Research Square

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Management of Enterococcal Catheter-associated Bloodstream Infections in Patients with Cancer

Hesham Awadh
The University of Texas Health Science Center at Houston
Anne-Marie Chaftari (achaftari@mdanderson.org)
The University of Texas MD Anderson Cancer Center
Melissa Khalil
The University of Texas MD Anderson Cancer Center
Johnny Fares
The University of Texas MD Anderson Cancer Center
Ying Jiang
The University of Texas MD Anderson Cancer Center
Rita Deeba
The University of Texas MD Anderson Cancer Center
Shahnoor Ali
The University of Texas MD Anderson Cancer Center
Ray Hachem
The University of Texas MD Anderson Cancer Center
Issam Raad
The University of Texas MD Anderson Cancer Center

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Abstract

Objective

Enterococcus species are the third most common organisms causing central line-associated bloodstream infections (CLABSIs). The management of enterococcal CLABSI, including the need for and timing of catheter removal, is not well defined. We therefore conducted this study to determine the optimal management of enterococcal CLABSI in cancer patients.

Methods

We reviewed data for 542 patients diagnosed with *Enterococcus* bacteremia between September 2011 to December 2018. After excluding patients without an indwelling central venous catheter, we classified the remaining 397 patients into 3 groups: Group 1 consisted of patients with CLABSI with mucosal barrier injury (MBI), Group 2 included patients with either CRBSI or CLABSI without MBI, and Group 3 consisted of patients who did not meet the CDC criteria for CLABSI. The impact of early (< 3 days after bacteremia onset and late (3–7 days) catheter removal was compared. The composite primary outcome included absence of microbiologic recurrence, 90-day infection-related mortality, and 90-day infection-related complications.

Results

Among patients in Group 2, those whose catheters were removed within 3 days of bacteremia onset was associated a better overall outcome than those whose catheters were removed later between days 3 to 7 (success rate 88% vs 63%). However, those who had catheters retained beyond 7 days had a similar successful outcome than those who had early catheter removal. Early CVC removal in in non-CLABSI cases (group-3) was not associated with higher success rates.

Conclusion

If removal of central venous catheters is clinically indicated in patients with enterococcal CLABSI earlier removal in less than 3 days may be associated with better outcomes.

Background

Although *Enterococcus* species are the third most common cause of central line–associated bloodstream infections (CLABSIs), the optimal management of these infections remains unclear (1). The incidence of *Enterococcus* bacteremia is increasing in the oncologic patient population, where it is emerging as an important nosocomial infection (2). *Enterococcus* species have a high affinity to form biofilms, which contributes to their virulence, antibiotic resistance, and ability to attach to medical devices and cause

device-related infections including CLABSI (3). The best strategy for catheter management in patients with enterococcal CLABSI is yet to be fully determined; the current guidelines recommend removal of long-term catheters when possible, with the option to use antibiotic lock therapy if the catheter must be retained (4). However, studies evaluating the impact of catheter removal have been sparse and limited by small sample sizes and usually the lack of a comparator group, particularly in the oncologic patient population. Thus, our primary objective was to evaluate the management of *Enterococcus* species bloodstream infections (BSIs) and their outcomes in cancer patients by comparing patients with CLABSI to those with non-CLABSI infections.

Methods

Study design and case definitions

This was a retrospective cohort study. Using our infection control team's database, we identified 872 episodes of enterococcal bacteremia (positive blood cultures for *Enterococcus* species) at MD Anderson Cancer Center between September 2011 and December 2018. We included adult cancer patients with a first episode of enterococcal bacteremia diagnosed in the presence of a central venous catheter (CVC) that had been in place for at least 48 hours prior to the onset of bacteremia. We excluded 330 patients with polymicrobial bacteremia, with no indwelling CVC at the onset of index bacteremia, or with a CVC placed less than 48 hours before onset. We classified the patients with bacteremia into CLABSI or non-CLABSI groups according to the Centers for Disease Control's definition of CLABSI (5). We further divided the CLABSI group into a CLABSI with mucosal barrier injury (MBI) subgroup and a CLABSI non-MBI subgroup. MBI was defined as the presence of either of the following criteria: 1) neutropenia with an absolute neutrophil count of < 500 cells/mm^3 on 2 separate days within 3 days of bacteremia diagnosis; 2) in a patient who received a hematopoietic stem cell transplant (HSCT) within 1 year of the positive blood culture, the presence of either grade III or IV gastrointestinal graft-versus-host disease or severe diarrhea of ≥ 1 L in a 24-hour period within the 7 days prior to the positive blood culture (5).

In addition, we identified the cases that met the criteria for catheter-related bloodstream infections (CRBSI) according to the Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection (4). We analyzed 3 groups of patients: group 1 (G1) included patients whose bacteremia met the definition of CLABSI with MBI (considered as possible CLABSI); G2 included patients who had either CRBSI or CLABSI without MBI (considered as definite CRBSI); and G3 included patients with non-CLABSI who had a CVC in place but likely had bacteremia from another source.

Data extraction and study outcomes: The protocol was approved by our Institutional Review Board and a waiver of informed consent were obtained prior to the conduct of the study.

Patient data were extracted from our institution's electronic medical records system (Epic). We collected data on patient demographics, underlying malignancy, neutropenic status, and risk factors for infection.

Microbiological data collected included date and source of positive blood cultures, bacterial species, phenotypic susceptibility pattern, and status of colonization with vancomycin-resistant enterococci (VRE). We recorded all the antibacterial agents that were used to treat the bacteremia starting from the date of positive blood culture and for the subsequent 2-week period. CVC management (removal or retention) was evaluated at 2 time intervals: early (within 72 hours bacteremia onset and late (at 3 to 7 days). CVCs that were removed after 7 days were considered to have been retained. The three-day cut off was chosen to mimic the clinical scenario where some time is elapsed between blood collection and organism identification. Patients were followed for 3 months after the onset of the index bacteremia, until lost to follow-up, or until death, whichever occurred first.

Clinical and microbiological outcomes were determined as follows. Clinical resolution was defined as defervescence within 72 hours. Microbiologic eradication was defined as resolution of the bacteremia within 96 hours. Recurrence of the bacteremia during the follow-up period was identified by positive blood cultures with isolates that shared a similar phenotypic antimicrobial susceptibility pattern to that of the baseline isolate. Infection-related complications included the occurrence of deep-seated infection, such as infective endocarditis, thrombophlebitis, or osteomyelitis, during follow-up. We collected all-cause mortality and infection-related mortality data. Death was attributed to enterococcal bacteremia based on the clinical impression of the treating physicians and available clinical data. A successful overall outcome was a composite of: absence of infection-related complications, absence of infection-related mortality, and absence of microbiological recurrence within 90 days. Patients who died within 7 days of onset of index bacteremia and patients who received antibiotic catheter lock therapy were excluded from the outcome analyses.

Statistical analysis (pending)

We used the χ^2 test or Fisher exact test to compare categorical variables, as appropriate. To compare continuous variables, we used the Kruskal-Wallis test for 3-group comparisons and Wilcoxon rank sum test for 2-group comparisons. If a significant result ($P < .05$) was detected for a test that compared 3 groups, then pairwise comparisons were performed, with α levels adjusted using Holm's sequential Bonferroni adjustment to control the type I error. A multivariate logistic regression model was used to identify factors that were independently associated with mortality. All tests were 2-sided, with a significance level of 0.05, except pairwise comparisons with the α adjustment. The statistical analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC).

Results

The final analysis included 397 patients, with 132 patients in G1 (CLABSI with MBI), 101 patients in G2 (CLABSI without MBI and CRBSI), and 164 in G3 (non-CLABSI) (Table 1). Patients in G1 (98%) were more likely than those in G2 (79%) and G3 (71%) to have hematologic malignancies (both *P* values < .0001). The rate of neutropenia was significantly higher in G1 (96%) than in G3 (52%) and G2 (15%) (all *P* values < .0001). Significantly more patients in G2 (45%) and G1 (37%) were HSCT recipients than in G3 (23%)

(G1 vs G3: *P* = .007; G2 vs G3: *P* < .001). There were no statistically significant differences in the number of admissions to the intensive care unit (ICU) among the 3 groups. In terms of microbiological characteristics, significantly more patients had *E. faecalis* isolates in G2 (62%) than in G3 (46%) (G2 vs G3: *P* = .01) or G1 (31%) (G1 vs G3: *P* = .01; G1 vs G2: *P* < .0001), whereas *E. faecium* isolates were identified in significantly more G1 patients (64%) than in G2 (37%, *P* < .0001) or G3 (48%, *P* = .004) patients. Patients in G1 also had a significantly higher rate of bacteremia caused by VRE than did patients in G3 (43% vs 29%, *P* = .016). Rates of VRE colonization were similar among the 3 groups.

Fifty-five percent of CVCs were removed in G2 patients, compared to 48% in G1 and 36% in G3; the difference between G2 and G3 was significant (*P* < .001). Similarly, early CVC removal (within 72 hours of bacteremia onset) was more common in G2 than in G3 (33% vs 20%, *P* < .01). There were no statistically significant differences among the 3 groups in all-cause mortality or infection-related mortality within 90 days of index bacteremia onset or in microbiologic recurrence within 90 days of microbiologic resolution (Table 1).

In group 1, early CVC removal in less than three days was associated with a better overall outcome compared to late removal between 3–7 days (78% vs 67%), but with a similar outcome than catheter retention. In group 2, there was a trend for a better overall outcome for early CVC removal in less than three days compared to late removal between 3–7 days (63% vs 88%) but again with a similar outcome for catheter retention. Early CVC removal was not associated with a higher success rate in group-3. (Table – 2).

Compared to patients with *E. faecalis* bacteremia, patients with *E. faecium* bacteremia had significantly higher rates of infection-related mortality (16% vs 2%; *P* < .0001) and all-cause mortality (57% vs 34%; *P* < .0001). Similarly, compared to those with non-VRE bacteremia, patients with VRE bacteremia had significantly higher all-cause mortality (53% vs 40%; *P* = .018) and infection-related mortality (17% vs 6%; *P* = .0004) rates and a significantly lower rate of microbiological eradication at 96 hours (59% vs 73%; *P* = .008). However, multivariate logistic regression analysis determined that higher mortality was independently associated with the isolation of *E. faecium* (odds ratio [OR], 2.38; 95% CI, 1.54 to 3.68; *P* < .0001) and ICU admission (OR, 3.66; 95% CI, 2.11 to 6.34; *P* < .0001). After adjusting for these factors, VRE infection was no longer associated with mortality (*P* = .53).

Discussion

To our knowledge, this is the largest study of enterococcal CLABSI in cancer patients and the first to have fully defined comparator groups. The predominance of *E. faecalis* isolates in G2 (patients with documented CRBSI and CLABSI without MBI) could be attributable to the superior capability of *E. faecalis* to form biofilms (6). From the data at hand it is difficult to make a definitive determination of the value of early catheter removal, however early catheter removal in less than 3 days was consistently associated with a better overall outcome than late catheter removal between 3–7 days in the CLABSI cases represented by group-1 and group-2, but not in group-3. Surprisingly, CVC retention was associated with a

high success rate in all three groups. Catheters could have been retained in more clinically stable cases which could explain the high success rate with catheter retention. Unfortunately, the rationale behind the decision to remove or retain the catheter was not available. Potential benefit of removal of CVC in the context of enterococcal CLABSI can be inferred from available literature, albeit with limited data and small sample sizes.

Sandoe et al. (7) evaluated treatment outcomes in 61 cases of enterococcal CRBSI. Cure was achieved in 40 of 48 (83%) episodes managed with CVC removal but only 5 of 13 (38%) episodes in which the CVC was retained (and patients received combined antimicrobial therapy including an active cell wall-acting agent and an aminoglycoside). The study did not address the timing of catheter removal. Despite the study's small sample size, the authors concluded that catheter removal resulted in higher cure rates and that combination therapy is needed if the CVC is to be retained (7).

Reigadas et al. (8) retrospectively examined 75 episodes (in 73 patients) of enterococcal CRBSI, focusing on patient characteristics and risk factors. They concluded that the high mortality rate observed in patients with enterococcal CRBSI required a better therapeutic approach (8).

In a retrospective review, Marschall et al. (9) compared outcomes of patients with retained CVCs to those who underwent CVC removal in a cohort of 111 patients with enterococcal CLABSI. They found that in-hospital crude mortality, 30-day mortality, and 90-day mortality were all associated with catheter retention, although they did not specify the time interval in which the catheters were removed. In addition, that study lacked a comparator group (9).

Enterococcus species are generally considered to be of low virulence, so the previously reported association of enterococcal infections with higher mortality and a poor prognosis could be due to the association of these infections with malignancy and ["other"?] chronic comorbid conditions (16, 17). In our current study, harboring an isolate displaying vancomycin resistance was associated with higher infection-related and all-cause mortality, attributed by multivariate analysis to isolation of *E. faecium* and hospitalization in a critical-care setting. The poor outcomes of VRE BSIs were reported in a retrospective review of 7128 adult and pediatric patients who had received their first HSCT. Multivariable models showed that VRE-BSI was associated with higher non-relapse mortality and lower overall survival (18). In our present study, most VRE isolates were found in G1 (CLABSI with MBI), which also happened to have a higher VRE colonization rate (Table 1). The majority of our VRE isolates speciated into *E. faecium* (90%). While the emergence of *E. faecium* as a pathogen with poorer outcomes than *E. faecalis* has been well reported in the literature (19), in our cohort, the poor outcomes may have been associated with its resistance to vancomycin.

Our study was limited by its retrospective nature, particularly in that the indications for CVC management were not consistently documented. The decision to remove the CVC was also based on the decision of the treating physician, with no clear pattern or time frame and often without a documented rationale and irrespective of clinical status at point of removal Another limitation is that some patients had missing data for some variable and were therefore excluded in the final analysis. This reduced the number of

cases and impacted the statistical significance of our data. We also depended on phenotypic susceptibility pattern to identify recurrent isolates, use of more accurate methods was not possible given the retrospective nature of the study (physical samples no longer available).

Conclusion

If CVC removal is clinically mandated in cases of enterococcal CLABSI, early removal in less than 3 days may be associated with better outcomes. Early CVC removal in non-CLABSI cases was not associated with better outcomes. Further prospective data are needed to determine the best therapeutic approach.

Declarations

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Author Contributions:

H.A. Designed the study, data collection, interpretation of the data and writing of the manuscript

A.M.C Designed the study, interpretation of data, and revised the manuscript

M.K. Performed data collection and revising the manuscript

J.F. Performed data collection and revising the manuscript

Y.J. Analyzed and interpreted the data

R.D. Performed data collection and revising the manuscript

S.A. Performed data collection and revising the manuscript

R.H. Designed the study, interpretation of data, and revised the manuscript

I.I.R Designed the study, interpretation of data, and revised the manuscript

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Conflicts of Interest:

None

Availability of data and materials

The data that support the findings of this study are not publicly available. Participants signed a waiver of informed consent that does not prohibit sharing of data. De-identified data could be made available upon reasonable request and with permission of the MD Anderson Institutional Review Board. Please contact Anne-Marie Chaftari, M.D. (achaftari@mdanderson.org) or Ying Jiang (yijiang@mdanderson.org) for de-identified data requests.

Ethical Approval:

This study was approved by the MD Anderson Cancer Center Institutional Review Board. Waiver of informed consent was obtained and waived by the MD Anderson Cancer Center Institutional Review Board. All experiment methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that they have no competing interests

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Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1ThreegroupcomparisonAMCAug312020.xlsx
- Table2Cathetermanagementforeachgroup.xlsx