion Arm and Creatinine Clearance

| Creatinine Clearance (mL/min)  | Intermittent Infusion Arm | Continuous Infusion Arm |
|--------------------------------|---------------------------|-------------------------|
| <b>Cefepime</b>                |                           |                         |
| >60                            | 2 g IV every 8 h          | 6 g IV daily            |
| 30–60                          | 2 g IV every 12 h         | 4 g IV daily            |
| 10–30                          | 2 g IV every 24 h         | 2 g IV daily            |
| <10                            | 1 g IV every 24 h         | 1 g IV daily            |
| <b>Meropenem</b>               |                           |                         |
| >50                            | 2 g IV every 8 h          | 6 g IV daily            |
| 25–50                          | 2 g IV every 12 h         | 4 g IV daily            |
| 10–25                          | 1 g IV every 12 h         | 2 g IV daily            |
| <10                            | 1 g IV every 24 h         | 1 g IV daily            |
| <b>Piperacillin/tazobactam</b> |                           |                         |
| >40                            | 4.5 g IV every 6 h        | 18 g IV daily           |
| 20–40                          | 3.375 g IV every 6 h      | 13.5 g IV daily         |
| <20                            | 2.25 g IV every 6 h       | 9 g IV daily            |

Gram-negative bacteria during the follow-up period that was not observed in baseline cultures. Microbiological cure was defined as the lack of bacterial growth during the follow-up period, with no subsequent positive cultures from any site. Clinical cure was assessed by an infectious disease physician at 7 days and the end of therapy and was defined as the resolution of infection-related symptoms, including normalization of body temperature, white blood cell count, removal of mechanical ventilation and/or vasopressors if applicable, and noninitiation of a new antibiotic within 48 hours of stopping the study antibiotic. Adverse events monitored for included neurotoxicity, a decrease in platelets ( $<125 \times 10^3$  cells/mm<sup>3</sup>), a decrease in white blood cells ( $<2500$  cells/mm<sup>3</sup>), increase in serum creatinine ( $\geq 1.3 \times$  baseline), and *Clostridioides difficile* colitis.

The primary objective of this study was to compare the incidence of Gram-negative bacterial resistance between participants receiving intermittent and continuous Bayesian-guided infusions of beta-lactams for severe pneumonia. Secondary objectives were to compare the outcomes of superinfection, microbiological cure, clinical cure, PK/PD target attainment, length of hospital and ICU stay, mortality rate, and incidence of adverse events.

Continuous data are presented as medians and interquartile ranges (IQR), whereas categorical data are presented as counts and percentages. Variables were compared using the Wilcoxon rank-sum or Fisher exact tests. Statistical significance was set at  $P < 0.05$  significant. Statistical analyses were performed using JMP Pro v17 software (SAS Institute, Cary, NC).

## RESULTS

In March 2023, the study was terminated because of slow enrollment. Between December 2021 and March 2023, 527 patients were screened. Eighteen participants were included in the final resistance and clinical outcome analysis and were enrolled in the study until 4 weeks ( $n = 3$ ), hospital discharge ( $n = 10$ ), death ( $n = 4$ ), or were unenrolled because of the clinical need for continuous infusion ( $n = 1$ ) (see **Figure S1, Supplemental Digital Content 1**, <http://links.lww.com/TDM/A689>).

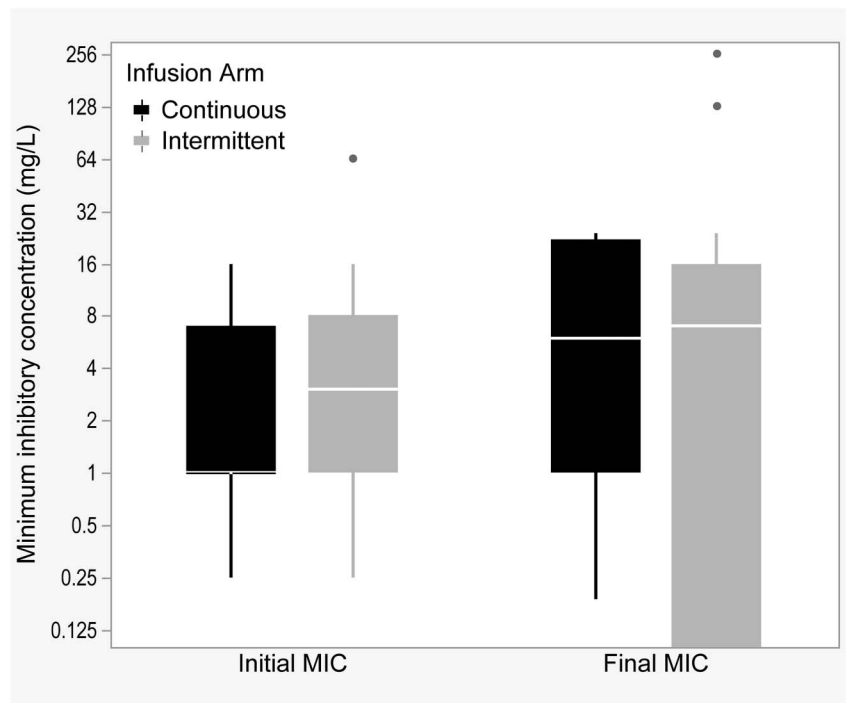
Seventeen (49%) participants were excluded from the final analysis, most commonly because of negative baseline cultures ( $n = 6$ ) or switching to nonstudy antibiotics on the same day of enrollment ( $n = 4$ ). The median (IQR) age was 68 (56–74) years, and 26 (74%) were males (Table 2). Common comorbidities included lung cancer (31%), chronic obstructive pulmonary disease (20%), and COVID coinfection (9%). At randomization, 22 (63%) patients were on cefepime, 8 (23%) on piperacillin/tazobactam, and 5 (14%) on meropenem. Nineteen (54%) participants were randomized to the continuous infusion arm and 16 (46%) to the intermittent infusion arm. The most commonly isolated bacteria were *P. aeruginosa* ( $n = 19$ ), followed by *Klebsiella pneumoniae* ( $n = 4$ ), *Enterobacter cloacae* ( $n = 3$ ), and *Klebsiella aerogenes* ( $n = 3$ ). Five participants in the intermittent infusion arm and 4 in the continuous infusion arm received continuous renal replacement therapy after enrollment. None of the patients underwent intermittent hemodialysis.

In the continuous infusion arm, the median MICs increased from 1 (1–4) mg/L in the initial culture to 6 (1–22) mg/L in the final culture ( $P = 0.2$ ) (Fig. 1). For intermittent infusions, the median MICs increased from 3 (1–8) mg/L to 7 (0.25–16) mg/L from the initial to the final culture ( $P = 0.87$ ). *P. aeruginosa*, median (IQR) MICs increased from 2.5 (0.25–8) mg/L to 16 (8–24) mg/L and from 4 (0.25–16) mg/L to 8 (0.25–256) mg/L in the continuous ( $P = 0.03$ ) and intermittent ( $P = 0.37$ ) groups, respectively. Despite these trends, no significant differences in resistance development were identified between continuous or intermittent infusions when resistance was defined as any increase in MIC ( $P = 0.79$ ) or an MIC increase of 2 tube dilutions ( $P = 0.67$ ; Table 3). Sixty percent of the participants in the continuous arm and 69% of the patients in the intermittent arm received adjusted beta-lactam therapy after therapeutic drug monitoring. Forty-five percent had a dose decrease, 22% had a dose increase, and 33% had no change in therapy. Beta-lactam PK/PD target attainment was high in both infusion arms before TDM, with median free drug concentrations achieving 100%  $fT_{>MIC}$  and 100%  $fT_{>4 \times MIC}$  for both infusion arms (Fig. 2).

**TABLE 2.** Participant Characteristics, n = 18, Median (IQR) or n (%)

| Demographics and Clinical Characteristics          | Intermittent infusion (n = 13) | Continuous infusion (n = 5) |
|--|--------------------------------|-----------------------------|
| Male   | 8 (62)                         | 4 (80)                      |
| Age, yr  | 69 (61–73)                     | 67 (49–74)                  |
| BMI, kg/m <sup>2</sup>                             | 22.4 (19.2–30.7)               | 31.6 (26.4–42.9)            |
| SCr at randomization (mg/dL)                       | 0.67 (0.54–1.09)               | 1.21 (0.66–2.16)            |
| CrCl at randomization (mL/min)                     | 83.7 (69.4–105.4)              | 92 (77.7–222.8)             |
| CRRT   | 5 (38)                         | 4 (80)                      |
| Comorbidities                                      |                                |                             |
| Lung cancer  | 3 (23)                         | 1 (20)                      |
| COPD   | 2 (15)                         | 2 (40)                      |
| COVID-19 Coinfection                               | 1 (8)                          | 1 (20)                      |
| Beta-lactam at randomization                       |                                |                             |
| Cefepime   | 7 (54)                         | 4 (80)                      |
| Meropenem  | 2 (15)                         | 0 (0)                       |
| Piperacillin/tazobactam                            | 4 (31)                         | 1 (20)                      |
| Respiratory Isolates, n                            |                                |                             |
| <i>Pseudomonas aeruginosa</i>                      | 7                              | 5                           |
| <i>Klebsiella pneumoniae</i>                       | 0                              | 1                           |
| <i>Klebsiella aerogenes</i>                        | 1                              | 1                           |
| <i>Enterobacter cloacae</i>                        | 2                              | 0                           |
| <i>Proteus mirabilis</i>                           | 1                              | 0                           |
| <i>Cronobacter sakazakii</i>                       | 0                              | 1                           |
| Concomitant antibiotics for Gram-negative coverage |                                |                             |
| Aminoglycoside                                     | 1 (7)                          | 0 (0)                       |
| Fluoroquinolone                                    | 2 (15)                         | 0 (0)                       |
| Sulfamethoxazole–trimethoprim                      | 0 (0)                          | 1 (20)                      |

BMI, body mass index; SCr, serum creatinine; CrCl, creatinine clearance; CRRT, continuous renal replacement therapy; COPD, chronic obstructive pulmonary disease.



**FIGURE 1.** Boxplot for initial to final median MICs between intermittent and continuous infusion arms.

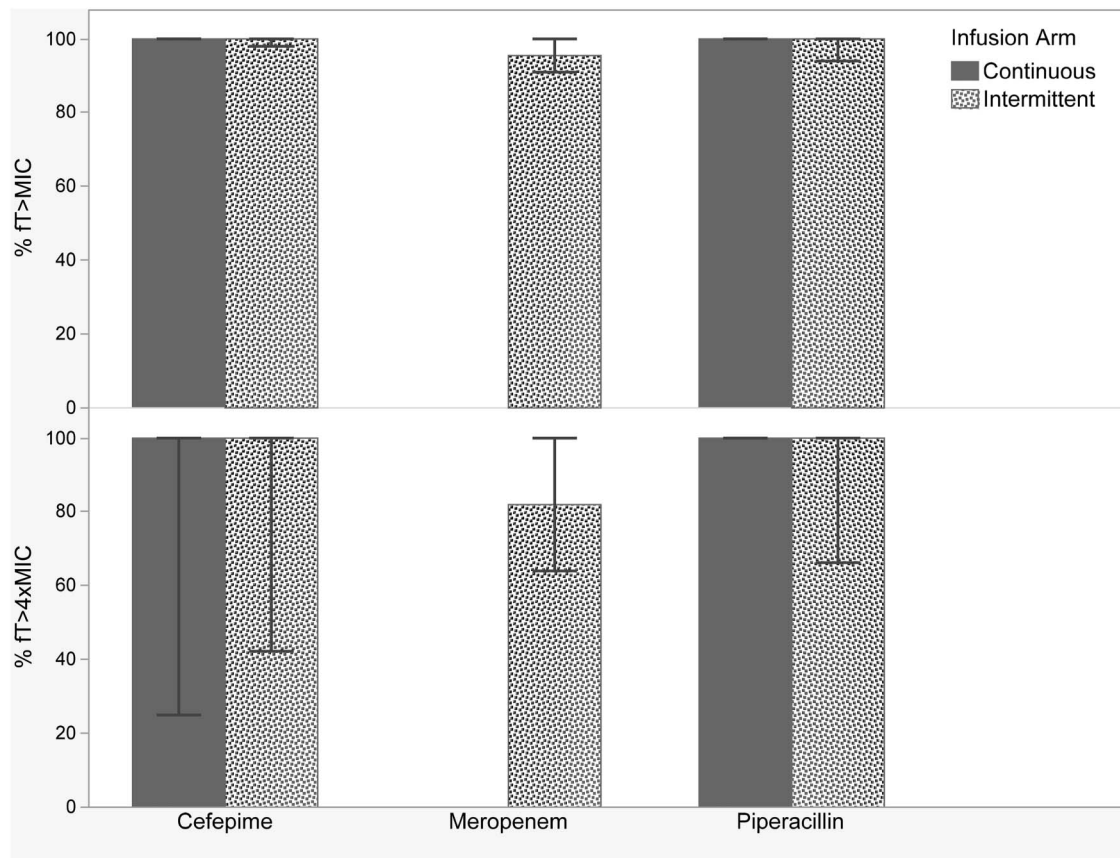


FIGURE 2. Median (IQR) beta-lactam target attainment of participants using the first plasma samples drawn (n = 18).

TABLE 3. Study Outcomes, n = 18

| Gram-Negative Bacterial Resistance Emergence      |                              |                           |      |
|---|------------------------------|---------------------------|------|
|   | Intermittent Infusion        | Continuous Infusion       | P    |
| Bacteria isolates, n                              | 18                           | 8                         | —    |
| Any increase in MIC                               | 8                            | 4                         | 0.79 |
| 2× Increase in MIC                                | 6                            | 2                         | 0.67 |
| Secondary Outcomes, Median (IQR) or n (%)         |                              |                           |      |
|   | Intermittent Arm<br>(n = 13) | Continuous Arm<br>(n = 5) | P    |
| Superinfection                                    | 0 (0)                        | 0 (0)                     | 1.00 |
| Microbiologic cure                                | 4 (31)                       | 1 (20)                    | 0.85 |
| Clinical cure                                     |                              |                           |      |
| At d 7  | 5 (38)                       | 0 (0)                     | 0.10 |
| At end of therapy                                 | 8 (62)                       | 3 (60)                    | 0.56 |
| Mortality   | 2 (15)                       | 2 (40)                    | 1.00 |
| Hospital length of stay, d                        | 18 (13–32)                   | 27 (12–32)                | 0.83 |
| ICU Length of stay, d                             | 9 (6–17)                     | 23 (7–26)                 | 0.37 |
| PK/PD target attainment fT <sub>&gt;MIC</sub>     | 100 (94–100)                 | 100 (100–100)             | 0.11 |
| PK/PD target attainment fT <sub>&gt;4 × MIC</sub> | 100 (58–100)                 | 100 (50–100)              | 0.68 |

MIC, minimum inhibitory concentration; ICU, intensive care unit; PK/PD, pharmacokinetic/pharmacodynamic.

One hundred percent fT<sub>>MIC</sub> was correlated with clinical cure at day 7 (P = 0.04), but was not associated with microbiologic eradication (P = 0.81), clinical cure at end of study (P = 1), mortality (P = 1), ICU length of stay (P = 0.42), or hospital length of stay (P = 0.2). 100% fT<sub>>4 × MIC</sub> was associated with clinical cure at day 7 (P = 0.02), but not microbiologic eradication (P = 0.59), clinical cure at end of therapy (P = 0.26), mortality (P = 0.26), ICU length of stay (P = 0.84), or hospital length of stay (P = 0.38). In the intermittent infusion arm, 1 participant died of *P. aeruginosa* pneumonia and 1 died of lymphoma. In the continuous infusion arm, 1 participant died of cardiac arrest and 1 died of right ventricular failure from a submassive pulmonary embolism. None of the participants experienced adverse effects attributable to the study drugs.

### DISCUSSION

This study was conducted to determine the impact of continuous versus intermittent beta-lactam infusion on Gram-negative bacterial resistance in patients with severe pneumonia. Neither infusion arm showed an increased risk of bacterial resistance and there was no difference in the secondary clinical outcomes between the arms. 100% fT<sub>>MIC</sub> and 100% fT<sub>>4 × MIC</sub> were associated with clinical cure at day

7 of therapy, providing additional support for early beta-lactam target attainment. This study was underpowered because of poor enrollment and early termination.

Evidence regarding the effect of beta-lactam infusion on Gram-negative bacterial resistance in patients with pneumonia is limited. Prolonged infusions may lead to longer periods in which drug concentrations remain above the MIC, potentially decreasing bacterial regrowth between doses and minimizing the emergence of resistance. In a retrospective study by Dhaese et al, the emergence of antimicrobial resistance in adult ICU patients receiving piperacillin–tazobactam or meropenem as intermittent versus continuous infusions was compared in adult ICU patients. Resistant strains emerged in 24 of the 205 patients (12%); however, no differences in resistance emergence were observed between the infusion arms. *P. aeruginosa* was considered a significant predictor of the emergence of resistance. The authors proposed that further evidence is needed regarding the PK/PD index most associated with the suppression of bacterial resistance, because  $C_{\min}/MIC$ , area under the time concentration curve to MIC (AUC/MIC), and measures involving mutant prevention concentration have all been proposed as potential targets.<sup>18–21</sup> The authors also concluded that the emergence of resistance was not because of the mode of infusion, which is similar to the results of the present study and the findings of Yusuf et al.<sup>18,22</sup> In addition, PK/PD target attainment in the present study was high, which may contribute to the finding that no differences in resistance emergence were observed between the infusion arms. Interestingly, Felton et al<sup>23</sup> suggested that prolonged infusions may not be sufficient to limit the emergence of resistance in *P. aeruginosa* infections with high bacterial burdens, such as pneumonia. This proposal could help explain the results of Dhaese et al and those of the present study. However, other evidence suggests that there may be a benefit to prolonging the infusion. Sumi et al<sup>24</sup> reported that prolonged beta-lactam infusions may suppress ESBL-producing bacteria. Sumi et al reported that the PK/PD index most likely to suppress the emergence of antibiotic resistance is  $C_{\min}/MIC \geq 4$ .<sup>25</sup> Although underpowered, in the present study, achieving  $100\% \text{ fT} >_{MIC}$  and  $100\% \text{ fT} >_{4 \times MIC}$  was significantly associated with clinical cure at day 7 of therapy, supporting evidence that early beta-lactam target attainment is essential for improved patient outcomes.<sup>7,26,27</sup>

In contrast to the published literature, this study did not find differences in the secondary outcomes between the infusion arms. Rhodes et. performed a systematic review and meta-analysis of 18 studies on the effect of prolonged piperacillin–tazobactam infusions. Approximately 57% of the patients received prolonged infusions, which were associated with 1.46-fold lower odds of mortality, 1.77-fold higher odds of clinical cure, and 1.22-fold higher odds of microbiological cure.<sup>28</sup> The mortality benefit of prolonged infusions has been further emphasized in other studies as well.<sup>29,30</sup> A randomized, open-label, controlled trial of patients receiving meropenem as a continuous infusion versus a bolus (over 30 minutes) demonstrated a decrease in ICU stay and duration of treatment.<sup>31</sup> Chan et al<sup>32</sup> reported a decreased length of hospital stay with prolonged infusions. None of the participants experienced adverse effects from the study drugs, thus providing additional safety support for beta-lactams.

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This study has several limitations. The primary limitation was the small enrollment size, which made the study underpowered. The inability to identify patients meeting the study criteria and the inability of critically ill patients to provide consent were the most common reasons for low enrollment. In addition, this study used MICs, which may only test 1 to 2 colonies with resistant subpopulations, potentially preventing detection.<sup>33</sup> In addition, it is generally accepted that MICs vary with repeated assessments, potentially producing MIC values that differ by 200%.<sup>34</sup> Finally, repeat-positive cultures may be because of colonization, especially in participants demonstrating a clinical cure before repeat cultures. To address these limitations, a multicenter study with a different study design is required. The proposed design for a future prospective study is a pragmatic, block randomized controlled trial that would automatically enroll all participants admitted to a specific ICU in a designated arm of the trial. However, even with this design, the percentage of candidates dropped may still be high, given the risk of baseline-negative or resistant cultures. Despite these limitations, this study had a strong design and followed previously published recommendations, including accounting for methodologic and biological variability of MIC, using continuous outcomes to improve study power, and performing therapeutic drug monitoring with Bayesian estimation to limit drug exposure as a confounder.<sup>35</sup>

## CONCLUSION

No differences were observed in the emergence of bacterial resistance between the intermittent and continuous infusions. There were no differences in mortality, clinical cure on day 7 or at the end of therapy, adverse effects, microbiological eradication, length of stay, or mortality between the 2 groups. PK/PD target attainment was associated with clinical cure on day 7. Although underpowered, this finding supports previously published findings that early target attainment improves clinical outcomes in patients. Further investigations into the beta-lactam infusion type and the emergence of Gram-negative bacterial resistance are needed before providing recommendations for patient treatment, and a multicenter study may help improve study recruitment.

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