Vol 11|Issue 2| 2022 | 20-26.

e-ISSN 2248 - 9169
Print ISSN 2248 - 9150

International Journal of
Experimental Pharmacology

www.ijepjournal.com

INFECTIONS CAUSED BY ENTEROCOCCI FROM CENTRAL LINES IN CANCER PATIENTS

Dr Minakshi Mitra, Dr Bala N*

Assistant Professor, Department of Physiology, Gouri Devi Institute of Medical Sciences and Hospital, Durgapur, West Bengal India.

ABSTRACT

Infections associated with central lines are caused by Enterococcus species in the third most common way. Whether and when catheters should be removed in enterococcal CLABSI are not well defined. Our study was therefore designed to determine how best to manage enterococcal CLABSI in cancer patients. Methods : An analysis was conducted of data collected from 542 patients with Enterococcus bacteremia. Our remaining 397 patients were divided into three groups, after we excluded patients with a central venous catheter (CVC) without bacteremia, those with polymicrobial bacteremia, and those with central venous catheter placement within 48 hours of onset of bacteremia. A catheter-related bloodstream infection (CRBSI) is defined as a bloodstream infection that occurs in a catheter. The catheter-related bloodstream infection (CLABSI) is defined as an infection that occurs in either one of the two groups. The International Society of Infectious Diseases (IDSA) has developed guidelines for diagnosing and treating intravascular catheter-related infections (CLABSI). Patients who don't meet the CDC's definition of CLABSI are placed in Group 3 (G3). A comparison was conducted between early and late CVC removal (* 3 days after bacterial infection onset). Comprised of absence of microbiologic recurrence, infection-related mortality over 90 days, and infection-related complications over 90 days, these were the composite primary outcomes. A trend towards better overall outcomes was observed among patients in G2 whose CVCs were removed within 3 days of bacteremia onset (success rate: 88%), as opposed to those who had them removed between days 3 and 7 (success rate: 63%). Nevertheless, the success rate for those who retained CVCs beyond 7 days was similar to that of those who removed CVCs within 3 days (92% vs. 88%). Those who retained their catheters longer (> 7 days) reported higher success rates than those who removed the catheters sooner (93% vs. 67%, $p = 0.003$). When CVCs were retained (withdrawal > 7 days) in non-CLABSI cases (G3), the success rate was significantly higher than when they were removed early (< 3 days) (90% vs. 64%, $p = 0.006$). Enterococcal bacteraemia is challenging to manage with a catheter. A less than 3 day CVC removal may positively affect outcomes when it is clinically indicated for patients with enterococcal CLABSI. Based on our data, we cannot determine whether increased outcomes are associated with earlier removal of CVCs for patients with enterococcal CLABSI whose CVCs are clinically indicated. A lower success rate was associated with catheter retention as opposed to insertion. This aspect of the procedure needs further study.

Keywords: Acute Bloodstream Infection Associated with Central Lines, Enterococci, Bacteremia.

Corresponding Author
Dr Bala N

Email: balanew0809@gmail.com

INTRODUCTION

CLABSIs caused by enterococci are becoming more and more common and can have poor outcomes, especially for oncology patients. There is still a lot of work to be done in determining the best catheter management protocol for such infections.

BACKGROUND

The optimal management of central line–associated bloodstream infections (CLABSIs) remains unclear despite Enterococcus species being the third most common cause [1]. It is becoming increasingly common to encounter Enterococcus bacteremia in oncology patients, The infections are now emerging as significant nosocomial infections [2]. Several Enterococci species are well suited to forming biofilms, which in turn makes them virulent, resistant to antibiotics, and capable of attaching to medical devices and causing infections such as CLABSI [3]. Current guidelines recommend removing long-term central venous catheters when possible, with antibiotic lock therapy available when necessary if the CVC must be retained. However, an optimal management strategy for enterococcal CLABSI is still to be established. Study evidence of the benefit of CVC removal is, however, sparse, limited by small sample sizes, and often lacking a comparator group, especially in cancer patients. Hence, our primary goal was to compare the outcomes of cancer patients with CLABSI versus those with non-CLABSI in terms of how Enterococcus species bloodstream infections (BSIs) are managed.

METHODS

STUDY DESIGN

An analysis of retrospective cohorts was conducted. We found 542 cases of enterococcal bacteremia (positive blood cultures for the species Enterococcus) Patients with cancer *10 years of age who were diagnosed with enterococcal bacteremia in the presence of a CVC that had been in place for at least 48 hours prior to bacteremia were included in the study. Our study excluded patients who had polymicrobial bacteremia, who had no CVC at the time of bacteremia onset, or who had received a CVC less than 48 hours earlier. Study participants had long-term central venous catheters. The Centers for Disease Control and Prevention's definition of CLABSI [5] was used to classify 397 patients' bacteremia according to their CLABSI status. In addition, our group was further divided into two subgroups, one with mucosal barrier injury (MBI), and another without. There were two criteria used to define MBI: 1) neutropenia with an absolute neutrophil count of * 500 cells/mm3 on 2 separate days within three days of bacteremia diagnosis, or 2) in a patient who had undergone a hematological stem cell transplant (HSCT) within one year of the positive blood culture, the presence of either grade III or IV gastrointestinal graft-versus-host disease or diarrhea of *1 L within a 24-hour period before the positive blood culture. To acknowledge that in patients with MBI, gastrointestinal infection may be a source of bloodstream infection, we classified CLABSI with or without MBI. If CLABSI with MBI occurs, it is more likely to result from bacterial translocation from the gut rather than from CVCs. However, if CLABSI occurs without MBI, it is more likely to be caused by CVCs if there is no apparent source other than CVCs.

Further, using the Clinical Criteria for Catheter-related Bloodstream Infections (CRBSI), we identified patients who met the clinical criteria CDC Guidelines for Diagnosing and Treating Infectious Diseases of Intravascular Catheters and Related Infections [4]. There were three groups of patients: Group 1 was made up of patients with bacteremia matching the CLARSI definition with MBI (considered as possibly CLARSI); Group 2 (G2) was made up of patients with CRBSI or CLARSI without MBI (considered as definite CLARSI); and Group 3 (G3) was made up of patients with non-CLABSI, known as bacteremia from elsewhere but who had a CVC in place.

STATISTICAL ANALYSIS

As appropriate, we compared categorical variables using the *2 test or Fisher exact test. Kruskal-Wallis tests were used for comparisons between three groups and Wilcoxon rank sum tests were used for comparisons between two groups. The type I error was adjusted by Holm's sequential Bonferroni adjustment when a significant result (P * .05) was detected for a test comparing three groups. Researchers identified factors independently associated with all-cause mortality using multivariate logistic regression. Except for pairwise comparisons with the * adjustment, all tests were two-sided and 0.05 was the significance level. In order to perform the statistical analyses, SAS Institute, Cary, North Carolina, used version 9.3 of its SAS software.

RESULTS

The final analysis included a total of 397 patients in three groups, which included 132 patients with CLABSSI and MBI, 101 patients with CLABSSI without MBI or CRBSIS, and 164 patients without CLABSSI (Table 1). In G1, nearly all patients (98%) had hematologic malignancies (both P values above .0001). In G2, about 80% and G3 about 71% of patients had hematologic malignancies. There was a significant difference in neutropenia among G-1 (96%) and G-3 (52%) and G-2 (15%) (all P values * .001). HSCT recipients were significantly more numerous in groups 1 and 2 than in group 3 (P = .007 and .001 respectively) (G1 vs G3: G2 vs G3: P .001). A comparison of the ICU admission rates among the three groups did not reveal any statistically significant differences. Microbiologically, a higher percentage of patients had E. G2 isolates of E. faecalis were 62 percent higher than G3 isolates (46 percent) or G1 isolates (31.9 percent) (G1 vs G3: P = .001; S2 vs S2: P* .00001), while E. falciparum isolates were significantly more common in G1 patients (64% vs 37%, P * .001), and in G3 patients (48%, P = .004). Additionally, G1 patients had significantly higher rates of more prone to contracting bacterial infections as a result of VRE infection (43% vs

29%, P .016). The group comparisons did not differ in the rate of colonization by VRE.

Infections associated with central line-associated bloodstream infections, vancomycin-resistant enterococci, mucosal barrier injury, central venous catheter, and VRE vancomycin-resistant enterococci; CLABSI central line-associated bloodstream infections, central venous catheter; and VRE vancomycin-resistant enterococci.

- The solid tumors in six of the hematologic malignancies also had hematologic malignancy
- Enterococcus spp. included E. gallinarum, E. casseiflavus, etc. unidetified
- Lock therapy patients were not included
- Patients whose recurrence data were unknown or had been unresolved microbiologically were excluded

The CVCs in G2 patients were removed in a higher proportion than CVCs in G1 patients or in G3 patients. A significant It was concluded that G2 differs from G3 (P .001). Moreover, group two had more early CVC removals (less than three days after bacteremia onset, P .01) than did group three (33% vs 20%). Within 90 days of the onset of index bacteremia or within 90 days of microbiologic failure, there were no statistically significant differences in mortality from any cause recurrence within 90 days of microbiologic resolution between the 3 groups (Table 1).
Compared with early removal between 3 and 7 days (78% vs 67%, p = 0.003), early removal in G1 was associated with a better overall outcome; however, CVC retention was not significantly different (success rate 93%). G2 identified a trend toward better outcomes There is a higher rate of early removal (88% vs 63%) than late removal (between 3 and 7 days) but again with similar results success rate for CVC retention (92%). There was a significant difference in outcome across groups in G3 resulting from delayed CVC removal (> 7 days) compared with Removal of CVCs within three days (< 3 days) (90% vs. 64%, p = 0.006) (Table 2).

Infections associated with central lines, MBI mucosal barrier injuries

- resulting from positive blood cultures
- Were excluded, as were patients receiving lock therapy.
- [c]Patients with catheters retained were also excluded.
- THE composite outcome is dependent on multiple factors. Within 3 months following bacteremia, the patient survived without infection-related complications, was alive without infection-related death, and did not recur with infection within 3 months following microbiological resolution.

eA patient without a microbiological diagnosis, or a patient who died within 7 days of bacteremia, or had missing data regarding an infection- Excluded from the analysis were complications related to the infection, or death related to the infection, or recurrence of the infection.
In comparison with Infections with bacteremia caused by E. faecalis, bacteriosis caused by Faecalis experienced significant increases in P-value .0001 is calculated for mortality from infections (16% compared to 2%) and total mortality (57% compared to 34%). Comparatively, VRE bacteremia in patients experienced Higher by a significant margin overall mortality (47% vs 33%; P = .018), infection-related mortality (17% vs 6%; In those with non-VRE bacteremia, the rates of microbiological eradication at 36 hours were significantly higher than those who had VRE bacteremia (P = .004). An analysis of multivariate logistic regression revealed an independent link between higher death rates from all causes and the Detection of E. ICU admission (odds ratio [OR], 3.66; 95% confidence interval [CI], 2.11 to 6.34; P * .0001) and faecium (OR, 2.38; 95% confidence interval [CI], 1.54 to 3.68; P * .0001). The association between VRE infection and all-cause mortality (P = .53) was no longer significant after adjusting for these factors.

Table 1: Characteristics of different groups and outcomes

Variables	**COLBSI and MBI (G1)**	**CRBSIS and CLABSIS without MBI (G2)**	**CLABSIS without MBI (G3)**	***Probability***	**Analysis of significantly different pairwise comparisons**
	(*n* = 131)	**(*n* = 102)**	**(*n* = 163)**		
	N (%)	**N (%)**	**N (%)**		
Median (range) Age (years)	57 (18–88)	56 (11–86)	57 (17–81)	0.94	
Gender, male	91 (67)	63 (62)	90 (54)	0.07	
Malignancy				< .0002	G1 vs G2:*P* < .0002; G1 vs G3: *P* < .0002
Malignancies of the blood	131 (97)	81 (78)	116 (70)		
Tumors	3 (1)	20 (20)	46 (28)		

Variables	COLBSI and MBI (G1)	CRBSIS and CLABSIS without MBI (G2)	CLABSIS without MBI (G3)	*Probability*	Analysis of significantly different pairwise comparisons
	(*n* = 131)	(*n* = 102)	(*n* = 163)		
	N (%)	N (%)	N (%)		
Donation	48 (36)	44 (44)	36/162 (22)	<.002	G1 vs G3: *P* = 0.006; G2 vs G3: *P* < .001
*Allogeneity	45/48 (94)	41/46 (92)	32/36 (88)		
autochthonous	2/48 (6)	2/44 (6)	3/38 (10)		
ANC (500 cells/microL) neutropenia	126 (95)	14 (14)	84 (51)	< .0002	G1 vs G2: *P* < .0002; G1 vs G3: *P* < .0002; G2 vs G3: *P* < .0002
The ICU is contacted as soon as bacteremia is diagnosed	26 (21)	25 (25)	27 (16)	0.23	
At bacteremia onset, grafts outnumbered hosts	5/130 (4)	5 (5)	11/158 (5)	0.80	
The onset of bacteremia was accompanied by the colonization of Vancomycin-resistant enterococci (VRE)	47/121 (38)	20/81 (25)	41/123 (33)	0.15	
species of enterococci					
E. faecalis	40 (30)	62 (61)	74 (45)	< .0002	G1 vs G2; *P* < .0002; G1 vs G3: *P* = .02; G2 vs G3: *P* = .02
E. faecium	84 (63)	36 (36)	77 (47)	< .0002	G1 vs G2: *P* < .0002; G1 vs G3: *P* = .003
During the Other Enterococcus species	7 (4)	1 (2)	10 (6)	0.08	
Positive for VRE	55/130 (43)	28/101 (28)	47 (28)	0.026	G1 vs G3: *P* = .015;
A median (IQR) of the days between insertion of the CVC and the positive culture	31 (15–90)	60 (16–124)	54 (20–178)	0.006	G1 vs G3: *P* = .001
Management of catheters				0.003	G2 vs G3: *P* < .002
Reduction	63 (47)	55 (54)	58 (37)		
Therapies based on locks	1 (1)	2 (2)	2 (2)		
Retained catheter (no lock therapy)	65 (51)	41 (41)	103 (62)		
Catheter removed after a positive blood culture result				0.007	G2 vs G3: *P* = .002
< 3 days	28/131 (21)	31/97 (32)	31/162 (21)		

Variables	COLBSI and MBI (G1)	CRBSIS and CLABSIS without MBI (G2)	CLABSIS without MBI (G3)	*Probability*	Analysis of significantly different pairwise comparisons
	(*n* = 131)	(*n* = 102)	(*n* = 163)		
	N (%)	N (%)	N (%)		
3–7 days	30/131 (23)	21/97 (21)	22/162 (13)		
> 7 days (including catheter retained)	71/131 (53)	43/97 (44)	107/162 (67)		
Vaccinations Received	124 (94)	95 (94)	148 (90)	0.31	
Median number of days of antibiotic treatment (IQR)	15 (10–21)	14 (8–17)	14 (11–21)	0.52	
3 months later complications	6/131 (4)	7/97 (7)	5/154 (3)	0.33	
Mortality rate for all causes within 3 months	68 (50)	38 (38)	70 (42)	0.16	
Mortality related to infection within 3 months	15/130 (11)	7/96 (7)	12/157 (7)	0.44	
Microbiologic resolution after 3 months	11/110 (8)	5/87 (6)	10/136 (7)	0.84	

Table 2: In different groups, the effect of catheter placement varies

1) CLABSI with MBI					
conclusion	**Dialysis catheter removal a,b**			***p0.001*	Significant differences between pairs
	< 3 Days	**3–7 Days**	**> 7 Days [c]**		
	(*n* = 24)	(*n* = 26)	(*n* = 61)		
	N (%)	N (%)	N (%)		
D, E Are the results				0.003	"3–7 days" vs "> 7 days": *P* = .004
Success	17 (77)	17 (66)	57 (94)		
Failure	4 (21)	8 (32)	3 (6)		
2) CRBSI or CLABSI without MBI					
analysis	**Removal of catheters a, b**			**p0.05*	when compared pairwise
	< 3 Days	**3–7 Days**	**> 7 Days [c]**		
	(*n* = 23)	(*n* = 18)	(*n* = 36)		
	N (%)	N (%)	N (%)		
The result is: d, e				0.024	*None (since multiple comparisons are adjusted by alpha)
Successful	20 (87)	11 (62)	33 (91)		
Error	3 (12)	7 (38)	2 (7)		
3) Non-CLABSI					

Assessment	**Removal of catheters a, b**			*Probability*	significantly different pairs of comparisons
	< 3 Days	**3–7 Days**	**> 7 Days [c]**		
	(*n* = 21)	(*n* = 18)	(*n* = 87)		
	N (%)	N (%)	N (%)		
The final result was d, e				0.007	"< 3 days" vs "> 7 days": *P* = .005
Success	13 (63)	15 (73)	78 (91)		
Failure	7 (35)	4 (25)	8 (11)		

DISCUSSION

This is the largest study we are aware of that has fully defined comparator groups for enterococcal in cancer patients. There is a high prevalence of E. faecalis isolates in G2 (patients with CRBSI and CLABSI but no MBI), which may be attributed to Superior to ability of the biofilms formed by E. faecalis. As of now, it is difficult to determine whether early CVC removal is beneficial; however, Trends emerged toward a better success rate with Removal of the CVC as early as possible G1 and G2 (* 3 days) than with early CVC removal between 3 and 7 days. It appeared surprising, however, that all three groups experienced high levels of CVC retention. In clinically stable patients, catheter retention may have been successful, explaining the high success rate. Despite our best efforts, we were unable to find out what the rationale was behind removing or keeping the CVC. The CVC has been removed unnecessarily in many cases when it was not the source of a CLABSI [7], however, guidelines from the Infectious Diseases Society of America recommend that CVCs should be removed when the CVC is most likely the cause of a infection is in the bloodstream. As long as the catheter remains, an antibiotic lock can be applied, especially if enterococcus, coagulase negative staphylococci, and gram-negative bacteria cause bloodstream infections [4]. Among cancer patients with Staphylococcus aureus-CLABSI, In the first three months, the CVC should be removed days has been linked to better outcomes and lower relapse risk . As well, removal within 48 to 72 hours of a CVC in patients with gram-negative bacteria an improved infectious outcome was associated with decreased mortality [9, 10]. Similarly, removing the CVC was associated with a lower relapse rate in patients who were infected with commensal bacteria (coagulase negative staphylococci and bacilli) causing CLABSIs [11, 12]. Despite limited data and small sample sizes, literature suggests a potential benefit of removing CVC for enterococcal CLABSI.

61 cases of enterococcal CRBSI were analyzed [13]. Among 48 episodes treated with CVC removal, the patients were cured in 40 of them (83%), but only in 5 out of 13 (38%) patients with CVCs who were treated with antibiotics retained their CVCs treatment A cell wall-acting agent and an aminoglycoside are included). Fig. timing of CVC removal was not addressed in the study. The authors of the study concluded that despite the small sample size, The CVC should be removed if possible, as it leads to higher cure rates [13].

The study by Reigadas and colleagues [14] examined risk factors and clinical characteristics of patients with enterococcal CRBSI, examining 75 episodes (in 73 patients). The researchers concluded that enterococcal CRBSI patients had a high mortality rate, requiring better therapeutic approaches [14].

The authors conducted a retrospective review of 111 patients with enterococcal CLABSI to compare outcomes of those who retained CVCs versus those who had them removed. According to their study, in- The 30-day and 90-day mortality rates after CVC retention are all associated with mortality at the hospital and at the 90-day mark. In their study, however, Remove the CVC after a certain period of time was not specified. A comparator group was also lacking in that study [15].

Generally, enterococcal species are considered Virulent organisms Enterococcal infections have previously been linked to antibiotic resistance malignancy and other chronic comorbid conditions may be due to these infections' association with malignancy. According to the present study, infection-related deaths and overall mortality were higher in patients harboring vancomycin-resistant isolates, which can be attributed to isolation of E. faecium and critical care hospitalization. An analysis of 7128 adults and children receiving their first HSC discovered poor outcomes related to VRE BSIs. Multiple multivariate models demonstrated that VRE-BSI leads to the mortality rate of non-relapse patients and the overall survival rate are higher [18]. G1 (CLABSI with MBI) was the most prevalent VRE isolate in this study, this isolate also had a higher colonization rate of VRE (Table 1). We isolated mostly E. faecium (90%). Although we have established that E. faecalis leads to worse Results of infection with E. faecalis have been thoroughly documented [19], we suspect that its resistance to vancomycin may be responsible for the poor outcomes.

In addition to the retrospective nature of our study, we found that it did not document consistently the indications for CVC management. Similarly, in removing

the CVC, the following factors were considered: clinical judgment Physicians who treat patients, without Any patterns or trends that stand out timeline, often without an explicit reason and regardless of the patient's clinical condition at the time. Moreover, the study was retrospective in design, so there was no defined prospective clinical protocol followed by patients. Since some patients were not able to have daily blood cultures repeated, and some variables were lacking data, we did not have follow-up data for all patients. The analysis therefore did not include them. Consequently, we were unable to collect as many cases as we might have, and our data may not be statistically significant. Due to Since physical samples are no longer available, the study is retrospective., we either had to use phenotypic susceptibility patterns or rely on phenotypic susceptibility patterns.

CONCLUSION

If the CVC is to be removed within 3 days of the onset of Enterococcal CLABSI, then early removal may provide better results than removal within 3-7 days. A group with the highest success rate were seen with retention (removal > 7 days). To determine the best approach, more prospective data is needed.

REFERENCES

1. See I, Freifeld AG, Magill SS. Causative organisms and associated antimicrobial resistance in healthcare-associated, central line-associated bloodstream infections from oncology settings, 2009-2012. *Clin Infect Dis.* 2016;62(10):1203–1209.
2. Conde-Estevez D, Grau S, Albanell J, Terradas R, Salvado M, Knobel H. Clinical characteristics and outcomes of patients with vancomycin-susceptible Enterococcus faecalis and Enterococcus faecium bacteraemia in cancer patients. *Eur J Clin Microbiol Infect Dis.* 2011;30(1):103–108.
3. Donelli G, Guaglianone E. Emerging role of Enterococcus spp in catheter-related infections: biofilm formation and novel mechanisms of antibiotic resistance. *J Vasc Access.* 2004;5(1):3–9.
4. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, Raad II, Rijnders BJA, Sherertz RJ, Warren DK. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;49(1):1–45.
5. El Zakhem A, Chaftari AM, Bahu R, et al. Central line-associated bloodstream infections caused by Staphylococcus aureus in cancer patients: clinical outcome and management. *Ann Med.* 2014;46(3):163–168.
6. Hanna H, Afif C, Alakech B, Boktour M, Tarrand J, Hachem R, Raad I. Central venous catheter-related bacteremia due to gram-negative bacilli: significance of catheter removal in preventing relapse. *Infect Control Hosp Epidemiol.* 2004;25(8):646–649.
7. Raad I, Kassar R, Ghannam D, Chaftari AM, Hachem R, Jiang Y. Management of the catheter in documented catheter-related coagulase-negative staphylococcal bacteremia: remove or retain? *Clin Infect Dis.* 2009;49(8):1187–1194.
8. Kassar R, Hachem R, Jiang Y, Chaftari AM, Raad I. Management of Bacillus bacteremia: the need for catheter removal. *Medicine (Baltimore)* 2009;88(5):279–283.
9. Sandoe JA, Witherden IR, Au-Yeung HK, Kite P, Kerr KG, Wilcox MH. Enterococcal intravascular catheter-related bloodstream infection: management and outcome of 61 consecutive cases. *J Antimicrob Chemother.* 2002;50(4):577–582.
10. Reigadas E, Rodriguez-Creixems M, Guembe M, Sanchez-Carrillo C, Martin-Rabadan P, Bouza E. Catheter-related bloodstream infection caused by Enterococcus spp. *Clin Microbiol Infect.* 2013;19(5):457–461.
11. Marschall J, Piccirillo ML, Fraser VJ, Doherty JA, Warren DK. Catheter removal versus retention in the management of catheter-associated enterococcal bloodstream infections. *Can J Infect Dis Med Microbiol.* 2013;24(3):e83–e87.
12. Murray BE. The life and times of the Enterococcus. *Clin Microbiol Rev.* 1990;3(1):46–65.
13. McBride SJ, Upton A, Roberts SA. Clinical characteristics and outcomes of patients with vancomycin-susceptible Enterococcus faecalis and Enterococcus faecium bacteraemia--a five-year retrospective review. *Eur J Clin Microbiol Infect Dis.* 2010;29(1):107–114.