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Major Article

Comparison of clinical outcomes and risk factors in polymicrobial versus monomicrobial enterococcal bloodstream infections

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Background: Enterococcal bloodstream infections (EBSIs) are frequently polymicrobial but scant data describe the outcomes and risk factors of polymicrobial EBSI. This study describes the outcomes and risk factors of polymicrobial versus monomicrobial EBSI.

Methods: In this single-center, retrospective, matched cohort study, patients with polymicrobial EBSI were matched 1:1 to patients with monomicrobial EBSI by age ± 10 years, EBSI source, Pitt bacteremia score, and enterococcal species. Conditional logistic regression was performed to determine independent predictors of 30-day mortality and polymicrobial EBSI.

Results: In 142 matched pairs, 30-day mortality was 18.3% versus 21.1% ($P = .551$) in monomicrobial and polymicrobial EBSI, respectively. In multivariable analysis, recent chemotherapy/radiation (adjusted odds ratio [OR], 4.799; 95% confidence interval [CI], 1.814-12.696), chronic renal disease (aOR, 2.310; 95% CI, 1.176-4.539), and Pitt bacteremia score (aOR, 1.399; 95% CI, 1.147-1.706) were associated with 30-day mortality. Recent chemotherapy/radiation (aOR, 2.770; 95% CI, 1.016-7.551), and recent antibiotic exposure (aOR, 1.892; 95% CI, 1.157-3.092) were positively associated with polymicrobial EBSI, whereas chronic hemodialysis was negatively associated (aOR, 0.496; 95% CI, 0.29-81).

Conclusions: Overall, polymicrobial EBSI were not independently associated with mortality. Risk factors for, and the clinical implications of, polymicrobial EBSI should be further studied to inform clinical management and improve outcomes.

Health care-associated infections (HAIs) are a growing public health concern in the United States. The National Healthcare Safety Network reported approximately 70,000 HAIs from more than 2,000 reporting institutions and enterococci were the second most common pathogen, accounting for 14% of HAIs. Moreover, enterococci have become an increasingly common cause of central line-associated bloodstream infections.[1] Collectively, *Enterococcus faecalis* and *Enterococcus faecium* are the second leading cause of central line-associated bloodstream infection.[1] This is especially concerning given the growing prevalence of vancomycin resistance, with 82.6% and 9.5% of *E faecium* and *E faecalis* bloodstream isolates demonstrating vancomycin resistance, respectively.[1] Considering the adverse clinical consequences of antibiotic resistance coupled with the rising prevalence, enterococcal bloodstream infections (EBSIs) have become a public health threat with regard to morbidity, mortality, and costs of care.[2,3]

Another important feature of EBSI is their proclivity to be polymicrobial in nature. Although the incidence of polymicrobial EBSI varies depending on the study population, available literature suggest upward of 25% of EBSI are polymicrobial.[3-5] Furthermore, enterococci are frequently reported as copathogens in polymicrobial bloodstream infection (BSI), present in up to 50% of cases.[6] Studies

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demonstrate worse outcomes among patients with polymicrobial BSI relative to monomicrobial BSI in both adults and children.[7-9] Mortality in those with polymicrobial BSI was approximately 2-fold those with monomicrobial BSI in some reports.[10] However, these studies used a heterogeneous group of monomicrobial BSI as a comparator by including BSI due to a variety of bacterial and fungal pathogens. To date, a focused and thorough evaluation of outcomes and risk factors associated with polymicrobial EBSI relative to monomicrobial EBSI has not been conducted. Such data would better characterize the clinical influence of polymicrobial EBSI and inform the clinical management of these patients given the tremendous burden of EBSI in the health care setting.[3] Therefore, we performed a retrospective, matched cohort study of patients with polymicrobial versus monomicrobial EBSI with the following objectives: compare 30-day mortality between those with poly- and monomicrobial EBSI and investigate potential risk factors associated with polymicrobial EBSI.

METHODS

This was a retrospective, matched cohort study conducted at the Detroit Medical Center from January 2010-July 2014. The study was reviewed and approved by the institutional review board at Wayne State University. Adult patients aged 18-99 years with 1 or more blood cultures positive for enterococci who received antimicrobial treatment for EBSI for at least 72 hours were included.[11] Patients with indwelling hardware or prosthesis as the primary EBSI source were excluded. Polymicrobial EBSI were defined as at least 1 nonenterococcal bacterial species isolated from the same blood culture as the *Enterococcus* spp and meeting Centers for Disease Control and Prevention criteria for BSI. Common skin contaminant organisms (eg, coagulase-negative staphylococci and viridans group streptococci) were considered pathogens only when present in 2 or more consecutive blood cultures drawn from separate blood draws.[11] Patients with polymicrobial EBSI were matched 1:1 to those with monomicrobial EBSI on the following criteria: age ± 10 years, source of EBSI, Pitt bacteremia score ≥ 4 or < 4, and enterococcal species.[12]

Data were extracted from patients' medical records retrospectively and managed using Research Electronic Data Capture (Vanderbilt University, Nashville, TN) hosted at Wayne State University.[13] Data elements included patient demographic characteristics, comorbid conditions (eg, liver disease, malignancy, diabetes mellitus, renal disease, decubitus ulcer, and HIV), and clinical characteristics such as corticosteroid use, surgery or trauma during the preceding 30 days, prior hospitalization in the preceding year, intensive care unit admission, recent antimicrobial exposure in the preceding 90 days, and current antimicrobial therapy. Current antimicrobial therapy was classified as empiric, defined as therapy employed before release of antibiotic susceptibility results, or definitive, defined as therapy given after release of antibiotic susceptibility results.[14] Severity of illness and comorbidity were quantified using the Pitt bacteremia score and Charlson comorbidity index (CCI), respectively.[12,15]

The source of bacteremia was defined at the diagnosing physician's discretion, with the exception of objective, criteria-based definitions for infective endocarditis[16] and osteomyelitis.[17] In cases where no clear EBSI source was identified, the source was classified as unknown.[11] Microbiologic data were obtained from the electronic medical record. Enterococcal BSI were classified as either hospital-onset, defined as an index enterococcal isolate cultured ≥ 48 hours after admission, or community onset. Community-onset BSI were further categorized as health care-associated on the following criteria: intravenous medication therapy in clinic or home care setting, hospitalization for ≥ 48 hours during the past 90 days, or residence in a nursing home or long-term-care facility.[11]

The primary outcome was 30-day mortality defined as death from any cause within 30 days from the date of index EBSI isolate. Secondary outcomes included in-hospital mortality; length of stay post-EBSI calculated from date of index EBSI isolate; composite clinical failure defined as presence of 1 or more of 30-day mortality, persistence of BSI > 7 days,[18] and recurrence of EBSI within 60 days of the cessation of EBSI therapy;[19] and switch in EBSI therapy due to physician-described clinical failure.

Statistical analysis

Categorical variables were compared by Pearson χ^2 or Fisher exact test and continuous/ordinal variables were compared by Student *t* test or Mann-Whitney *U* test, where appropriate. The primary analysis compared outcomes of interest between patients with poly- and monomicrobial EBSI. Secondary analysis examined patient baseline and clinical characteristics associated with polymicrobial infection. Following initial bivariate comparisons, backward-conditional multivariable logistic regression was conducted to determine independent predictors of 30-day mortality and polymicrobial EBSI. Variables associated with the outcome or exposure of interest at a P value ≤ .2 with biologic plausibility were included in the multivariable models. The Hosmer-Lemeshow goodness-of-fit test was used to assess the fitness of the model. For 2-tailed tests, a P value < .05 was considered to be statistically significant.

Following the a priori primary analysis, a post hoc stratified subgroup analysis was conducted to explore for potential moderating/confounding variables. The cohort was unmatched and stratified by variables independently associated with monomicrobial or polymicrobial EBSI in the multivariable analysis. The incidence of 30-day mortality was compared between monomicrobial and polymicrobial EBSI within the subgroups.

A sample size of 274 was determined a priori based on the primary end point of 30-day mortality, assuming 20% mortality in the monomicrobial,[20] and 30% in the polymicrobial group for a statistical power of 80% and 2-sided alpha of 0.05. All calculations were performed using SPSS Statistics software version 22.0 (IBM-SPSS Inc, Armonk, NY).

RESULTS

A total of 715 patients at the Detroit Medical Center had EBSI from January 2010-July 2014. Of these, 284 patients were matched and included in the analysis (Fig 1). The mean ± standardized deviation age of the study population was 63 ± 14.9 years, 48.9% were men, and 78.9% were African American. The median (interquartile range) CCI, and Pitt bacteremia score were 7 (5-8) and 3 (3-4), respectively. Of the 284 matched patients, 38% had hospital-onset EBSI; the remaining 175 were community-onset infections, with 64% being health care-associated. The primary sites of EBSI were intravascular catheter related 38.7%, gastrointestinal tract 16.9%, skin and soft tissue 16.9%, urinary tract 15.5%, unknown 7.7%, and infective endocarditis 4.2%.

The most common enterococcal species isolated was *E faecalis* (69.7%) with 39.9% of these being vancomycin-resistant, followed by *E faecium* (29.6%), with 84.5% being vancomycin-resistant. The most common copathogens identified among those with polymicrobial EBSI were coagulase-negative staphylococci (23.6%), followed by *Staphylococcus aureus* (14.6%), and *Escherichia coli* (11.2%). A complete description of other polymicrobial BSI copathogens is listed in Supplemental Table S1.

The overall 30-day mortality was 19.7%. The outcomes of patients with poly- and monomicrobial EBSI are displayed in Table 1. No significant difference in 30-day mortality was observed between