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The Impact of Concomitant Empiric Cefepime on Patient Outcomes of Methicillin-Resistant Staphylococcus aureus Bloodstream Infections Treated With Vancomycin

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Background. Data suggest that vancomycin + β-lactam combinations improve clearance of methicillin-resistant Staphylococcus aureus (MRSA) bloodstream infections (BSIs). However, it is unclear which specific β-lactams confer benefit. This analysis evaluates the impact of concomitant empiric cefepime on outcomes of MRSA BSIs treated with vancomycin.

Methods. Retrospective cohort study of adults with MRSA BSI from 2006 to 2017. Vancomycin + cefepime therapy was defined as ≥24 hours of cefepime during the first 72 hours of vancomycin. The primary outcome was microbiologic failure, defined as BSI duration ≥7 days and/or 60-day recurrence. Multivariable logistic regression was used to evaluate the association between vancomycin + cefepime therapy and binary outcomes. Cause-specific and subdistribution hazard models were used to evaluate the association between vancomycin + cefepime and BSI clearance.

Results. Three hundred fifty-eight patients were included, 129 vancomycin and 229 vancomycin + cefepime. Vancomycin + cefepime therapy was independently associated with reduced microbiologic failure (adjusted odds ratio [aOR], 0.488; 95% confidence interval [CI], 0.271–0.741). This was driven by a reduction in the incidence of BSI durations ≥7 days (vancomycin + cefepime aOR, 0.354; 95% CI, 0.202–0.621). Vancomycin + cefepime had no association with 30-day mortality (aOR, 0.952; 95% CI, 0.435–2.425). Vancomycin + cefepime was associated with faster BSI clearance in both cause-specific (HR, 1.408; 95% CI, 1.125–1.762) and subdistribution hazard models (HR, 1.264; 95% CI, 1.040–1.536).

Conclusions. Concomitant empiric cefepime improved MRSA BSI clearance and may be useful as the β-lactam component of synergistic vancomycin + β-lactam regimens when empiric or directed gram-negative coverage is desired.
is particularly true in the United States, where flucloxacillin, the single agent with the strongest clinical evidence at the present time, is not commercially available [18]. Although ongoing studies may address this need by studying specific narrow-spectrum β-lactams, clinical data evaluating broad-spectrum β-lactams will still be needed [21]. Such data would be crucial in adopting a vancomycin + β-lactam approach to inform empiric prescribing before MRSA is identified and directed therapy when patients require continued gram-negative coverage. Given the frequency with which cefepime is used concomitantly with vancomycin for empiric antibiotic therapy for suspected antibiotic-resistant infections and the in vitro synergy between these 2 agents, the objective of this analysis was to evaluate the impact of concomitant empiric cefepime on patient outcomes of MRSA BSI treated with vancomycin.

METHODS

Study Design and Population
This was a retrospective, observational cohort study of adult patients with MRSA BSI from 2006 to 2017 at the Detroit Medical Center (DMC), an eight-hospital healthcare system in Southeast Michigan. Patients aged ≥18 years with ≥1 positive blood culture for MRSA initially treated with ≥72 hours of vancomycin were eligible for inclusion [22]. Patients who received ≥24 hours of concomitant MRSA-active therapy or a β-lactam other than cefepime during the initial 72 hours of vancomycin therapy were excluded. Patients without follow-up blood cultures and those with repeat MRSA BSI episodes were also excluded. Patients who received ≥24 hours of concomitant cefepime during the initial 72 hours of vancomycin therapy were considered to have received vancomycin + cefepime. Patients who received <24 hours of cefepime were considered to have received vancomycin monotherapy. This study was approved by the DMC Research Review Committee and the institutional review board at Wayne State University (WSU), and a waiver of informed consent was granted.

Patient Data Elements and Collection
Methicillin-resistant *Staphylococcus aureus* BSIs for inclusion were identified through a list of positive MRSA blood cultures at the DMC during the study period. Patient data were extracted from the medical record by trained reviewers using a structured data collection form within the Research Electronic Data Capture (REDCap; Vanderbilt University) data capture tool hosted at WSU [23]. Data elements included demographics, medical history, comorbid conditions, antibiotic therapy and associated laboratory parameters, infectious diseases consult, and pursuit of source control. The degree of patient comorbidity was quantified using the Charlson comorbidity index [24]. Severity of illness was quantified using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score using the worst physiological parameters within 24 hours of index MRSA blood culture [25]. The source of the MRSA BSI was based on the treating physician’s notes and available clinical/diagnostic data. Microbiologic data including antibiotic susceptibilities by Microscan, Phoenix, and/or Etest were collected from the medical record.

Outcomes
The primary outcome was microbiologic failure, defined as a BSI duration ≥7 days and/or MRSA BSI recurrence within 60 days of the end of MRSA BSI therapy. Secondary outcomes included each individual component of microbiologic failure, mortality from any cause within 30 days of index MRSA blood culture, time to MRSA BSI clearance in days, and hospital-length of stay (LOS) post–MRSA BSI onset in days.

Data Analysis
The primary analysis focused on examining the association between concomitant vancomycin + cefepime therapy and microbiologic failure. Bivariate analysis was conducted comparing covariates between patients who did and did not experience microbiologic failure. Categorical variables were compared between groups using the χ² or Fisher exact test, whereas continuous variables were compared using the Student t test or Mann Whitney U test. The independent association between concomitant vancomycin + cefepime therapy and microbiologic failure was then examined using multivariable logistic regression. Vancomycin + cefepime therapy, along with all the variables associated with microbiologic failure at a P value <.2 in bivariate analysis with biologic plausibility, were entered into logistic regression models simultaneously and removed in a backward, stepwise fashion. Covariates were retained in the final model if the P value for the likelihood ratio test for their removal was <.1. Because vancomycin + cefepime was the exposure of interest, it was forced to remain in the final step of the regression models even if no statistical association was observed. Model fit was assessed with the Hosmer-Lemeshow goodness-of–fit test; models with a nonsignificant result were considered adequate. Multicollinearity of candidate regression models was assessed via the variance inflation factor, with values between 1 and 5 considered acceptable.

Given the imbalance in the proportion of patients with an endovascular BSI source between treatment groups and the well-documented association between endovascular sources and prolonged, recurrent BSI, a secondary post hoc matched analysis was conducted to further examine the association between vancomycin + cefepime therapy and microbiologic failure. Patients were matched 1:1 on endovascular source, and conditional logistic regression was conducted on the resulting matched data set as described above for the primary analysis.

Additional secondary analyses were conducted to examine the association between vancomycin + cefepime therapy and the secondary outcomes. Any statistically significant associations
between vancomycin + cefepime therapy and secondary outcomes in bivariate analysis were examined further through multivariable analysis using model-building strategies congruent with those explained above for the primary analysis. The independent association between vancomycin + cefepime therapy and BSI clearance was evaluated using both a cause-specific proportional hazard model (patients experiencing mortality before BSI clearance were censored) and a subdistribution hazards model (simultaneous model of survival and BSI duration) to account for the competing risks of death and BSI clearance [26].

All statistical tests were 2-sided; P values ≤.05 were considered statistically significant. Analyses were performed using SPSS Statistics, IBM SPSS software, version 25.0 (IBM Corp., Armonk, NY), and SAS, version 9.4 (Cary, NC).

RESULTS

A total of 358 patients were included. A full description of demographics, clinical characteristics, and outcomes of the cohort is available in Supplementary Table 1. The cohort was predominantly African American (79.6%), majority male (64.8%), and had a median (interquartile range [IQR]) age of 60 (52–69) years. Common comorbidities were diabetes (38.0%), moderate/severe renal disease (35.5%), chronic hemodialysis (25.4%), heart failure (23.5%), intravenous drug use (15.1%), and liver disease (15.6%). The median (IQR) Charlson comorbidity index and APACHE II scores were 3 (1–5) and 18 (11–24), respectively. The most common MRSA BSI sources were endovascular (23.5%), lower respiratory tract (21.5%), skin and soft tissue (21.2%), and intravenous catheter (20.4%). The median (IQR) duration of vancomycin therapy was 5 (4–9) days. The majority of patients (79.5%) had their vancomycin therapy dosed and monitored to a trough concentration target range of 15–20 mg/L, whereas the remaining had their vancomycin therapy dosed and monitored to an AUC of 400–600 mg·h/L [27, 28]. Two hundred twenty-nine patients (64.0%) received concomitant cefepime therapy with a median (IQR) duration of 3 (2–4) days. The most common cefepime dose and interval were 1000 mg (52.4%) and every 8 hours (41.5%), respectively. Microbiologic failure was observed in 107 patients (30.4%), with 83 (23.3%) having a BSI duration ≥7 days. Thirty-day mortality was observed in 57 (15.9%) patients.

Bivariate comparisons between patients receiving vancomycin or vancomycin + cefepime are displayed in Table 1. Patients receiving vancomycin + cefepime were significantly older, had a higher proportion of baseline acute kidney injury, and had significantly higher APACHE II scores. Although select individual comorbid conditions differed between groups, no difference in Charlson comorbidity index was observed. Patients receiving vancomycin + cefepime were more likely to have been admitted from a nursing facility or have a polymicrobial bloodstream infection. Endovascular MRSA BSI source, including endocarditis, and lower respiratory tract source were more common among vancomycin + cefepime patients, whereas skin and soft tissue and bone/joint source were more common among vancomycin monotherapy patients. Patients in the vancomycin + cefepime group were more likely to have AUC-guided vancomycin therapy. Microbiologic failure was significantly more common among vancomycin monotherapy patients (Figure 1). This difference was primarily driven by a greater incidence of BSI durations ≥7 days in the vancomycin monotherapy group. No difference in the incidence of 60-day recurrence was observed. Thirty-day mortality was significantly more common among vancomycin + cefepime patients. No difference in safety outcomes, including vancomycin-associated nephrotoxicity, neurotoxicity, or CDI, was observed between treatment groups (Table 1).

The results of logistic regression analysis for independent predictors of microbiologic failure are displayed in Table 2. Accounting for endovascular BSI source, African American race, and unknown BSI source, vancomycin + cefepime therapy was independently associated with less frequent microbiologic failure (adjusted odds ratio [aOR], 0.488; 95% confidence interval [CI], 0.271–0.741). Results were consistent in post hoc analysis in the cohort of 258 patients (129 vancomycin, 129 vancomycin + cefepime) who were matched on endovascular BSI source (Supplementary Table 2). Patients receiving vancomycin + cefepime were significantly less likely to experience microbiologic failure (aOR, 0.517; 95% CI, 0.298–0.899).

Because the difference in microbiologic failure was primarily due to BSI duration ≥7 days, logistic regression analysis was also performed for this outcome (Supplementary Table 3). Accounting for endovascular source, vancomycin + cefepime therapy was associated with reduced incidence of BSI duration ≥7 days (aOR, 0.354; 95% CI, 0.202–0.621). The results of logistic regression analysis for independent predictors of mortality are displayed in Table 3. Accounting for lower respiratory tract BSI source, endocarditis source, APACHE II score, age, and ID consult, vancomycin + cefepime therapy was not associated with 30-day mortality (aOR, 0.952; 95% CI, 0.435–2.425).

The results of proportional hazards regression models for BSI clearance are shown in Table 4. Accounting for endovascular source, patients receiving vancomycin + cefepime were more likely to experience BSI clearance (HR, 1.408; 95% CI, 1.125–1.762). Similar results were observed using a subdistribution hazard model (HR, 1.264; 95% CI, 1.040–1.536).

DISCUSSION

This study sought to examine the impact of concomitant cefepime on the outcomes of patients with MRSA BSIs initially treated with vancomycin. The results suggest that concomitant cefepime improved BSI clearance, reducing the number
Table 1. Bivariate Comparisons of Demographics, Clinical Characteristics, and Outcomes Between Patients Receiving Vancomycin or Vancomycin + Cefepime

| Covariate                        | Vancomycin (n = 129) | Vancomycin + Cefepime (n = 229) | PValue |
|----------------------------------|-----------------------|----------------------------------|--------|
| **Demographics**                 |                       |                                  |        |
| Age, y                           | 56 (48–66.5)          | 61 (53.5–71)                     | .001   |
| Male                             | 86 (66.7)             | 146 (63.8)                       | .580   |
| Race                             |                       |                                  | .548   |
| African American                 | 105 (81.4)            | 180 (78.6)                       |        |
| Caucasian                        | 20 (15.5)             | 45 (19.7)                        |        |
| Hispanic                         | 2 (1.6)               | 3 (1.3)                          |        |
| Other/unknown                    | 2 (1.6)               | 1 (0.4)                          |        |
| **Comorbidities & medical history** |                     |                                  |        |
| Myocardial infarction            | 4 (3.1)               | 20 (8.7)                         | .047   |
| Heart failure                    | 26 (20.2)             | 58 (25.3)                        | .268   |
| Peripheral vascular disease      | 27 (20.9)             | 43 (18.8)                        | .622   |
| Cerebrovascular disease          | 18 (14.0)             | 45 (19.7)                        | .174   |
| Dementia                         | 8 (6.2)               | 36 (15.7)                        | .008   |
| Chronic pulmonary disease        | 25 (19.4)             | 66 (28.8)                        | .049   |
| Chronic obstructive pulmonary disease | 21 (16.3)                     | 59 (25.8)                        | .039   |
| Asthma                           | 5 (3.9)               | 12 (5.2)                         | .560   |
| Connective tissue disease        | 19 (14.7)             | 24 (10.5)                        | .235   |
| Peptic ulcer disease             | 2 (1.6)               | 5 (2.2)                          | 1.000  |
| Liver disease                    | 25 (19.4)             | 31 (13.5)                        | .144   |
| **Mild**                         | 23 (17.8)             | 27 (11.8)                        | .114   |
| **Moderate/severe**              | 2 (1.6)               | 4 (1.7)                          | 1.000  |
| Diabetes                         | 47 (36.6)             | 89 (38.9)                        | .649   |
| With end-organ damage            | 37 (28.7)             | 56 (24.5)                        | .381   |
| Hemiplegia                       | 3 (2.3)               | 5 (2.2)                          | 1.000  |
| Moderate/severe renal disease    | 41 (31.8)             | 86 (37.6)                        | .273   |
| Chronic hemodialysis             | 29 (22.5)             | 62 (27.1)                        | .338   |
| Solid tumor without metastasis   | 2 (1.6)               | 5 (2.2)                          | 1.000  |
| Leukemia                         | 0                    | 0                                | —      |
| Lymphoma                         | 0                    | 0                                | —      |
| Metastatic solid tumor           | 5 (3.9)               | 8 (3.5)                          | 1.000  |
| HIV                              | 5 (3.9)               | 7 (3.1)                          | .679   |
| AIDS                             | 3 (2.3)               | 2 (0.9)                          | .261   |
| Charlson comorbidity index       | 2 (1–5)               | 3 (1–5)                          | .303   |
| Intravenous drug use             | 25 (19.4)             | 29 (12.7)                        | .088   |
| Prior hospitalization (90 d)     | 48 (37.2)             | 97 (42.4)                        | .341   |
| Prior IV vancomycin (90 d)       | 31 (24.0)             | 51 (22.3)                        | .704   |
| Prior MRSA infection (1 y)       | 26 (20.2)             | 28 (12.2)                        | .044   |
| **Clinical data**                |                       |                                  | .011   |
| Admitted from:                   | 98 (76.0)             | 146 (63.8)                       | .017   |
| Home                             | 20 (15.5)             | 68 (29.7)                        | .003   |
| Transferred from another hospital | 11 (8.5)              | 15 (6.6)                         | .489   |
| Weight, kg                       | 75 (66.8–87.5)        | 76.9 (65.1–91.6)                 | .541   |
| Creatinine clearance, e,f mL/min  | 72.9 (49.2–98.1)      | 56.5 (33.2–89.2)                 | .009   |
| Acute kidney injury g            | 34 (26.4)             | 84 (36.7)                        | .046   |
| APACHE II score h                | 13 (8–19)             | 20 (15–27)                       | <.001  |
| Neutropenia i                    | 0                    | 1 (0.4)                          | 1.000  |
| **Infection data**               |                       |                                  | .834   |
| Vancomycin MIC, i mg/L           |                       |                                  |        |
| 2                                | 50 (38.8)             | 96 (41.9)                        |        |
| 1                                | 78 (60.5)             | 131 (57.2)                       |        |
| ≤0.5                             | 1 (0.8)               | 2 (0.9)                          |        |
| Polymicrobial BSI                | 0                    | 16 (7.0)                         | .001   |
| **BSI source**                   |                       |                                  | .008   |
| Endovascular                     | 20 (15.5)             | 64 (27.9)                        |        |
| Infective endocarditis           | 20 (15.5)             | 54 (23.6)                        | .070   |
Vancomycin + Cefepime for MRSA BSI • OFID • 5

of patients experiencing BSI durations ≥7 days. Although a larger proportion of patients in the vancomycin + cefepime group experienced 30-day mortality, this difference did not persist after accounting for clinical factors influencing mortality risk, such as age, infection source, and severity of illness. Care was also taken to ensure that the reduced BSI duration in

Table 1. Continued

| Covariate                                | Vancomycin* (n = 129) | Vancomycin + Cefepime* (n = 229) | PValue |
|------------------------------------------|------------------------|----------------------------------|--------|
| Other endovascular                       | 0                      | 11 (4.8)                         | .009   |
| Intra-abdominal                          | 0                      | 1 (0.4)                          | 1.000  |
| Lower respiratory tract                  | 6 (4.7)                | 72 (31.4)                        | <.001  |
| Bone/joint                               | 30 (23.3)              | 23 (10.0)                        | .001   |
| Invasive prosthetic device               | 7 (5.4)                | 13 (5.7)                         | .921   |
| Skin/soft tissue                         | 39 (30.2)              | 37 (16.2)                        | .002   |
| CNS abscess                              | 5 (3.9)                | 4 (1.7)                          | .293   |
| Intravenous catheter                     | 24 (18.6)              | 49 (21.4)                        | .529   |
| Urinary                                  | 3 (2.3)                | 6 (2.6)                          | 1.000  |
| Unknown                                  | 10 (7.8)               | 23 (10.0)                        | .472   |
| Treatment data                           |                        |                                  |        |
| Infectious diseases consult              | 103 (79.8)             | 197 (86.0)                       | .128   |
| Source control pursued                   | 57 (44.2)              | 80 (34.9)                        | .084   |
| Vancomycin TDM target                    |                        |                                  | .015   |
| Trough concentration 15–20 mg/L          | 115 (89.1)             | 181 (79.0)                       |        |
| AUC 400–600 mg·h/L                      | 14 (10.9)              | 48 (21.0)                        |        |
| Cefepime dose, mg                        |                        |                                  |        |
| 1000                                     | —                      | 120 (52.4)                       |        |
| 2000                                     | —                      | 109 (47.6)                       |        |
| Cefepime dose interval                   |                        |                                  |        |
| Every 6 h                                | 2 (0.9)                |                                  |        |
| Every 8 h                                | 95 (41.5)              |                                  |        |
| Every 12 h                               | —                      | 52 (22.7)                        |        |
| Every 24 h                               | 62 (27.1)              |                                  |        |
| Post-hemodialysis                        | 18 (7.9)               |                                  |        |
| Inpatient vancomycin duration, d         | 6 (4–10)               | 5 (4–9)                          | .071   |
| Inpatient cefepime duration (n = 229), d | —                      | 3 (2–4)                          | —      |
| Switched to daptomycin                   | 36 (27.9)              | 70 (30.6)                        | .597   |
| Switched to cefotaxime                    | 8 (6.2)                | 25 (10.9)                        | .139   |
| Switched to linezolid                    | 8 (6.2)                | 13 (5.7)                         | .839   |
| Switched to alternative anti-MRSA therapy before day 5 | 8 (6.2) | 22 (9.6) | .264 |
| Total duration inpatient antibiotics, d  | 9 (5–18)               | 9 (6–13.5)                       | .335   |
| Outcomes                                 |                        |                                  |        |
| Microbiologic failure                    | 49 (38.0)              | 58 (25.3)                        | .012   |
| BSI duration ≥7 d                        | 40 (31.0)              | 43 (18.8)                        | .008   |
| 60-d MRSA BSI recurrence                 | 15 (11.6)              | 19 (8.3)                         | .302   |
| 30-d mortality                           | 10 (7.8)               | 47 (20.5)                        | .002   |
| LOS post–BSI onset, d                    | 4 (3–7)                | 3 (2–5.5)                        | .003   |
| Vancomycin-associated nephrotoxicity*    | 7 (5.4)                | 12 (5.2)                         | .940   |
| Neurotoxicity attributed to antibiotic(s)* | 0                    | 1 (0.4)                          | 1.000  |
| Clostridium difficile infection*          | 2 (1.6)                | 8 (3.5)                          | .341   |

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; AUC, area under the concentration time curve; BSI, bloodstream infection; CNS, central nervous system; IV, intravenous; LOS, length of stay; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant Staphylococcus aureus; TDM, therapeutic drug monitoring.

*Data presented as number (percentage) or median (interquartile range).

**Mild liver disease defined as chronic hepatitis without cirrhosis.

***Severe liver disease defined as portal hypertension or cirrhosis.

†Moderate/severe renal disease defined as chronic kidney disease stage 3 or greater or receiving chronic dialysis.

⊥Calculated using the Cockroft-Gault formula using actual body weight for body mass index <30 and adjusted body weight for body mass index >30.

‡At time of index MRSA blood culture.

§Automated susceptibility testing performed by Microscan or Phoenix.

*Vancomycin-associated nephrotoxicity defined as a serum creatinine increase of 0.5 mg/L and 50% from baseline on 2 consecutive measurements from initial vancomycin dose to 72 hours after the last dose.

†Neurotoxicity defined as seizure, encephalopathy, or altered mental status specifically attributed to vancomycin and/or cefepime by treating physician(s).

‡Clostridium difficile infection defined as signs/symptoms along with positive laboratory test at least 48 hours after initiation of study antibiotics.
the vancomycin + cefepime group was not due to the differential mortality in the combination group through cause-specific and subdistribution hazard models designed to account for this competing risk.

These data contribute to a growing body of clinical evidence that receipt of concomitant vancomycin and β-lactam antibiotics in patients with MRSA BSI improves BSI clearance and may improve microbiologic outcome. This includes a pilot randomized controlled trial of vancomycin + flucloxacinil and multiple small observational cohort studies of vancomycin in combination with various β-lactams [18–20]. Like the currently published observational studies, the β-lactam combination therapy in this present study was not given with the intent of providing synergy against MRSA but to provide broad-spectrum coverage. Although this diminishes the ability to measure the potential impact of a purposeful vancomycin + β-lactam combination therapy approach, it provides evidence that the in vitro synergy between vancomycin and β-lactams translates into patients. The present study advances knowledge of vancomycin + β-lactam combination therapy in 2 important ways. First, it focuses on cefepime, whereas previous studies included a heterogenous group of β-lactams, making it difficult to surmise which β-lactams confer benefit. Second, it accounts for the differential mortality risk typically seen in combination patients, which could otherwise be posited as a potential explanation for the observed shortened BSI duration with combination therapy (i.e., combination patients may have had shorter BSI durations because they were more likely to die before clearance of BSI could occur or be confirmed).

Although vancomycin + cefepime combination therapy improved MRSA BSI clearance, this does not indicate that cefepime should be the β-lactam of choice for directed MRSA BSI combination regimens. In vitro data coupled with pilot data of flucloxacinil suggest that antistaphylococcal penicillins and cefazolin can likely be used with vancomycin for directed MRSA BSI synergy [14–16, 18]. This would limit the potential unnecessary collateral damage that may come with the expanded gram-negative spectrum of cefepime. However, if a vancomycin + β-lactam approach is to be implemented, cefepime may be an ideal candidate for empiric therapy, provided that the institution's gram-negative antibiogram permits. Because it is usually 24 hours before staphylococci are identified and often an additional 24–48 hours to detect methicillin resistance, MRSA-directed combination therapy may be delayed. Considering the importance of the initial 48 hours of therapy in *Staphylococcus aureus* bloodstream infection mortality, it would be ideal to provide empiric synergy [29–31]. In situations where empiric vancomycin + cefepime is already warranted, cefepime would satisfy the synergistic β-lactam role in patients ultimately found to have MRSA BSI. Upon isolation of *Staphylococcus aureus* or MRSA, cefepime could be switched to antistaphylococcal penicillin or cefazolin. If ongoing gram-negative coverage were required, synergy could be provided by continuing cefepime without the need to add a second β-lactam.

There are a number of considerations to bear in mind when interpreting these findings. Most importantly, the intention of the concomitant cefepime therapy was to provide either empiric or directed coverage of gram-negative organisms rather than synergy against MRSA. As such, it is unclear what the impact of purposeful vancomycin + β-lactam therapy would have been. This fact also resulted in considerable selection bias between

### Table 2. Multivariable Logistic Regression for Factors Independently Associated With Microbiologic Failure

| Variable                        | OR (95% CI)     | Adjusted OR (95% CI) |
|---------------------------------|-----------------|----------------------|
| Vancomycin + cefepime           | 0.554 (0.348–0.881) | 0.488 (0.271–0.841)  |
| Endovascular source             | 3.215 (1.930–5.356) | 3.321 (1.925–5.730)  |
| African American                | 2.542 (1.306–4.948) | 2.121 (1.064–4.228)  |
| Unknown source                  | 0.297 (0.102–0.868) | 0.360 (0.118–1.102)  |
| Invasive prosthetic device source | 2.004 (0.805–4.986) | —                    |
| Intravenous drug use            | 1.943 (1.072–3.523) | —                    |
| Bone/joint source               | 1.519 (0.826–2.791) | —                    |
| Chronic hemodialysis            | 1.484 (0.896–2.457) | —                    |
| Acute kidney injury             | 1.404 (0.875–2.253) | —                    |
| Lower respiratory tract source  | 0.487 (0.263–0.901) | —                    |

Hosmer-Lemeshow goodness-of-fit test: *P* = .335; variance inflation factor 1–5 for all variables included at model entry.

Abbreviations: CI, confidence interval; OR, odds ratio.

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Figure 1. Comparison of efficacy outcomes between patients receiving vancomycin or vancomycin + cefepime. Abbreviation: BSI, bloodstream infection.
the treatment groups, with vancomycin + cefepime patients having a substantially higher baseline mortality risk. Although various statistical techniques were used to account for this, the extraordinarily disproportionate mortality risk between treatment groups may have precluded our ability to observe a potential mortality benefit with combination therapy. Although no studies to date have demonstrated improved in hard outcomes with vancomycin + β-lactam combination therapy for MRSA BSI, the known link between prolonged BSI and mortality make it reasonable to hypothesize that there is some benefit to a combination approach [32, 33]. Whether the effect size of this benefit is large enough to be feasibly measured in a clinical trial or is clinically meaningful is unknown. We did not observe increased adverse drug reactions in the combination group to indicate that the risk of combination may outweigh the potential benefit. However, it should be noted that this analysis was not specifically designed or powered to fully evaluate safety.

It is also important to note that the study population was derived from a single health system in Southeastern Michigan, which may limit the external generalizability of the findings. In particular, the MRSA strain epidemiology and practice pattern may differ from other sites, and it is unclear how this could have influenced the findings. The automated susceptibility testing MIC results from the hospital clinical microbiology laboratory did not indicate a difference in vancomycin susceptibility between the treatment groups. However, the Microscan platform used for the majority of the study period is known to consistently overcall vancomycin MIC relative to nonautomated broth microdilution [34, 35]. This likely explains the large proportion of isolates with a vancomycin MIC of 2 mg/L in this study; this limited our ability to fully control for phenotype. Finally, because only a small proportion of the patients were monitored by vancomycin AUC, we were unable to control for vancomycin exposure [36]. Given the fact that AUC-guided dosing was more common in the vancomycin + cefepime group and is associated with reduced vancomycin dose and exposure, it is implausible that AUC-guided dosing would explain the improved BSI clearance observed in the combination patients [28, 37].

In conclusion, cefepime given concomitantly during the first 72 hours of vancomycin therapy was associated with improved MRSA BSI clearance. Although the cefepime was not given with the intention of providing synergy against MRSA, these data lend further support to the notion that vancomycin + β-lactam therapy may be a potential avenue to improve treatment outcomes of MRSA BSI. Although further study evaluating the impact of purposeful vancomycin + β-lactam therapy for MRSA BSI is needed before widespread clinical implementation, this study suggests that cefepime can be used as the β-lactam component of synergistic vancomycin + β-lactam regimens when empiric or directed gram-negative coverage is desired.

### Table 4. Proportional Hazards Models for Bloodstream Infection Clearance

| Variable                        | Hazard Ratio (95% CI) | P-Value |
|---------------------------------|-----------------------|---------|
| Cause-specific hazard model     |                       |         |
| Vancomycin + cefepime          | 1.408 (1.125–1.762)   | .003    |
| Endovascular source             | 0.542 (0.418–0.703)   | <.001   |
| Subdistribution hazard model    |                       |         |
| Vancomycin + cefepime          | 1.264 (1.040–1.536)   | .019    |
| Endovascular source             | 0.569 (0.457–0.708)   | <.001   |

Abbreviation: CI, confidence interval.

*Based on the results of the cause-specific model, only vancomycin + cefepime and endovascular were included in the model.

### Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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### Potential conflicts of interest

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