Enterococcal intravascular catheter-related bloodstream infection: management and outcome of 61 consecutive cases

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Enterococci are an increasingly important cause of intravascular catheter-related bloodstream infection (CRBSI), but the evidence base for treating such cases is limited. Successful antimicrobial treatment of CRBSI while leaving the central venous catheter (CVC) in situ has been reported for some bacteria, such as coagulase-negative staphylococci, but the effectiveness of this approach for treating enterococcal CRBSI is unknown. We aimed to determine the effectiveness of treatment options for enterococcal CRBSI and whether CVC removal is mandatory. Treatment and outcome was determined in a 3 year cohort of patients with enterococcal CRBSI from a university teaching hospital. All episodes of enterococcal bacteraemia during the study (n = 268) were examined to identify the cohort of 61 CRBSIs. Outcomes were determined for various antimicrobial regimens with or without CVC removal. Forty-eight episodes were managed with CVC removal and 13 were managed with the CVC in situ. Forty of 48 (83%) and five of 13 (38%) episodes were cured with the CVC removed or left in situ, respectively. All five episodes cured with the CVC in situ were treated with a cell wall-acting antimicrobial plus an aminoglycoside. This antimicrobial combination was significantly more effective than either ampicillin or vancomycin monotherapy (P < 0.05), or antimicrobials to which isolates were not susceptible (P < 0.01) when the CVC remained in situ. We conclude that enterococcal CRBSI can be treated successfully without CVC removal. The combination of a cell wall-acting antimicrobial with an aminoglycoside was the most effective regimen when the CVC remained in situ in this small group of patients. Although CVC removal was associated with a high cure rate, it did not guarantee treatment success.

Keywords: Enterococcus, intravascular catheter, bloodstream infection

Introduction

Enterococci are the fourth most common cause of bloodstream infection in Europe, accounting for ~7% of episodes.1 In the USA, enterococci were the third most common cause of bloodstream infection in intensive care units between 1989 and 1999, accounting for 10% of all episodes.2 Of all hospital-acquired bacteraemias, approximately one-third are associated with intravascular catheters.3 The proportion of enterococcal bacteraemias associated with central venous catheters (CVCs) has increased dramatically since the early 1980s, reaching 35% in one UK study.7 The propensity of enterococci to cause infections associated with medical devices such as intravascular catheters, together with inherent resistance to antimicrobials such as cephalosporins, has probably contributed to the increasing incidence of nosocomial enterococcal infection. Acquired resistance to β-lactams, glycopeptides and aminoglycosides has further complicated antimicrobial treatment of enterococcal infections. The recognition of microbial biofilms associated with medical devices and their relative resistance to antimicrobials has led to the belief that infected devices require removal to achieve cure.8 While this still holds true for many such infections, recent publications have
reported successful treatment of CRBSI using antimicrobials while leaving the catheter in situ. Recent guidelines for the management of CRBSI did not include evidence-based recommendations for the treatment of enterococcal infections. This study was therefore undertaken to determine whether current antimicrobial treatment regimes for enterococcal CRBSI lead to differences in outcome and whether there is a need for CVC removal to achieve cure.

Patients and methods

Patient population

All patients with enterococcal bacteraemia at the General Infirmary Leeds, Leeds, UK between 1 January 1998 and 31 December 2000 were identified using the diagnostic microbiology laboratory database. Patients with CRBSI were identified retrospectively. The following data were recorded: patient age, gender, underlying condition, type of intravascular access device, dates of placement and removal, evidence of systemic inflammatory response syndrome (SIRS), antimicrobial treatment, catheter management and outcome. When complete data sets were not recorded in microbiology records, patient case notes were reviewed retrospectively. Underlying medical conditions were categorized as described previously.

Definitions of enterococcal CRBSI

CRBSI was defined as isolation of an Enterococcus sp. from at least one bottle of a pair of blood culture bottles plus at least one of the following: (i) semiquantitative culture of the removed catheter tip positive for an Enterococcus sp. (>15 cfu) with the same antibiogram as the blood culture isolate; (ii) through-line blood cultures yielded >1000 cfu/mL Enterococcus sp. with the same antibiogram as the blood culture isolate; (iii) differential time to positivity of paired peripheral and through-line blood cultures was >2 h in favour of through-line cultures; (iv) purulent exit site with a swab culture yielding an Enterococcus sp. with the same antibiogram as the bloodstream isolate; (v) clinical picture consistent with CRBSI, but with no other identifiable focus of infection and resolution of signs of infection following catheter removal. Cuffed, tunnelled CVCs intended for long-term use such as Hickman, Broviac, subcutaneous port and Tessio catheters were classified as ‘permanent’. Other CVC types intended for short-term use were classified as ‘temporary’.

Definitions of response to therapy

The day on which the first positive blood culture was drawn was defined as day 1 of an infective episode. All enterococcal blood culture isolates, with the same antibiogram and colonial morphology as the initial isolate, recovered from a patient within 10 days of the first positive blood culture were considered part of a single infective episode. Cure was defined as resolution of clinical signs of infection within 10 days of starting antimicrobial treatment and failure to recover an Enterococcus sp., with the same antibiogram and whole-cell DNA restriction enzyme profile, from blood cultures during the following 3 months. Death during the acute episode or persistent signs of infection beyond 10 days was regarded as treatment failure. Recurrence was defined as isolation of an Enterococcus sp., with the same DNA restriction enzyme profile as the original isolate, between 10 days and 3 months after the initial positive blood culture, following an initial clinical response to treatment. For the purposes of treatment analysis, each recurrence was considered a new episode. Enterococcal bloodstream infection was considered to have contributed to mortality if death resulted from uncontrolled infection, or if infection resulted in death from uncontrollable infection and death from an underlying condition within 10 days of the first positive blood culture, as described previously. If death occurred during the 3 month follow-up period, but was not a result of infection, follow-up for recurrence continued until the date of death.

Antimicrobial treatment

Choice of antimicrobial agent was left to the discretion of the attending physician but treatment advice had been provided by medical microbiologists in each case. Treatment regimens were considered ‘appropriate’ or ‘inappropriate’ as described previously. If the causative bacterium was found to be susceptible in vitro, appropriate regimens comprised: (i) penicillin, piperacillin or a carbapenem in combination with an aminoglycoside; or (ii) ampicillin or a glycopeptide alone, or in combination with an aminoglycoside. Treatment of enterococcal CRBSI with retention of the catheter was only considered appropriate if antimicrobials were administered through the infected line. All other regimens were considered inappropriate.

Microbiological methods

Isolates were confirmed as enterococci if they were catalase-negative Gram-positive cocci that could grow in 6.5% sodium chloride, hydrolyse aesculin in the presence of 40% bile and possessed Lancefield group D antigen. Identification to species level was carried out according to standard biochemical methods or API 20 strep (bioMérieux, Marcy l’Étoile, France). Antimicrobial susceptibility testing was determined using a standardized disc diffusion method. Genotyping was performed by PFGE of Smal-digested whole-cell DNA based on a method described previously.
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Data handling

Episode and isolate information was stored on a Microsoft Access database and statistical analysis carried out using Statview software (SAS Institute, Inc.). Fisher’s exact test was used for univariate analysis of categorical variables, and the Mann–Whitney U-test was used for analysis of non-normally distributed continuous variables. Logistic regression was used for multivariate analysis.

Results

Patients

Sixty-one episodes of enterococcal CRBSI were identified during the study period from 268 episodes of enterococcal bacteraemia. Mean age of patients was 54 years (median 63 years; range 2 months to 80 years) and 35 (57%) episodes occurred in male patients. Fifty-four episodes (86%) occurred in adults (>18 years of age). Enterococcal CRBSI showed a bimodal age distribution with peak incidence occurring in infants and the elderly (data not shown). The majority of episodes (38 of 61, 62%) occurred on the renal unit, primarily in patients with end-stage renal disease on haemodialysis. Three episodes occurred on general surgical wards, 10 on adult intensive care, two on paediatric intensive care, five on paediatric/neonatal wards, two on the haematology ward and one on a general medical ward. Of all episodes occurring in adult patients, 29 of 54 (54%) fulfilled the criteria for sepsis syndrome. All seven patients that failed therapy died within 10 days of the first positive blood culture; five of these had sepsis syndrome and enterococcal CRBSI was considered to have contributed to death in each case. Eight adults who did not have sepsis syndrome or fever at presentation had suffered from non-specific symptoms and general malaise. In three episodes the patients were asymptomatic.

Microbiology

The majority of episodes, 50 of 61 (82%), were caused by Enterococcus faecalis, with the remainder caused by Enterococcus faecium. Eighteen per cent of isolates were ampicillin resistant, 5% vancomycin resistant and 16% gentamicin resistant. Enterococci occurred with other organisms in 11 of 61 (18%) episodes, comprising coagulase-negative staphylococci (four), Staphylococcus aureus (three), Candida albicans (one), Enterobacter cloacae (one), Acinetobacter sp. (one) and Pseudomonas aeruginosa (one). Infection was mixed in two episodes in which the CVC was retained: one of these was an Enterobacter, the other a coagulase-negative staphylococcus.

CRBSI management

A summary of management and outcome is shown in Table 1. Overall, of 61 episodes, 45 were cured, nine recurred and seven were associated with treatment failure. Dates of CVC insertion and removal were available for 43 of the episodes. Median duration of catheter placement was 14 days (mean 30 days; range 1–184 days); 18 and 43 episodes occurred in permanent and temporary catheters, respectively. Forty-eight (79%) catheters were removed during the study because of enterococcal infection; salvage of the CVC was attempted with antimicrobial treatment in the remaining 13 episodes. Despite removal, treatment failed in six of 48 (12.5%) episodes and infection recurred in a further two (4%). Forty-one
episodes (69%) were treated with appropriate antimicrobials and the remainder received no antimicrobials or a regimen that was considered inappropriate. The median duration of treatment was 5 days (mean 6.4 days; range 0–21 days).

Univariate analysis of variables that may have influenced outcome such as age, gender, underlying condition, presence of sepsis syndrome, type of vascular access device, mixed infection, species of *Enterococcus*, resistance to vancomycin, gentamicin or ampicillin, appropriate antimicrobial therapy or duration of antimicrobial therapy did not have a significant impact when all 61 episodes were analysed ($P > 0.05$, Fisher’s exact test). Line removal, however, was significantly associated with cure ($P = 0.003$, Fisher’s exact test). Multivariate (logistic regression) analysis of all 61 episodes confirmed that only catheter removal was significantly associated with cure ($P = 0.001$).

**Management with CVC in situ**

In episodes in which the CVC was left in situ, a cell wall-acting antimicrobial plus gentamicin combination was associated with cure in five of five (100%) episodes; the combination was prescribed for a median duration of 11.4 days (mean 10 days; range 9–14 days). Monotherapy with an appropriate antimicrobial was curative with the CVC in situ in only one of four (25%) episodes. One of the cases managed successfully with the CVC in situ was an exit site infection treated with piperacillin/tazobactam and gentamicin. The isolate causing this episode was subsequently found to exhibit high-level resistance to gentamicin on disc testing; formal synergy testing would be required to determine whether the antimicrobial combination retained bactericidal activity, and this is the subject of ongoing investigation. Univariate analysis showed that the cell wall-acting agent plus gentamicin combination was significantly more effective than monotherapy with a cell wall-acting agent in the subgroup of cases treated with the CVC in situ ($P < 0.05$, Fisher’s exact test). This remained true if the two cases with mixed infection were excluded from the analysis. Univariate analysis of variables that may have influenced the outcome of episodes managed with the CVC in situ, such as age, underlying condition, presence of sepsis syndrome, type of vascular access device, mixed infection, species of *Enterococcus* and resistance to vancomycin, gentamicin or ampicillin was not significantly different between episodes treated with a cell wall-acting agent plus aminoglycoside compared with those treated with a cell wall-acting antimicrobial alone ($P > 0.05$).

Inappropriate or no antimicrobial treatment with the CVC in situ failed to eradicate infection in four of four (100%) cases. Of the two episodes in which the CVC was left in situ and no antimicrobials were prescribed, neither was associated with symptoms or sepsis syndrome. Both of these episodes occurred in patients with cuffed, tunneled permanent access devices, which had been in place for at least 100 days, and both episodes recurred without treatment.

**Discussion**

Management of enterococcal CRBSI is an increasing clinical challenge for which specific clinical data are lacking. Like many other organisms capable of causing CRBSI, enterococci can adhere to biomedical polymers and form a biofilm, thereby making antimicrobial treatment problematic. For example, viability of *E. faecalis* growing as a biofilm in vitro was found to be unaffected by therapeutic concentrations of vancomycin. Such observations have fuelled the belief that infected devices require removal to achieve cure. However, successful treatment of CRBSI in situ using antimicrobials is clearly possible in some cases. Surgically implanted, cuffed, tunneled, vascular access devices are more difficult to insert and to remove than non-tunnelled catheters intended for short-term use. The risks associated with removal, e.g. in patients at increased risk of bleeding, have led to attempted treatment of catheter-related infection in situ with through-line antimicrobials. *Marr et al.*, for example, although they did not use the same strict definition of CRBSI, reported successful salvage of 12 catheters out of 62 episodes of catheter-related bacteraemia caused by a variety of pathogens in patients undergoing haemodialysis.

Although the proportion of all enterococcal bacteraemias attributable to intravascular catheter infection is increasing, case definitions, patient populations and period of data collection vary considerably between studies. Among all causes of CRBSI, enterococci were the aetiological agents in 0% (in totally implantable catheters) to 14% of cases. Enterococcal CRBSI comprised 23% of all episodes of enterococcal bacteraemia occurring in our institution during the study period. The vast majority of enterococcal CRBSI occurred in renal patients, but the reasons for this are unclear. Eighteen of 37 episodes on the renal unit were caused by isolates that were closely related by PFGE, suggesting the presence of an endemic strain with a particular predisposition to cause CRBSI (data not shown). Although generally considered to be low-grade pathogens, 54% of adult patients in this study had sepsis syndrome at presentation, and enterococcal CRBSI may have contributed to the death of seven (11%) patients.

The ratio of *E. faecalis* to *E. faecium* CRBSIs was similar to that reported for enterococcal infections in general. Only 5% CRBSI were caused by vancomycin-resistant enterococci (VRE). Following a cluster of VRE infections on the renal unit during the study period, a new policy for the empirical antimicrobial treatment of suspected catheter-related infection was introduced, which used fluoroquinolones in preference to vancomycin and is consistent with national (IDSA) guidelines. This policy may account for ‘inappropriate’ antimicrobial management of enterococcal CRBSI in some cases.

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Although advice was given to change empirical antimicrobials to appropriate agents once susceptibilities were known, this did not always happen. The IDSA guidelines for the treatment of enterococcal CRBSI caused by susceptible isolates advise either ampicillin or vancomycin alone, or in combination with an aminoglycoside. We found that treatment of enterococcal CRBSI in situ with either vancomycin or ampicillin monotherapy was associated with recurrence of infection. Although the isolates appeared susceptible to these antimicrobials in vitro, using a disc diffusion technique, the failure to eradicate infection is indirect evidence of the presence of biofilm and the bacteriostatic activity of these agents against most enterococci. The only regimen that was successful in curing CRBSI in situ was the combination of a cell wall-acting antimicrobial plus gentamicin; this regimen was statistically superior to ampicillin or vancomycin monotherapy. In other clinical settings that require organism eradication to achieve cure, such as endocarditis, in vitro and animal model evidence of bactericidal activity has led to recommendations for the combined use of ampicillin and gentamicin therapy. When resistance (e.g. to gentamicin or vancomycin) precludes the use of a bactericidal antimicrobial combination, attempted catheter salvage may not, therefore, be appropriate. A lack of any statistical difference in outcome between the groups treated by catheter removal plus appropriate antimicrobials ($n = 32$) or catheter removal without antimicrobials (or with inappropriate antimicrobials) ($n = 16$) suggests that catheter removal alone may be sufficient treatment for enterococcal CRBSI; however, recurrence occurred in two patients who received no antimicrobial treatment. Although it was not possible to determine the optimal duration of antimicrobial treatment in this study, the five episodes successfully treated in situ received a bactericidal combination of antimicrobials for a median duration of 11.4 days (range 9–14 days). Further studies will be required to confirm these findings.

Secondary endocarditis may complicate the management of enterococcal CRBSI, however, no cases of nosocomial endocarditis were observed during this study, even in patients who experienced recurrent enterococcal infection. It should be noted, however, that routine echocardiography was not undertaken as part of follow-up. Unlike S. aureus CRBSI, secondary enterococcal endocarditis in our experience appears to be a rare complication.

Enterococcal CRBSI is an important clinical problem that causes loss of CVCs, morbidity and may contribute to mortality. We found that enterococcal CRBSI can, in some cases, be successfully treated with antimicrobial therapy without CVC removal. In conclusion, our preliminary data suggest that a cell wall-acting antimicrobial in combination with gentamicin is required to reliably treat enterococcal CRBSI in situ. Further data are required to confirm these findings. In the setting of permanent vascular access devices, the risks of attempted cure in situ must be balanced against those associated with CVC removal.

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References

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