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Catheter-related bloodstream infection caused by *Enterococcus* spp.

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Abstract

The role of *Enterococcus* spp. as a cause of catheter-related bloodstream infections (CR-BSI) is almost unexplored. We assessed the incidence and clinical characteristics of enterococcal CR-BSI (ECR-BSI) over an 8-year period in our hospital. We performed a retrospective study (January 2003 to December 2010) in a large teaching institution. We recorded the incidence, and the microbiological and clinical data from patients with ECR-BSI. The incidence per 10 000 admissions for enterococcal BSI and ECR-BSI was 25 and 1.7, respectively. ECR-BSI was the fourth leading cause of CR-BSI in our institution (6%). A total of 75 episodes of ECR-BSI were detected in 73 patients (6% of all enterococcal BSI). The incidence of ECR-BSI increased by 17% annually (95% CI 19.0–21.0%) during the study period. Nineteen percent of ECR-BSI episodes were polymicrobial. Overall mortality was 33%. ECR-BSI is an emerging and increasingly common entity with a high mortality. This finding should be taken into account when selecting empirical treatment for presumptive CR-BSI.

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Introduction

Catheter-related bloodstream infections (CR-BSI) are one of the most important types of nosocomial infections, with high rates of morbidity and mortality and high healthcare costs [1,2]. CR-BSI are mainly caused by gram-positive bacteria, particularly coagulase-negative *Staphylococcus* and *Staphylococcus aureus*.

Enterococci are a common cause of bloodstream infections in the USA [3] and in Europe [4]. However, the literature contains little information on *Enterococcus* spp. as a cause of CR-BSI [5–10].

The aim of our study was to assess how the incidence and clinical characteristics of enterococcal CR-BSI (ECR-BSI) evolved over an 8-year period in a large teaching institution.

Material and Methods

Setting

We performed a retrospective study from January 2003 to December 2010 in a tertiary teaching hospital serving a reference population that ranged from 704 030 to 806 769 inhabitants during the study period. Patients with ECR-BSI were identified using the microbiology laboratory database.

Data collected

Patient data were collected from hospital medical records. Clinical data included demographics, McCabe and Jackson prognosis of underlying diseases, and the Charlson comorbidity index [11,12]. For adult intensive care unit (ICU) patients, we calculated the Acute Physiological Assessment and Chronic Health Evaluation (APACHE) II score at the time of catheter withdrawal. We also recorded microbiological data from catheter and blood cultures. Other data included neutropenia (neutrophil count ≤500/μL) within the 7 days before catheter withdrawal, transplantation, and immunosuppressive treatment during the previous month.

Surgical procedures on admission and antibiotic treatment and outcome were also recorded.

Definitions

The definitions for CR-BSI are those detailed in the Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infections [13]. Diagnosis of proven CR-BSI was based on growth of the same *Enterococcus* spp. (at species level) from at least one percutaneous blood culture and from a culture of the catheter tip within a period of 7 days of the positive blood culture.

All enterococcal isolates from blood from the same patient within 1 week are considered as a single episode.

Polymicrobial CR-BSI was defined as the presence of colonization of the catheter tip and bacteraemia caused by two or more significant microorganisms.

Laboratory procedures

Our institution recommends extraction of three blood samples (10 mL each in adults) for evaluation of all episodes of suspected bacteraemia. Blood cultures were processed according to routine methods using a semiautomatic culture detector (Bactec 9240; Becton Dickinson Microbiology Systems, Maryland, DE, USA). Catheter tips were cultured using the Maki roll-plate technique [14,15] considering significant growth as ≥15 CFU/plate. Microorganisms were identified and antibiotic susceptibility was tested using the automated MicroScan system (DADE Behring, Sacramento, CA, USA).

Statistical analysis

The incidence of enterococcal BSI, ECR-BSI and CR-BSI was calculated as episodes per 10 000 admissions (the number of episodes detected during the study period divided by the number of admissions during the same period). We used SPSS 12.0 (SPSS Inc., Chicago, IL, USA) for the statistical analysis.

Ethics

The study was approved by the Ethics Committee of Hospital General Universitario Gregorio Marañón.

Results

During the study period, *Enterococcus* spp. was the fourth leading cause of CR-BSI (after coagulase-negative *Staphylococcus*, *S. aureus*, and *Candida* spp.) and represented 6% of all episodes of CR-BSI (75/1208 episodes). Of the 333 catheters colonized with *Enterococcus* spp., 75 were ECR-BSI (23%); of 1193 episodes of enterococcal bacteraemia, 6% (75/1193) were catheter-related.

The overall incidence of proven CR-BSI and ECR-BSI was 25 and 1.7 episodes per 10 000 admissions, respectively. We recorded a 17% annual increase in incidence (95% CI 16.1–17.9%), ranging from 0.9 episodes per 10 000 admissions in 2003 to 1.8 episodes per 10 000 admissions in 2010 (Poisson regression, $p < 0.001$).

The yearly change of ECR-BSI is compared with the yearly changes of other gram-positive CR-BSI in Fig. 1.

The incidence of ECR-BSI due to *Enterococcus faecalis* increased by 20.0% annually (95% CI 19.0–21.0%) during the study period ($p < 0.001$) whereas the incidence of ECR-BSI due to *Enterococcus faecium* remained stable.

The yearly changes of ECR-BSI due to *E. faecalis* is compared with the yearly changes of ECR-BSI due to *E. faecium* in Fig. 2.

Most episodes of ECR-BSI were caused by *E. faecalis* (85%); the remaining episodes were caused by *E. faecium* (15%). In 19% of cases, ECR-BSI was polymicrobial. The associated pathogens were gram-negative bacilli (43.75%), coagulase-negative *Staphylococcus* (43.75%) and *S. aureus* (12.5%). The same species of enterococci were isolated concurrently from another site in 15% (11/73) of patients.

All *E. faecalis* isolates were susceptible to ampicillin, whereas only 10% of *E. faecium* isolates were susceptible to ampicillin. Thirty-three percent of *Enterococcus* spp. isolates were resistant to gentamicin. There were no vancomycin-resistant isolates.

The characteristics of the catheters from patients with ECR-BSI are detailed in Table 1. Most catheters (76%) were

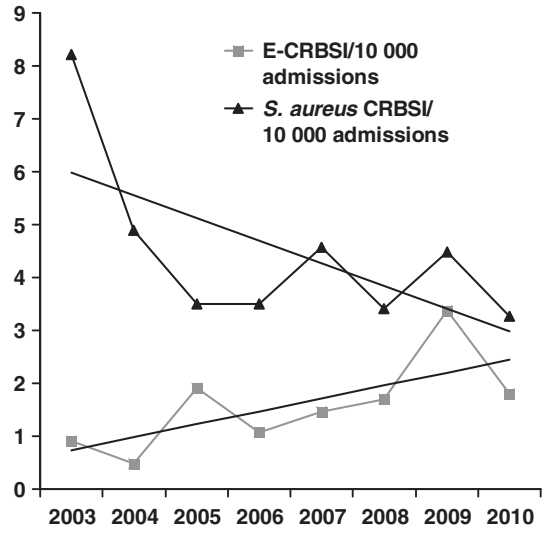

FIG. 1. Yearly incidence of enterococcal and *Staphylococcus aureus* catheter-related bloodstream infections per 10 000 admissions. ECR-BSI, enterococcal catheter-related bloodstream infection; *S. aureus* CR-BSI, *Staphylococcus aureus* catheter-related bloodstream infection.

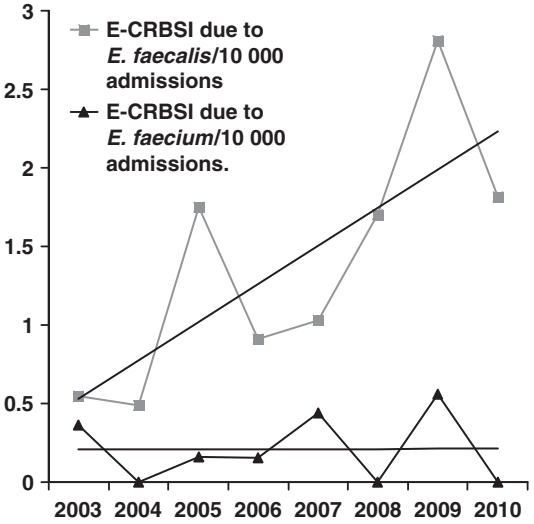

FIG. 2. Yearly incidence of *Enterococcus faecalis* and *Enterococcus faecium* catheter-related bloodstream infections per 10 000 admissions. ECR-BSI, enterococcal catheter-related bloodstream infection.

TABLE 1. Catheter characteristics of enterococcal catheter-related bloodstream infection

Variable	Overall (*n* = 75)
Catheter days[a]	15 (12–25)
Insertion site[b]	
Subclavian vein	26 (34.6)
Jugular vein	20 (26.6)
Femoral vein	15 (20)
Upper extremities	11 (14.6)
Other	3 (4)
Type of catheter[b]	
Central venous catheter	57 (76)
Peripherally inserted central catheter	10 (13)
Swan–Ganz	3 (4)
Arterial	2 (3)
Port-A-Cath	2 (3)
Hickman	1 (1)
Reason for catheter withdrawal[b]	
Suspicion of bloodstream infection	53 (71)
Unknown	15 (20)
End of use	4 (5)
Obstruction	2 (3)
Suspicion of local infection	1 (1)

[a]Values expressed as median (interquartile range).
[b]Values expressed as no. (%) of patients.

central venous catheters. The most frequent site of insertion was the subclavian vein (34.6%), followed by the jugular vein (26.6%), femoral vein (20%), upper extremities (14.6%), and other (4%). Median indwelling time was 15 days (interquartile range 12–25). In most cases (70%), the reason for catheter withdrawal was suspicion of bloodstream infection.

We identified 75 episodes of ECR-BSI in 73 patients. Demographic and clinical data are summarized in Table 2.

Slightly more than half of all ECR-BSI episodes (53%) occurred in units other than adult ICUs. Cardiovascular disease was the most common underlying condition, followed

TABLE 2. Clinical features of patients with enterococcal catheter-related bloodstream infection

Variable	Overall (*n* = 75)
Age[a]	60 (11–71)
Male[b]	42 (56)
Hospitalization unit[b]	
Intensive-care unit	35 (47)
Medical	12 (16)
Surgical	9 (12)
Paediatric	19 (25)
Underlying disease[b]	
Cardiovascular	26 (35)
Malignancy	15 (20)
Gastrointestinal	12 (16)
Other	22 (29)
McCabe and Jackson severity of underlying disease score[b]	
Rapidly fatal	2 (3)
Ultimately fatal	4 (5)
Non-fatal	69 (92)
Charlson comorbidity score[a]	2 (0–3)
Previous neutropenia[b]	2 (3)
Surgical procedure during admission[b]	61 (81)
Recent immunosuppressive therapy[b]	11 (15)
HIV infection[b]	2 (3)
Transplantation[b]	4 (5)
Antimicrobials received in the previous month[b]	70 (93)
Need for ICU admission[b]	64 (85)
APACHE II score[a] (*n* = 35)	13 (11–15)
Length of hospital stay, days[a]	29 (14–53)
Length of ICU stay, days[a]	24 (11–46)
Complications[b]	
Endocarditis	3 (4)
Recurrent bacteraemia	3 (4)
Mediastinitis	1 (1.3)
Abdominal abscess	1 (1.3)
Global mortality at discharge[b]	27 (36)

ICU, intensive care unit; HIV, human immunodeficiency virus; ECR-BSI, enterococcal catheter-related bloodstream infection.
[a]Values expressed as median (interquartile range).
[b]Values expressed as no. (%) of patients.

by malignancy and gastrointestinal disease. Sixty-one patients underwent at least one surgical procedure during admission (44% abdominal, 38% cardiac and 18% other).

Complications occurred in 11% of the episodes. Endocarditis was diagnosed in 4% of cases of ECR-BSI. The remaining complications were recurrent bacteraemia in three patients (4%), mediastinitis in one patient (1.3%), and abdominal abscess in one patient (1.3%). Overall mortality was 36%.

Discussion

Enterococcus spp. are the fourth most common cause of CR-BSI in our institution. ECR-BSI accounts for 6% of all episodes of CR-BSI and 6% of all enterococcal BSI and occurs in patients with severe underlying conditions. It is polymicrobial in 19% of episodes and is associated with significant rates of morbidity and mortality.

Enterococcal-BSI has classically been related to intra-abdominal, urinary tract and soft-tissue infections [16]. Enterococcal endocarditis has been reported to occur in 8% of cases of enterococcal bacteraemia [17]. Enterococci are

the fourth commonest cause of nosocomial infections and the third commonest cause of bacteraemia, accounting for 10.2% of BSI [18]. In Europe, enterococcal bacteraemia accounts for 7.2% of all BSIs [18].

Our data show that enterococcal CR-BSI is an emerging condition whose incidence has been increasing in recent years. Previous studies have reported catheter-related infection as a source in 2–13% of enterococcal BSI [5,16]. In our experience, at least 6% of all episodes of enterococcal bacteraemia originate from a catheter; therefore, this site should be taken into consideration when searching for an origin in patients with enterococcal bacteraemia.

A survey of CR-BSI that collected data from 21 European countries revealed an overall incidence of 0.6 episodes of ECR-BSI per 10 000 admissions [19]. In our institution, the incidence of ECR-BSI was significantly higher, accounting for 1.7 episodes per 10 000 admissions. This figure doubled over an 8-year period, to the detriment of other gram-positive microorganisms such as *S. aureus*.

The incidence of CR-BSI outside the ICU has received little attention in the medical literature [20,21]. However, in our study, most ECR-BSI episodes occurred in units other than adult ICUs.

The vast majority of the patients in our series had underlying clinical conditions with high morbidity and mortality rates, making it difficult to attribute mortality, especially in the case of ECR-BSI. Enterococcal BSI mortality has been reported to range from 13% to 68% [22,23]. We identified three endocarditis episodes secondary to ECR-BSI, all due to *E. faecalis*, and three patients presented recurrent bacteraemia, all with high-level gentamicin resistance. Enterococcal BSI that exhibit high-level gentamicin resistance have been associated with more severe underlying disease and higher mortality than non-high-level gentamicin resistance infections [24]. In our study, a high proportion (28%) of the patients who died had ECR-BSI with high-level gentamicin resistance. We did not find any correlation between outcome and resistance to ampicillin. The absence of vancomycin-resistant enterococcal isolates prevented us from analysing a potential association between vancomycin-resistant enterococci and outcome.

Nosocomial enterococcal bacteraemia is often polymicrobial [8,16,17]. A high proportion (19%) of the ECR-BSI episodes we detected were polymicrobial (two or more microorganisms in both the catheter and the blood culture). Patterson *et al.* [8] found that the most common *Enterococcus* spp. polymicrobial infection was CR-BSI.

Nine of the 75 patients with ECR-BSI had one or more different microorganisms present in blood cultures that were not present in the catheter-tip culture. We think that these cases could have an intra-abdominal origin and that the catheter could have become infected as a result of metastatic seeding.

Our study was limited by its retrospective design and the fact that it did not include a control group; therefore, we were unable to analyse attributable mortality and compare the clinical outcome of ECR-BSI with that of CR-BSI caused by other microorganisms. Moreover, the absence of vancomycin-resistant enterococci limited the applicability of our findings to other scenarios. However, ours is the largest series collected to date from a single centre.

In conclusion, *Enterococcus* spp. is an emerging cause of CR-BSI, which should be considered when selecting empirical treatments of presumptive CR-BSI. The episodes of ECR-BSI frequently had polymicrobial blood cultures, suggesting a potential intra-abdominal origin with secondary catheter involvement. The high mortality rate of patients with ECR-BSI means that every effort should be made to establish the optimal therapeutic approach.

Moreover, the high proportion of ECR-BSI occurring in units other than adult ICUs highlights the need to expand CR-BSI surveillance programmes to include non-ICU areas.

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Transparency Declaration

The authors declare no conflicts of interest.

References

1. Tacconelli E, Smith G, Hieke K, Lafuma A, Bastide P. Epidemiology, medical outcomes and costs of catheter-related bloodstream infections in intensive care units of four European countries: literature- and registry-based estimates. *J Hosp Infect* 2009; 72: 97–103.
2. Smith MJ. Catheter-related bloodstream infections in children. *Am J Infect Control* 2008; 36: S173.e1–S173.e3.
3. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis* 2004; 39: 309–317.

4. Fluit AC, Schmitz FJ, Verhoef J, European SPG. Frequency of isolation of pathogens from bloodstream, nosocomial pneumonia, skin and soft tissue, and urinary tract infections occurring in European patients. *Eur J Clin Microbiol Infect Dis* 2001; 20: 188–191.
5. NNIS. National nosocomial infections surveillance (NNIS) system report, data summary from January 1992–June 2001, issued August 2001. *Am J Infect Control* 2001; 29: 404–421.
6. Gray J, Marsh PJ, Stewart D, Pedler SJ. Enterococcal bacteraemia: a prospective study of 125 episodes. *J Hosp Infect* 1994; 27: 179–186.
7. Malone DA, Wagner RA, Myers JP, Watanakunakorn C. Enterococcal bacteremia in two large community teaching hospitals. *Am J Med* 1986; 81: 601–606.
8. Patterson JE, Sweeney AH, Simms M *et al.* An analysis of 110 serious enterococcal infections. Epidemiology, antibiotic susceptibility, and outcome. *Medicine (Baltimore)* 1995; 74: 191–200.
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: 577–582.
10. Shlaes DM, Levy J, Wolinsky E. Enterococcal bacteremia without endocarditis. *Arch Intern Med* 1981; 141: 578–581.
11. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373–383.
12. McCabe WR, Jackson GG. Gram-negative bacteremia: I. Etiology and ecology. *Arch Intern Med* 1962; 110: 847–855.
13. Mermel LA, Allon M, Bouza E *et al.* 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: 1–45.
14. Bouza E, Alvarado N, Alcala L, Perez MJ, Rincon C, Munoz P. A randomized and prospective study of 3 procedures for the diagnosis of catheter-related bloodstream infection without catheter withdrawal. *Clin Infect Dis* 2007; 44: 820–826.
15. Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-catheter-related infection. *N Engl J Med* 1977; 296: 1305–1309.
16. Garrison RN, Fry DE, Berberich S, Polk HC Jr. Enterococcal bacteremia: clinical implications and determinants of death. *Ann Surg* 1982; 196: 43–47.
17. Maki DG, Agger WA. Enterococcal bacteremia: clinical features, the risk of endocarditis, and management. *Medicine (Baltimore)* 1988; 67: 248–269.
18. Biedenbach DJ, Moet GJ, Jones RN. Occurrence and antimicrobial resistance pattern comparisons among bloodstream infection isolates from the SENTRY antimicrobial surveillance program (1997–2002). *Diagn Microbiol Infect Dis* 2004; 50: 59–69.
19. Munoz P, Bouza E, San Juan R *et al.* Clinical–epidemiological characteristics and outcome of patients with catheter-related bloodstream infections in Europe (ESGNI-006 Study). *Clin Microbiol Infect* 2004; 10: 843–845.
20. Vonberg RP, Behnke M, Geffers C *et al.* Device-associated infection rates for non-intensive care unit patients. *Infect Control Hosp Epidemiol* 2006; 27: 357–361.
21. Marschall J, Leone C, Jones M, Nihill D, Fraser VJ, Warren DK. Catheter-associated bloodstream infections in general medical patients outside the intensive care unit: a surveillance study. *Infect Control Hosp Epidemiol* 2007; 28: 905–909.
22. Caballero-Granado FJ, Cisneros JM, Luque R *et al.* Comparative study of bacteremias caused by *Enterococcus* spp. with and without high-level resistance to gentamicin. The Grupo Andaluz para el estudio de las Enfermedades Infecciosas. *J Clin Microbiol* 1998; 36: 520–525.
23. Bryan CS, Reynolds KL, Brown JJ. Mortality associated with enterococcal bacteremia. *Surg Gynecol Obstet* 1985; 160: 557–561.
24. Jang HC, Lee S, Song KH *et al.* Clinical features, risk factors and outcomes of bacteremia due to enterococci with high-level gentamicin resistance: comparison with bacteremia due to enterococci without high-level gentamicin resistance. *J Korean Med Sci* 2010; 25: 3–8.