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Original article

Clinical features of enterococcal bacteremia due to ampicillin-susceptible and ampicillin-resistant enterococci: An eight-year retrospective comparison study

Yohei Hamada [a, *], Hiroki Magarifuchi [a], Megumi Oho [b], Koji Kusaba [b], Zenzo Nagasawa [c], Mami Fukuoka [d], Hiroki Yamakuchi [a], Toshiharu Urakami [a], Yosuke Aoki [a]

[a] Division of Infectious Disease and Hospital Epidemiology, Saga University Hospital, Japan
[b] Clinical Laboratory, Saga University Hospital, Japan
[c] Department of Medical Technology and Sciences, International University of Health and Welfare, Japan
[d] Division of Infection Control and Prevention, Saga Prefectural Medical Center Koseikan, Japan

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ABSTRACT

Enterococcus consists human bowel flora, but sometimes behave as an important nosocomial pathogen. In order to identify clinical characteristics that help discriminate between ampicillin-susceptible and ampicillin-resistant enterococcal bacteremia in advance for antimicrobial susceptibility testing, a retrospective eight-year study was carried out in patients with enterococcal bacteremia experienced in Saga University Hospital, Japan. A total of 143 patients were included in the analysis: 85 (59.4%) with bacteremia caused by ampicillin-susceptible enterococci and 58 (40.6%) by ampicillin-resistant strains. Hospital-acquired bacteremia was present in 79.0% (113/143) of patients. Abdominal infections, urinary tract infections, and unknown source were predominant foci for the two groups. Patients with ampicillin-resistant enterococcal bacteremia was significantly associated with hematological cancer, immunosuppressive therapy, prior use of antibiotics, and mucositis associated with febrile neutropenia. The 28-day mortality was significantly higher in ampicillin-resistant enterococcal bacteremia.

On multivariate analysis, independent risk factors for ampicillin-resistant enterococci were as follows: prior exposures to penicillins and carbapenems, and bacteremia related to mucositis with febrile neutropenia.

These findings would assist physicians in deciding whether glycopeptide antibiotics should be included as an empiric antibiotic therapy in patients with suspected enterococcal infections and also those with persistent neutropenic fever refractory to fourth generation cephalosporin.

A few cases of MALDI-TOF MS-identified *Enterococcus faecium* that turned out ampicillin-sensitive were also described to emphasize the importance of taking epidemiological aspects of patients into considerations when deciding initial antimicrobial treatment.

1. Introduction

Enterococci are minority members of the bacterial community inhabiting gastrointestinal tracts of humans. They have been considered to be harmless to humans. However, enterococci have emerged as a major cause of nosocomial and community-acquired infections [1].

Enterococcus faecalis (*E. faecalis*) and *Enterococcus faecium* (*E. faecium*) are the two major species associated with enterococcal infections. *E. faecalis* is most likely to be susceptible to ampicillin and vancomycin. *E. faecium*, much less frequently isolated than *E. faecalis*, has a higher incidence of resistance to multiple antimicrobial agents [1]. In addition, approximately ten species, including *Enterococcus avium*, *Enterococcus casseliflavus*, *Enterococcus durans*, *Enterococcus gallinarum*, *Enterococcus raffinosus*, also occasionally cause infections [1].

* Corresponding author. Division of Infectious Disease and Hospital Epidemiology, Saga University Hospital, 5-1-1 Nabeshima, Saga 849-8501, Japan. Tel./fax: +81 952 34 3294.
E-mail address: sh2440@cc.saga-u.ac.jp (Y. Hamada).

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The worldwide spread of vancomycin-resistant *enterococcus* (VRE) is of particular concern. However, in countries where the prevalence of VRE is still low as in Japan, whether the clinical isolate of enterococci is susceptible or resistant to ampicillin is the major issue when choosing an initial antimicrobial agent. Since, little data has been published in this regard, a case–control study was conducted to identify clinical characteristics that help distinguish between ampicillin-susceptible and ampicillin-resistant enterococcal bacteremia prior to antimicrobial susceptibility testing.

2. Patients and method

We performed retrospective chart review of demographic, microbiological and clinical data on all patients with enterococcal bacteremia admitted to Saga University Hospital, which is a 604-bed tertiary-care hospital, over the past eight years, from 2006 to 2013.

All blood cultures were processed by the hospital microbiology laboratory using BacT/ALERT 3D (Sysmex-BioMérieux Japan, Tokyo, Japan). Between 2006 and 2011, Enterococcus species were identified with VITEK 2 (Sysmex-BioMérieux Japan). Enterococcal bacteremia was defined by the isolation from one or more sets of blood culture with drawn aseptically. Since 2012, we have introduced MALDI Biotyper system (Bruker Daltonics, Inc., Billerica, MA) with MALDI-TOF MS (matrix-assisted laser desorption ionization-time of flight mass spectrometry) for species identification. Minimum inhibitory concentrations (MICs) were measured with broth microdilution test and interpreted based on the standard criteria of the Clinical and Laboratory Standards Institute (CLSI) [2].

Patients were identified by a search of computerized database for all blood cultures positive for *enterococcus* species between 2006 and 2013.

Medical records of patients were retrospectively reviewed regarding demographic characteristics, acquisition data (community-acquired or nosocomial) and the clinical information, including underlying diseases, likely source of bacteremia, risk factors that predispose patients to healthcare-associated infections (management in the intensive care unit, recent surgery, placement of medical devices, prior antibiotic use), and patients' prognosis (crude mortality at 28 days after the onset of bacteremia). The analyses of microbiological data included bacterial identification to the species level, antimicrobial susceptibility. Polymicrobial bacteremia was defined by the isolation of enterococci together with non-enterococcal species from the blood culture drawn at the same time. A single concomitant isolation of skin commensals, such as coagulase-negative *staphylococcus*, *Bacillus* species, *Corynebacterium* species, from only one bottle of simultaneous blood cultures was considered contaminant.

Statistical analysis was performed using the SPSS statistics version 20.0 (IBM Japan, Tokyo, Japan). Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate, and continuous variables were compared using Student's *t*-test or Mann–Whitney U test. Results with *P*-values ≤ 0.05 were considered to be statistically significant.

Logistic regression analysis was carried out to determine independent factors associated with ampicillin-resistant enterococcal bacteremia. Variables with *P*-values >0.05 in the univariate analysis were excluded from the multivariate analysis. Results were reported as adjusted odds ratio with 95% confidence intervals.

This study was approved by the institutional review board of Saga University Hospital (Approval No. 2014–12-14).

3. Results

There were a total of 2180 episodes of bacteremia in the study period, and 152 episodes (7.0%) were caused by enterococci, except for only one enterococcal isolate from the blood culture that was considered contaminant, because the patient's skin was covered with his fecal incontinence when the blood culture was drawn. Nine episodes in eight patients of either recurrent or persistent bacteremia were excluded. Therefore, 143 patients were included in the analysis: 85 (59.4%) with bacteremia caused by ampicillin-susceptible enterococci (ASE) and 58 (40.6%) by ampicillin-resistant enterococci (ARE). The most commonly isolated species was *E. faecalis*, comprising 52% (75/143), followed by *E. faecium* (37%; 53/143), *E. avium* (n = 5), *E. casseliflavus* (n = 5), *E. gallinarum* (n = 4), *E. raffinosus* (n = 1). A comparison of demographic and clinical characteristics between the two groups is shown in Table 1.

Enterococcal bacteremia was significantly more frequent in the hospital setting (113/143, 79.0%), occuring at a density of 0.07/1000 patient-days (ASE 0.04/1000 patient-days and ARE 0.03 patient-days). Patients with ARE bacteremia had been hospitalized an average of 5.0 days longer than those with ASE bacteremia when they developed laboratory-confirmed-bacteremia.

Hematological malignancy, neutropenia (absolute neutrophil count $\leq 500/\mu L$), current use of immunosuppressive drugs, including glucocorticoids and anti-TNF agents, placement of central intravenous catheter, and previous use of penicillins, cephalosporins, carbapenems and sulfamethoxazole/trimethoprim were significantly less common in ASE than ARE bacteremia. Patients with ASE bacteremia were more likely to have undergone recent surgery. ARE bacteremia was significantly associated with higher mortality ($P = 0.004$).

Microbiological comparisons are shown in Table 2. The 75 episodes of 85 ASE bacteremia were caused by *E. faecalis* (88.2%), and only two by *E. faecium*. In contrast, *E. faecium* was the most common organism in patients with ARE bacteremia (51/58, 87.9%). No vancomycin-resistant enterococci were isolated.

The most common primary focus of enterococcal bacteremia was intra-abdominal infections (46/143, 32.2%), followed by urinary tract infections (22/143, 15.4%). Four were diagnosed as primary catheter-related bloodstream infection (CRBSI). Importantly, mucositis, a symptomatic diagnosis based on the presence of oral ulcer and/or diarrhea that are common manifestations induced by mucosal damage due to anti-cancer chemotherapy, associated with neutropenia was a significant predictor for ARE bacteremia (17/58, 29.3%) rather than for ASE bacteremia (5/85, 5.9%) ($P < 0.001$).

52 episodes (36.4%) were polymicrobial bacteremia, with *Enterobacteriaceae* being the most common organisms isolated at the same time.

Multivariate logistic regression analysis showed that prior exposures to penicillins and carbapenems, and enterococcal bacteremia related to mucositis with febrile neutropenia were significant risk factors for the susceptibility-confirmed ARE bacteremia (Table 3).

Although species identification as *E. faecium* might as well empirically indicate being resistant to ampicillin in the majority of the instances as described above, it should be noted that *E. faecium* particularly in the community setting, even though fairly exceptional, could be sensitive to ampicillin. Anecdotal case of *E. faecium* bacteremia that is sensitive to penicillin sometimes presents in the community setting. To illustrate:

An 85-year-old woman with a remote-past history of cholecystectomy due to gall stone presented with upper abdominal pain, and elevation of the liver and cholangiogenic enzymes. The positive blood culture was identified by MALDI-TOF MS as *E. faecium*, which was subsequently revealed penicillin-sensitive. The preceding administration of vancomycin (VCM) that was added to empiric sulbactam/ampicillin (SBT/ABPC) treatment based on the species identification prior to the susceptibility results was restored to monotherapy of SBT/ABPC.