

Catheter removal versus retention in the management of catheter-associated enterococcal bloodstream infections

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BACKGROUND: Enterococci are an important cause of central venous catheter (CVC)-associated bloodstream infections (CA-BSI). It is unclear whether CVC removal is necessary to successfully manage enterococcal CA-BSI.

METHODS: A 12-month retrospective cohort study of adults with enterococcal CA-BSI was conducted at a tertiary care hospital; clinical, microbiological and outcome data were collected.

RESULTS: A total of 111 patients had an enterococcal CA-BSI. The median age was 58.2 years (range 21 to 94 years). There were 45 (40.5%) infections caused by *Enterococcus faecalis* (among which 10 [22%] were vancomycin resistant), 61 (55%) by *Enterococcus faecium* (57 [93%] vancomycin resistant) and five (4.5%) by other *Enterococcus* species. Patients were treated with linezolid (n=51 [46%]), vancomycin (n=37 [33%]), daptomycin (n=11 [10%]), ampicillin (n=2 [2%]) or quinupristin/dalfopristin (n=2 [2%]); seven (n=6%) patients did not receive adequate enterococcal treatment. Additionally, 24 (22%) patients received adjunctive gentamicin treatment. The CVC was retained in 29 (26.1%) patients. Patients with removed CVCs showed lower rates of in-hospital mortality (15 [18.3%] versus 11 [37.9]; P=0.03), but similar rates of recurrent bacteremia (nine [11.0%] versus two (7.0%); P=0.7) and a similar post-BSI length of hospital stay (median days [range]) (11.1 [1.7 to 63.1 days] versus 9.3 [1.9 to 31.8 days]; P=0.3). Catheter retention was an independent predictor of mortality (OR 3.34 [95% CI 1.21 to 9.26]).

CONCLUSIONS: To the authors' knowledge, the present article describes the largest enterococcal CA-BSI series to date. Mortality was increased among patients who had their catheter retained. Additional prospective studies are necessary to determine the optimal management of enterococcal CA-BSI.

Key Words: Bacteremia; Central venous catheter; Enterococcus; Management

Enterococci are the third most frequent cause of nosocomial bloodstream infections, constituting 9.4% to 11.1% of the pathogens recovered in two large United States studies (1,2). They also rank as the third most frequent bacterial cause of catheter-associated bloodstream infections (CA-BSI) (3). Clinical isolates most commonly belong to one of two subspecies, *Enterococcus faecalis* and *Enterococcus faecium* (4). Biofilm formation has been observed more frequently both in device-related bloodstream infections due to *E faecalis* (5) and *E faecium* (6) when compared with other sources of infection or commensal enterococci, respectively. It has, therefore, been suggested as a marker of virulence. Biofilm formation also decreases local antimicrobial susceptibility (7,8). Because eradication of an established biofilm from an indwelling device is difficult to

Le retrait ou le maintien du cathéter dans la prise en charge des bactériémies liées à un cathéter

HISTORIQUE : Les entérocoques constituent une cause importante de bactériémies liées à un cathéter veineux central (CVC). On ne sait pas s'il est nécessaire de retirer le CVC pour réussir la prise en charge de ce type de bactériémie.

MÉTHODOLOGIE : Les auteurs ont mené une étude rétrospective de cohorte de 12 mois auprès d'adultes ayant une bactériémie liée à un CVC dans un hôpital de soins tertiaires. Ils ont colligé des données cliniques, des données microbiologiques et des données d'issue.

RÉSULTATS : Au total, 111 patients étaient atteints d'une bactériémie à entérocoque liée à un CVC. Ils avaient un âge médian de 58,2 ans (plage de 21 à 94 ans). Les chercheurs ont constaté 45 infections (40,5 %) causées par l'*Enterococcus faecalis* (dont 10 [22 %] résistantes à la vancomycine), 61 infections (55 %) causées par l'*Enterococcus faecium* (dont 57 [93 %] résistantes à la vancomycine) et cinq (4,5 %) causées par d'autres espèces d'*Enterococcus*. Les patients ont été traités au linézolide (n=51 [46 %]), à la vancomycine (n=37 [33 %]), à la daptomycine (n=11 [10 %]), à l'ampicilline (n=2 [2 %]) ou à la quinupristine-dalfopristine (n=2 [2 %]). Sept patients (n=6 %) n'ont pas reçu de traitement convenable contre les entérocoques. De plus, 24 patients (22%) ont reçu un traitement d'appoint à la gentamicine. Vingt-neuf patients (26,1 %) ont conservé leur CVC. Les patients à qui on l'avait retiré présentaient des taux de mortalité hospitalière plus faibles (15 [18,3 %] par rapport à 11 [37,9]; P=0,03), mais des taux similaires de bactériémie récurrente (neuf [11,0 %] par rapport à deux (7,0 %); P=0,7) et une durée d'hospitalisation similaire après la bactériémie (jours médians [plage]) (11,1 [1,7 à 63,1 jours] par rapport à 9,3 [1,9 à 31,8 jours]; P=0,3). Le maintien du cathéter était un prédicteur indépendant de mortalité (RRR 3,34 [95 % IC 1,21 à 9,26]).

CONCLUSIONS : En autant que le sache les auteurs, le présent article décrit la plus grosse série de bactériémies liées à un CVC. La mortalité était plus élevée chez les patients qui conservaient leur cathéter. D'autres études prospectives s'imposent pour déterminer la prise en charge optimale de la bactériémie à entérocoque liée à un CVC.

achieve, some experts recommend removing catheters in the setting of enterococcal bloodstream infection (9). However, enterococcal CA-BSI as a separate entity have been infrequently investigated (10-12) and the recommendation to remove the catheter is based on the findings of a single retrospective study (11). On the other hand, there are disadvantages to catheter replacement including material and procedural costs, and potential adverse events related to the insertion procedure.

The aim of the present study was to examine the epidemiology, treatment and subsequent outcomes of patients with enterococcal CA-BSI, comparing patients with retained versus removed catheters. Our hypothesis was that catheter management does not affect patient outcomes.

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METHODS

Setting

Barnes-Jewish Hospital (BJH), a 1250-bed teaching hospital, is the largest hospital in Missouri (USA), and has a referral base that includes the St Louis Metropolitan area, eastern Missouri and western Illinois. It houses all medical specialties, including a stem cell transplantation unit. BJH is affiliated with the Washington University School of Medicine (St Louis, Missouri, USA).

Study design

A retrospective cohort study of patients with enterococcal CA-BSIs during their hospital stay was performed. CA-BSI was defined as enterococcal bacteremia in a patient with a central venous catheter (CVC) in place for at least 48 h and no alternative source of infection. The hospital's medical informatics database was queried for blood cultures positive for any *Enterococcus* species; this dataset was merged with a manually collected dataset of CVC usage in the hospital, which is part of the hospital infection control database.

Inclusion and exclusion criteria

Adult patients admitted to BJH between January 1, 2006 and December 31, 2006, who presented with, or developed, an enterococcal bloodstream infection and had a CVC present at the time of detection of this infection were included. All types and locations of CVCs were included. Blood cultures were obtained during routine care either peripherally and/or from the CVC. Patients who presented to the hospital with a CVC already in place were included. Patient history and physical examination as well as admitting diagnosis and microbiology results were reviewed to determine whether the catheter was the primary focus of the bacteremia. Patients with a primary focus of bacteremia other than the catheter, patients with a CVC in place for <48 h, and patients who died on the day of the positive blood culture were excluded. Polymicrobial infections were included except concurrent *Staphylococcus aureus* bacteremia or candidemia within ± 3 days of the enterococcal bacteremia (n=20) because both entities are established indications for catheter removal.

Data collection

Demographic characteristics, medical history, clinical presentation, diagnostic and therapeutic procedures, antibiotic treatment and key markers of outcome (recurrence of bloodstream infection, length of hospital stay after the bloodstream infection, crude mortality) were abstracted from the medical records. Admission Charlson comorbidity and McCabe severity of illness scores were determined. Duration of catheter retention time after the bacteremia was recorded. Information on antibiotic lock therapy was collected; however, this treatment modality was not used in patients from this cohort.

Postdischarge mortality at both 30 days and three months after bacteremia was obtained from the Social Security Death Index (www.sssi-search.com).

Definitions

Renal insufficiency was defined by a serum creatinine level >132.6 $\mu\text{mol/L}$. Sepsis and sepsis-induced hypotension were defined using established criteria (13). Appropriate therapy was defined as pathogen-directed treatment with antibiotics matching susceptibilities. A catheter was considered to be retained if it was present for the duration of the hospitalization after the first positive blood culture. Recurrence of bacteremia (used here synonymously with intermittent bacteremia) was defined as a second positive blood culture after ≥ 1 negative blood culture and an interval of ≥ 1 day during their hospitalization. Community-onset enterococcal bloodstream infection was defined as having the first positive blood culture drawn within 48 h of hospital admission.

Data analysis and statistical methods

Data entry was performed using Access and Excel (Microsoft Corporation, USA). Data analysis was performed using SPSS 17 (IBM

Corporation, USA). Univariate comparisons among categorical variables and outcome measures were performed using the χ^2 test or Fisher's exact test. A two-sided $P < 0.05$ was considered to be statistically significant. Also calculated was the absolute difference in proportion (Δ_p) of rates of outcome measures including the 95% CI of this difference to describe the precision of this point estimate. Analysis of the difference in proportions and 95% CI enabled the interpretation of statistical significance (if the 95% CI did not cross zero) as well as clinical significance (if the upper limit of the 95% CI exceeded a pre-defined difference). An absolute difference in recurrence of bacteremia and mortality rates of 15% was considered to represent a clinically significant difference; this estimate was chosen based on previous literature regarding catheter management and clinical experience (14,15). Comparisons among continuous independent variables were performed using the Student's *t* test or Mann-Whitney U test as appropriate. Variables found to have $P < 0.1$ in univariate testing were considered for entry into a forward, stepwise multivariate logistic regression model.

The study was approved by the Washington University Human Research Protection Office (#07-0690).

RESULTS

Demographics, comorbidities and clinical presentation

There were 111 patients with enterococcal CA-BSI who met inclusion criteria. The mean (\pm SD) age was 58.2 ± 15.3 years; 56 (50.5%) patients were male; and 77 (69.4%) were white. There were 36 (32%) patients admitted to the oncology/bone marrow transplant service. The most frequent comorbidities were malignancies (n=62 [55.9%]), diabetes (n=35 [31.5%]) and renal insufficiency (n=31 [27.9%]). Twenty-five (22.5%) patients had metastatic solid tumours, 28 (25.2%) had leukemia, six (5.4%) had lymphomas and three (2.7%) had non-metastatic solid tumours. There were 20 (18%) patients who were neutropenic at the time of bloodstream infection. Of all bloodstream infections, 90 (81%) were hospital-acquired. None of the patients were diagnosed with infective endocarditis during the admission.

Microbiology

Of the enterococcal bloodstream infections, 45 (40.5%) were caused by *E faecalis* and 61 (55.0%) by *E faecium*. Of the bacteremias caused by *E faecalis*, 10 (22.2%) were due to vancomycin-resistant isolates while 57 (93.4%) of the bacteremias caused by *E faecium* were vancomycin resistant. An additional five (4.5%) infections were caused by other *Enterococcus* species. A total of 37 patients (33.3%) had polymicrobial infections in which the most common polymicrobial organism was coagulase-negative *Staphylococcus* (n=26 [23.4%]). There were 24 (34.9%) polymicrobial *E faecalis* bacteremias and 10 (27.0%) polymicrobial *E faecium* bacteremias. Additionally, there was no difference in polymicrobial bacteremias among patients who had their catheter removed versus retained (28 [34.1%] versus nine [31.0%]; $P=0.8$).

Vancomycin-susceptible *E faecalis* caused 30 (36.6%) of 82 infections in which catheters were removed during the hospitalization and five (17.2%) of 29 infections in which they were retained ($P=0.09$). Vancomycin-resistant *E faecium* (VRE) caused 42 (51.2%) of infections in which catheters were removed and 15 (51.7%) in which they were retained ($P=0.9$). Overall, there was no difference in the number of vancomycin-resistant isolates regardless of whether a catheter was removed (49 of 82 [59.8%] versus 18 of 29 [62.1%]; $P=1.0$). Of the 26 patients who died during hospitalization, 19 (73.1%) had vancomycin-resistant enterococcal bacteremia.

Antibiotic treatment

Patients were treated most frequently with linezolid (n=51 [45.9%]) or vancomycin (n=37 [33.3%]). Smaller subsets were given daptomycin (n=11 [9.9%]), ampicillin (n=2 [1.8%]) or quinupristin/dalfopristin (n=2 [1.8%]). Of the seven (6.3%) patients who did not receive adequate enterococcal treatment, five had their catheter removed

TABLE 1
Comparison of characteristics of patients with enterococcal catheter-associated bloodstream infections managed with catheter removal versus catheter retention during hospitalization

Variable	Catheter		P
	Removed (n=82)	Retained (n=29)	
Demographics and clinical characteristics			
Age, years, mean \pm SD	58.7 \pm 15.6	56.6 \pm 14.7	0.52
Charlson comorbidity index score, mean \pm SD	3.1 \pm 3.0	3.4 \pm 3.4	0.58
McCabe severity score, mean \pm SD	2.0 \pm 0.82	1.8 \pm 0.76	0.29
Service on admission			
General internal medicine	29 (35.4)	10 (34.5)	0.93
Oncology/bone marrow transplant	25 (30.5)	11 (37.9)	0.46
Comorbidities			
Malignant tumour	46 (56.1)	16 (55.2)	0.93
Diabetes mellitus	27 (32.9)	8 (27.6)	0.59
Renal insufficiency (Cr >132.6 μ mol/L)	22 (26.8)	9 (31.0)	0.66
Metastatic solid tumour	18 (22.0)	7 (24.1)	0.81
Sepsis	71 (86.6)	25 (86.2)	1.00
Sepsis-induced hypotension	28 (34.1)	12 (41.4)	0.49
Multiorgan dysfunction	7 (8.5)	1 (3.4)	0.68
Neutropenic at time of positive blood culture	17 (20.7)	3 (10.3)	0.27
Microbiology			
<i>Enterococcus faecalis</i>	37 (45.1)	8 (27.6)	0.10
<i>E faecalis</i> , vancomycin resistant	7 (8.5)	3 (10.3)	0.72
<i>Enterococcus faecium</i>	44 (53.7)	17 (58.6)	0.64
<i>E faecium</i> , vancomycin resistant	42 (51.2)	15 (51.7)	0.87
Polymicrobial bacteremia	28 (34.1)	9 (31.0)	0.76
VRE detection in stool (tested in n=100)	41/82 (50.0)	17/29 (58.6)	0.42
Treatment			
Duration of antibiotic treatment, days, mean \pm SD	10.8 \pm 8.4	7.5 \pm 6.0	0.06
Adjunctive gentamicin treatment	19 (23.2)	5 (17.2)	0.50

Data presented as n (%) unless otherwise indicated. Cr Creatinine; VRE Vancomycin-resistant *Enterococcus faecium*

during the admission. In addition to one of the antibiotics above, 24 (21.6%) patients received adjunctive treatment with gentamicin. Due to discharge or in-hospital mortality, the mean duration of in-hospital antibiotic treatment was limited to 10.0 \pm 8.0 days. Data regarding postdischarge antibiotics were not collected.

Catheter management

The CVC was retained during the hospitalization in 29 (26.1%) patients. In univariate analysis, patients with removed CVCs were similar to patients whose CVC was retained (Table 1).

In terms of outcomes, however (Table 2), patients with removed CVCs showed both lower in-hospital mortality (15 [18.3%] versus 11 [37.9%]; Δ_p =16% [95% CI 2% to 39%]; P=0.03), and lower 30-day mortality (21 [25.6%] versus 13 [44.8%]; Δ_p =16% [95% CI -0.2% to 39%]; P=0.05). In contrast, rates were similar in patients who had their CVC removed or retained for recurrent bacteremia (nine [11.0%] versus two [7.0%]; Δ_p =4% [95% CI -14% to 12%]; P=0.7), median (range in days) post-bacteremia length of hospital stay (11.1 [1.7 to 63.1 days] versus 9.3 [1.9 to 31.8 days]; Δ_p =1.8 days [95% CI -2.1 to 5.6 days]; P=0.31) and three-month mortality (32 [39.0%] versus 15 [51.7%]; Δ_p =10% [95% CI -8% to 32%]; P=0.2).

TABLE 2
Comparison of outcome measures of patients with enterococcal catheter-associated bloodstream infections managed with catheter removal versus catheter retention during hospitalization

Outcome measure	Catheter, n (%)		P	Δ_p *, %	95% CI†
	Removed (n=82)	Retained (n=29)			
Recurrence of enterococcal bloodstream infection	9 (11.0)	2 (7.0)	0.72	4	(-14% to 12%)
In-hospital crude mortality	15 (18.3)	11 (37.9)	0.03	16	(2% to 39%)
Mortality within 30 days of the first positive culture	21 (25.6)	13 (44.8)	0.05	16	(-0.2% to 39%)
Mortality within three months of the first positive culture	32 (39.0)	15 (51.7)	0.23	10	(-8% to 32%)

* Δ_p represents the difference in proportions between the two catheter management groups; †The 95% CI represents the precision of this estimate by describing statistical significance (95% CI does not cross 0) as well as clinical significance (the upper bound of the 95% CI exceeds the predetermined 'clinically significant' change in outcome rates of 15%)

Risk factors for mortality

A number of risk factors for mortality were identified in univariate analyses (Table 3). Patients who had VRE detected in stool were more likely to die in the hospital (19 of 58 [32.8%] versus five of 42 [11.9%] with negative VRE screening; P=0.02), as were those with *E faecium* bloodstream infection (18 of 61 [29.5%] versus eight of 50 [16.0%] with other enterococcal species; P=0.09), and patients managed with CVC retention (11 of 29 [37.9%] versus 15 of 82 [18.3%] in whom the CVC was removed; P=0.03).

These three factors – VRE colonization, *E faecium* bloodstream infection and catheter retention – were entered in a multivariate model using logistic regression. The analysis showed that VRE colonization (OR 3.19 [95% CI 1.02 to 10.01]) and catheter retention (OR 3.34 [95% CI 1.21 to 9.26]) were independently associated with in-hospital mortality.

DISCUSSION

Removal of an intravascular catheter is, with few exceptions, considered to be an essential part of managing CA-BSI. However, robust data to support this approach are only available for a limited number of pathogens responsible for these infections. Despite the lack of sufficient data to provide an evidence-based recommendation with regard to CA-BSI caused by *Enterococcus* species, national guidelines recommend removing the involved catheters (9). To our knowledge, the present study represents the largest investigation into catheter management and outcomes of enterococcal bloodstream infections.

The main finding of the present study was increased mortality in patients whose catheters were retained during the hospitalization. Our findings suggest that catheter removal should be considered to improve patient survival. Also, the difference in the two outcome proportions exceeded the predetermined clinically meaningful difference of 15%, which gives us a quantitative estimate of the impact of catheter removal. The patient groups were very similar with respect to demographic characteristics and comorbidities, including adjunctive antibiotic treatment with the aminoglycoside gentamicin. These findings are congruent with the single study encountered in the scientific literature that scrutinized outcomes of enterococcal CA-BSI and specifically investigated catheter management, albeit in a smaller number of

TABLE 3
Risk factors for hospital mortality in patients with enterococcal catheter-associated bloodstream infections (CA-BSI)

Variable	Died (n=26)	Survived (n=85)	P	OR (95% CI)
Age, years, mean ± SD	59.0±17.3	57.9±14.8	0.8	
Male sex	13 (50.0)	43 (50.6)	1.0	
Body mass index, kg/m ²	29.9 (9.0)	28.4 (7.2)	0.4	
Comorbidities				
Charlson comorbidity index score, mean ± SD	4.3±4.5	2.8±2.4	0.1	
Malignant tumour	15 (57.7)	44 (51.8)	0.6	
Diabetes mellitus	11 (42.3)	24 (28.2)	0.2	
Renal insufficiency (Cr >132.6 µmol/L)	9 (34.6)	22 (25.9)	0.4	
Metastatic solid tumour	5 (19.2)	20 (23.5)	0.6	
Sepsis	24 (92.3)	72 (84.7)	0.5	
Sepsis-induced hypotension	14 (53.8)	26 (30.6)	0.03	
Multiorgan dysfunction	6 (23.1)	2 (2.4)	0.002	
Development of neutropenia	7 (26.9)	19 (22.4)	0.6	
Neutropenic at time of positive blood culture	3 (11.5)	17 (20.0)	0.4	
Hospital-acquired CA-BSI	23 (88.5)	67 (78.8)	0.4	
Recurrence of enterococcal bloodstream infection	5 (19.2)	6 (7.1)	0.1	
Microbiology				
<i>Enterococcus faecalis</i>	8	37	0.2	
<i>E faecalis</i> , vancomycin-resistant	2	8	1.0	
<i>Enterococcus faecium</i>	18	43	0.09	1.37 (0.48-3.90)
<i>E faecium</i> , vancomycin-resistant	17	40	0.1	
Polymicrobial bacteremia	7 (26.9)	30 (35.7)	0.4	
VRE detection in stool, n/n (%) (tested in n=100)	19/24 (79.2)	39/76 (51.3)	0.02	3.19 (1.12-10.01)
Treatment				
Catheter retained	11 (42.3)	18 (21.2)	0.03	3.34 (1.21-9.26)
Duration of antibiotic treatment, days, mean ± SD	9.2±7.4	10.2±8.2	0.6	
Adjunctive gentamicin treatment	8 (30.8)	16 (18.8)	0.2	

Data presented n (%) unless otherwise indicated. Cr Creatinine; VRE Vancomycin-resistant *E faecium*

patients (11). There, the authors retrospectively examined 61 enterococcal CA-BSI, with 82% of the episodes due to *E faecalis* and polymicrobial infections found in 18% of the study population. Of note, they did not exclude patients with concurrent *Staphylococcus aureus* or yeast bloodstream infections, although these infections likely guided catheter management significantly more than the detection of enterococci. Sandoe et al (11) evaluated whether successful treatment of a bloodstream infection was possible without removal of the catheter, which was achieved in five of 13 cases (38%). If the catheter was removed, the chance for cure was higher (40 of 48 [83%]). They found a combination of a cell wall-active agent with an aminoglycoside to be significantly more effective than monotherapy when the catheter was retained. The authors concluded that, although the removal of the catheter was performed in the majority of cases, it did not appear to be a necessary part of the management as long as antimicrobial treatment was optimized. In our study, even though we did not set cure as an end point, 67 (81.7%) of 82 patients with catheters removed survived the hospital admission and 61 (74.4%) survived at 30 days postbacteremia. These rates were much lower for patients with retained catheters. In summary, these data suggest that although enterococcal CA-BSI are

not an absolute indication for catheter removal, removal should be favoured over catheter retention.

Reasons for catheter retention may have been that the treating physicians of patients who were severely ill at the time of enterococcal bloodstream infection were reluctant to remove the catheter because it was essential for nonantibiotic medications; that the patients had limited options for alternative intravenous access; or that their comorbidities increased the risk of catheter removal and replacement. Catheter management may have been driven by reasons other than the infection alone, and removing the catheter could have been a lower priority or higher risk in the patients' overall medical management. Because we collected crude mortality data, it is also conceivable that patients died from causes not related to the CA-BSI. Of note, we did not observe a difference in recurrence of infection depending on catheter management; it is possible that the size of the cohort prevented us from noting a statistically significant difference.

Our patients are notable for a high percentage of comorbid conditions, including metastatic solid tumours (23%) and leukemia (25%); accordingly, the crude in-hospital mortality rate was high in our study population. An independent factor associated with death was the detection of VRE in the stool, which may be a marker for frequent health care exposure. Despite this finding, CA-BSIs with vancomycin-resistant *E faecium* did not result in increased mortality compared with non-VRE infections. This is different from an earlier prospective study and a more recent meta-analysis, in which vancomycin resistance was found to be associated with increased mortality (16,17). Most likely, we could not replicate this association due to the small sample size. However, the association of VRE colonization with mortality has been demonstrated previously in a cohort of bone marrow transplant patients (18).

Limitations of the present study include its retrospective design, the fact that the diagnosis of recurrent infection depended on the treating physician ordering blood cultures and that postdischarge outcomes, including completion of planned antibiotic therapy, follow-up blood cultures, and catheter removal postdischarge, were not studied. In addition, catheter management is potentially influenced by other reasons for retention (difficulty of finding alternative access, bleeding diathesis) and we did not report outcomes for different catheter types. Finally, changes in the usage of daptomycin and linezolid have occurred since the time of the study. Although this was the largest study of enterococcal CA-BSI to date, it is still a relatively small sample to detect rare outcomes.

CONCLUSIONS

Based on our study findings, catheter removal is preferable to retention in patients with enterococcal CA-BSI. A large prospective or multicentre study should be performed to identify patients at highest risk for mortality and to add strength to our results.

DECLARATIONS: None of the following authors has a conflict of interest to declare: J Marschall, ML Piccirillo, J Doherty. VJ Fraser is a consultant for Merck and Member of the Speakers' Bureau for Pfizer, Merck and Cubist Pharmaceuticals. DK Warren is a consultant for 3M Healthcare and Cardinal Health, and receives research funding from Sage Products Inc, Cubist Pharmaceuticals and 3M Healthcare.

AUTHORS' CONTRIBUTIONS: JM and DKW devised the study; JAD generated the query based on the Medical Informatics and Infection Control databases; VJF assisted in study design; JM and MLP collected and analyzed the data, and wrote the manuscript; all authors critically reviewed the final draft of the manuscript.

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