American Journal of Infection Control 44 (2016) 47-9

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major article

# Comparison of outcomes between patients with single versus multiple positive blood cultures for *Enterococcus*: Infection versus illusion?

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*Key Words:*
Bloodstream infection
Contamination
Enterococci
Inpatient mortality

Enterococci represent one of the most common causative pathogens of bloodstream infections (BSIs). There is debate in the literature regarding the clinical importance of single versus multiple positive blood cultures for *Enterococci*. This single-center retrospective study found that patients with multiple positive blood cultures experienced increased inpatient mortality and a shorter median survival. Additionally, BSIs >6.7 days resulted in approximately 20% increased mortality. These results are preliminary and require further exploration.



According to the National Healthcare Safety Network's report, enterococci represent one of the most common causes of health care–associated infections, accounting for >15% of central line–associated bloodstream infections.[1] Enterococcal bloodstream infections (EBSIs) occur in patients with substantial comorbidities and are associated with high mortality.[2-5] The Centers for Disease Control and Prevention surveillance definition for bloodstream infection (BSI) requires only a single positive blood culture from a recognized pathogenic organisms.[6] There is debate regarding the clinical relevance of a single positive blood culture, as reports have documented that 10%-15% of cases, including enterococci, may be secondary to contamination.[7-9] The current study aimed to evaluate the importance of one positive blood culture for enterococci by comparing outcomes between patients with single versus multiple positive blood cultures treated for EBSI.

This was a retrospective cohort study of patients diagnosed and treated for EBSIs at the Detroit Medical Center from 2010-2014. Patients were included if there was at least one positive blood culture for *Enterococcus* spp. and received at least 72 hours of therapy directed toward the isolated organism. Study sites included did not provide primary care for patients with solid organ or bone marrow transplant, or those with active cancer. Sample size was determined *a priori* to detect a 15% difference in all-cause inpatient mortality among one versus multiple cultures at a power of 80% and an $\alpha$ of 0.05 to be 236 cases. Variables collected from the electronic medical record included patient demographics, clinical characteristics, and outcomes (eg, length of stay, length of bacteremia, all-cause and infection-attributable inpatient mortality). Hospital-onset BSI was defined as isolation of enterococci after at least 48 hours of admission.[10] Microbiologic data (eg, *Enterococcus* spp, *in vitro* susceptibility) were also collected. Mortality was attributed to enterococcal infection if blood cultures were positive for enterococci at time of death, if death occurred in the setting of active clinical infection with enterococci, or as determined by treating physician. Univariate analysis was performed to determine differences in clinical characteristics between patients with one versus multiple positive enterococcal blood cultures. A multivariable Cox proportional hazard model was used to examine variables independently associated with inpatient mortality. Classification and regression tree analysis was performed to discover a potential

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Previous presentation: These data were presented at the 25th European Congress of Clinical Microbiology and Infectious Diseases, April 2015, Copenhagen, Denmark.

Conflicts of interest: MJR received grant support from Cubist, Cepheid, Cerexa, Forest, Durata, NIH, and Michigan Department of Community Health, has served as a consultant to Cubist, Forest, and Cepheid, served on speaker's bureau for Cubist, Novartis, Forest, and Theravance. KCC, EJZ, AML has no conflicts of interest to report.


http://dx.doi.org/10.1016/j.ajic.2015.08.002

**Table 1**
Unadjusted and adjusted hazard ratios for inpatient mortality

| Factor (n = 446) | Unadjusted hazard ratios (95% CI) | Adjusted hazard ratios (95% CI) |
|---|---|---|
| Charlson score | 1.20 (1.11-1.31) | 1.16 (1.06-1.27) |
| Pitt bacteremia score | 1.18 (1.03-1.45) | 1.31 (1.11-1.29) |
| >1 culture | 1.68 (1.02-2.76) | 1.89 (1.13-3.16) |
| *Enterococcus faecium* | 1.16 (0.71-1.91) | — |
| ICU admission | 1.45 (0.75-2.78) | — |
| Hemodialysis | 1.78 (1.09-2.89) | — |
| Liver disease | 1.32 (0.71-2.43) | — |
| Chemotherapy-radiation | 2.81 (1.46-5.42) | 2.43 (1.20-4.91) |
| Vancomycin resistance | 1.11 (0.68-1.83) | — |
| Unknown source | 2.43 (1.35-4.36) | — |

NOTE. Variables entered in Cox regression model based on univariate analysis with $P < .10$ or *a priori* clinical relevance. Adjusted hazard ratios for variables included in the final model.
*CI*, confidence interval; *ICU*, intensive care unit.

exploratory breakpoint in length of EBSI (days) associated with increased inpatient mortality. All statistical analysis was performed with SPSS version 21.0 (IBM, Armonk, NY).

There were 535 cases of EBSI from 2010-2014: 446 were included in the analysis, and 214 (47.9%) had one positive blood culture for enterococci. By univariate analysis there were no significant differences in patient characteristics, such as age, neutropenia (Absolute neutrophil count < 500/μL), or previous health care exposure Supplemental Table. Single cultures were more often isolated from patients with skin as the primary source of infection (20.6% versus 7.3%, $P = .003$), whereas infective endocarditis had more cases of multiple positive blood cultures (3.3% versus 12.6%, $P = .004$). The median Pitt bacteremia score was 3 (interquartile range [IQR], 3-4 versus IQR, 3-5, respectively), and the median Charlson score was 7 (IQR, 5-8 versus IQR, 5-9, respectively). Patients with one positive blood culture more frequently had hospital-onset EBSI (51.9% versus 38.4%, $P = .012$), vancomycin resistance (56.1% versus 40.9%, $P = .001$), or *E faecium* isolated (41.1% versus 23.8%, $P < .001$). There were 165 patients (36.9%) who had polymicrobial blood cultures, with no difference between those with one versus multiple positive blood cultures (36.9% versus 37.2%, $P = .945$). Additionally, there was no difference in the isolation of skin flora (7.5% versus 10.0%, $P = .355$). Infectious diseases was consulted in a similar proportion of patients (76.2% versus 78.4%, $P = .747$), as was the performance of source control (34.6% versus 40.3%, $P = .240$). Length of stay in patients with one positive culture was significantly longer (17 days; IQR, 10-30 days versus 14 days; IQR, 9-25 days; $P = .043$), but there was no difference in post-EBSI length of stay.

Inpatient all-cause mortality was 14.6% and was not significantly different between patients with one versus multiple positive blood cultures (12.5% versus 17.2%, $P = .158$). Of those experiencing inpatient mortality, infection-attributable mortality was significantly lower among patients with one positive blood culture (23.1% versus 51.3%, $P = .039$). On univariate analysis of all-cause survivors versus nonsurvivors, Charlson score, Pitt bacteremia score, intensive care unit admission, multiple positive blood cultures, hemodialysis, receipt of chemotherapy or radiation (30 days), *E faecium*, and vancomycin resistance were all associated with inpatient mortality ($P < .01$). Only 4 variables remained in the Cox regression model (Table 1), including multiple positive blood cultures. Adjusted analysis demonstrated a decreased median inpatient survival for patients with multiple positive blood cultures (65 ± 7.9 versus 82 ± 8.6 days) (Fig 1). In the exploratory classification and regression tree analysis, inpatient mortality was approximately 20% higher among patients with >6.7 days of bacteremia; however, the terminal node size was small (n = 11).

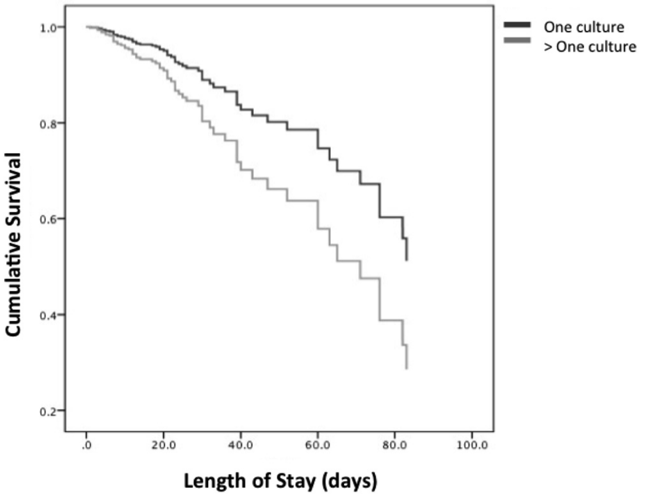


**Fig 1.** Cox regression 90-day survival analysis.

To our knowledge, this is the first analysis to demonstrate a difference in outcomes between patients with one versus multiple positive blood cultures for enterococci. A recent retrospective analysis of patients with one versus multiple positive blood cultures did not demonstrate a difference in inpatient mortality.[9] There was nearly a 2-fold increased risk of inpatient mortality through adjusted survival analysis. Additionally, infection-attributable mortality was significantly higher in patients with multiple positive cultures. Previous studies have not examined infection-attributable mortality or survival analysis, which may contribute to our unique results. Despite the differences in outcomes, the retrospective nature of this study limited the ability to discern whether this disparity is caused by a larger proportion of contamination among patients with a single positive culture. In particular, the ability to ensure that patients have 2 blood cultures taken simultaneously with daily serial blood cultures would strengthen the capacity to ensure these inferences. Additionally, there is limited ability to ensure that patients with multiple positive blood cultures had these cultures drawn from separate anatomical sites. Finally, the population included in the analysis consisted primarily of patients who were not immunocompromised, which aids in internal validity, but may limit external validity. The small number of patients with coisolation of skin flora also negated our ability to complete a separate subgroup analysis of outcomes as done by Freeman et al.[7] Of additional interest is the increase in mortality among patients with EBSI >6.7 days. However, this finding should be interpreted with caution given that it occurred at a small terminal node size.

## SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ajic.2015.08.002

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