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Original Article

A 10-year profile of enterococcal bloodstream infections at a tertiary-care hospital in Japan

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ABSTRACT

Objectives: The first aim of this study is to characterize the epidemiology of enterococcal bloodstream infections (BSIs) at a Japanese tertiary-care hospital. The second aim is to identify predictive factors for 30-day mortality.
Methods: We conducted a single center retrospective observational study. All patients with enterococcal BSI between 2005 and 2014 were enrolled. Univariate and multivariate analysis were performed to evaluate predictive factors for 30-day mortality.
Results: A total of 410 patients with enterococcal BSI were enrolled. *Enterococcus faecalis* was identified in 200 patients (48.8%) and *Enterococcus faecium* in 124 patients (30.2%). Isolates were susceptible to ampicillin and vancomycin (67.3% and 97.8%, respectively). Isolates that were not susceptible to vancomycin were either *Enterococcus casseliflavus* or *Enterococcus gallinarum*. All strains of *E. faecalis* and 10.8% of *E. faecium* strains were susceptible to ampicillin. Thirty-day mortality was 24.8%. Predictive factors for 30-day mortality were Charlson Comorbidity Index (CCI) 1–2 (adjusted odds ratio [OR] 6.07, 95% confidence interval [CI]: 1.22–30.2), CCI 3–4 (adjusted OR 8.79, 95% CI: 1.70–45.4), CCI ≥5 (adjusted OR 17.6, 95% CI: 3.52–88.2), *E. faecium* bacteremia (adjusted OR 2.19, 95% CI: 1.27–3.76), Pitt Bacteremia Score (PBS) ≥5 (adjusted OR 15.1, 95% CI: 6.41–35.6), and source control (adjusted OR 0.39, 95% CI: 0.22–0.72).
Conclusion: Vancomycin-resistant strains of *E. faecalis* and *E. faecium* were not seen in this cohort. In addition, all strains of *E. faecalis* and 10.8% of *E. faecium* strains were susceptible to ampicillin. Predictive factors for 30-day mortality were CCI score, *E. faecium* bacteremia, PBS score, and source control.

1. Introduction

Enterococcus species are a major cause of bloodstream infection (BSI). In-hospital mortality associated with enterococcal BSI of 25%–50% was reported in previous studies [1–6]. Enterococci are generally resistant to all cephalosporins. In addition, acquired resistance to various antibiotics including penicillins, aminoglycosides, and glycopeptides has increased. Vancomycin-resistant enterococcus (VRE), in particular, has been shown to be associated with increased mortality [3]. Other factors associated with mortality include age, Charlson Comorbidity Index (CCI), solid organ transplant, nosocomial infection, primary bacteremia, pulmonary infection, severity of illness, resistance to ampicillin, and inappropriate antibiotic treatment [5–7]. In contrast, enterococcal BSI caused by VRE is very rare in Japan [8,9]. The epidemiology of enterococcal BSI and risk factors associated with 30-day mortality in Japan is still unclear. Only a few retrospective studies about enterococcal BSI have been performed. The purpose of this study is to further characterize the epidemiology of enterococcal BSI and investigate the factors associated with 30-day mortality in Japan.

2. Patients and methods

We reviewed the medical records of all patients who had an enterococcal BSI at the Kameda Medical Center, a tertiary care center with 925 beds in Kamogawa, Japan. This study was approved

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by the Committee for Ethics of Kameda Medical Center, Japan, under the condition that personal data were kept confidential. Because of the retrospective, observational nature of the study, the requirement for informed consent was waived by the committee.

Patients with positive blood cultures between 2005 and 2014 were screened using our laboratory database. Blood cultures positive for *Enterococcus* spp. were identified and investigated using electronic medical records. Patients with true bacteremia were included, and those with positive culture results owing to contamination were excluded. A patient was considered to have had true bacteremia if more than two sets of blood cultures were positive for *Enterococcus* spp. Furthermore, a patient with one positive blood culture for *Enterococcus* spp. and signs of sepsis was also considered to have had true bacteremia. However, one positive blood culture in the absence of clinical signs of sepsis was considered to be the result of contamination.

We gathered information on age, sex, number of positive blood cultures, clinical setting (community or nosocomial onset), underlying health conditions (solid tumor, lymphoma, leukemia, congestive heart failure, myocardial infarction, peripheral vascular disease, cerebrovascular disease, hemiplegia, dementia, chronic pulmonary condition, connective tissue diseases, peptic ulcer disease, diabetes mellitus, moderate to severe chronic kidney disease, liver disease, and acquired immunodeficiency syndrome [AIDS]), steroid use, previous detection of *Enterococcus faecium*, previous use of antibiotics within 3 months, vital signs on the day of the positive blood culture, source of infection, susceptibility of organism isolated to various antibiotics, choice of initial antibiotic treatment, performance of source control, and 30-day mortality. Appropriate initial antibiotics were defined as penicillins (e.g., penicillin G, ampicillin, piperacillin, ampicillin/sulbactam, or piperacillin/tazobactam) or agents that work against resistant gram-positive bacteria (e.g., vancomycin, teicoplanin, daptomycin, or linezolid) for ampicillin-susceptible isolates, and agents that work against resistant gram-positive bacteria for ampicillin-resistant isolates that were administered before the blood culture sample yielded bacterial growth. We also calculated the Charlson Comorbidity Index (CCI) using the information about the comorbidities. The source of infection was determined in patients when another specimen was positive for *Enterococcus* spp. or there was a clinically evident site of infection. If there was no clinically evident site of infection in a patient with true bacteremia, it was recorded as primary bacteremia. The severity of the bacteremia on the day of onset was graded by the Pitt Bacteremia Score (PBS).

Blood specimens were processed in the microbiology laboratories using the BACTEC blood culture system (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). For blood culture bottles, we used BD BACTEC Plus Aerobic/F Culture Vials (92F, 23F), BD BACTEC Plus/10 Anaerobic/F Culture Vials (93F, 21F), and BD BACTEC Myco/F Lytic Culture Vials (all Becton, Dickinson and Company). Bottles were incubated at 37 °C and examined daily for 7 days. Organisms were identified to the species level using the MicroScan WalkAway system (Beckman Coulter, Miami, FL, USA). Broth microdilution methodology was used to determine the minimal inhibitory concentrations of the antibiotics that were tested. Isolate susceptibility to various antibiotics was judged according to criteria recommended by the Clinical and Laboratory Standards Institute (CLSI) M100-S24 [10].

The OR for 30-day mortality was calculated with 95% CIs for each variable in univariate logistic regression. All variables with clinical importance and those with a p value of <0.1 in the univariate analysis were included in the multivariate analysis. A backward stepwise method was used to select the most useful predictors for the outcome. All analyses were performed using the R version 3.0.2 (http://www.r-project.org) with the EZR frontend [11].

3. Results

In total, there were 440 cases with blood cultures positive for *Enterococcus* spp. Of these, 30 cases were considered to be the result of contamination. Thus, there were a total of 410 enterococcal BSI cases during the study period. Patient demographics, clinical characteristics, microbiological characteristics, therapy, and outcomes are summarized in Table 1. A total of 237 cases (57.8%) received antibiotic treatment within 3 months before the onset of bacteremia. The type of antibiotics administered were cephalosporins in 113 cases, penicillins in 98 cases, vancomycin in 41 cases, quinolones in 38 cases, and carbapenems in 34 cases. The most common species identified was *Enterococcus faecalis* in 200 cases (48.8%), followed by *E. faecium* in 124 cases (30.2%). In nine cases, two species of *Enterococcus* spp. were identified. Among the nine cases, seven cases involved *E. faecalis*. The other species identified, along with *E. faecalis*, were *E. faecium* in five cases and *E. casseliflavus* and *E. raffinosus* in one case each. Another case involved both *E. avium* and *E. raffinosus*. The last case involved both *E. faecium* and *E. avium*. Polymicrobial bacteremia was seen in 182 cases (44.4%). Organisms belonging to the Enterobacteriaceae family were most commonly identified along with *Enterococcus* spp., followed by gram-positive cocci, and anaerobes. The most common source of infection was intra-abdominal infection, followed by urinary tract infection. Infective endocarditis was seen in 22 cases (5.4%). Among them, 10 cases involved the aortic valve, four cases involved the mitral valve, and two cases involved both the aortic and mitral valves. Other sources of infection included bone and joint infections in six cases, skin and soft tissue infections in four cases, gynecological infections in three cases, pulmonary infections in two cases, and bacterial meningitis in one case. Source control was performed in 160 cases (39.1%). Endoscopic retrograde cholangiopancreatography (ERCP) was performed in 94 cases, percutaneous transhepatic biliary drainage (PTBD) in 29 cases, urinary stenting in 16 cases, and open surgery in 14 cases. Susceptibility to ampicillin was 67.3%. All strains of *E. faecalis* and 10.8% of *E. faecium* strains were susceptible to ampicillin. Susceptibility to vancomycin was 97.8%. Of the nine strains that were not susceptible to vancomycin, seven were *Enterococcus gallinarum* isolates and two were *E. casseliflavus* isolates. Thirty-day mortality was 24.8%. In univariate analysis, variables identified as predictors for 30-day mortality were CCI $\geq$5, steroid use, prior antibiotics use within three months, nosocomial bacteremia, bacteremia due to *E. faecium*, PBS $\geq$5, urinary tract infection as a source of infection, primary bacteremia, appropriate initial antibiotics, source control, and non-susceptibility to ampicillin (Table 2). These variables and CCI 1–2 and CCI 3–4 were included in the final multivariate logistic regression model (Table 3). Multivariate analysis revealed CCI (1–2, 3–4, $\geq$5), bacteremia due to *E. faecium*, PBS $\geq$5, and source control were independently associated with 30-day mortality.

4. Discussion

We conducted a single center retrospective observational study to describe the epidemiological and clinical features of enterococcal BSI and identify factors associated with 30-day mortality in patients admitted at a Japanese tertiary-care hospital. A total of 410 cases were diagnosed with enterococcal BSI over the past 10 years. Neither vancomycin-resistant *E. faecalis* nor *E. faecium* were seen in this cohort. All strains of *E. faecalis* and 10.8% of *E. faecium* were susceptible to ampicillin. In addition, we identified that independent factors associated with 30-day mortality were CCI (1–2, 3–4, and $\geq$5), bacteremia due to *E. faecium*, PBS $\geq$5, and source control.

The sources of bacteremia frequently identified in this cohort were intra-abdominal infection, urinary tract infection, and