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Original Article

Vancomycin-resistant enterococcal bacteremia: comparison of clinical features and outcome between *Enterococcus faecium* and *Enterococcus faecalis*

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Background and Purpose: Vancomycin-resistant enterococci (VRE) have emerged as important nosocomial pathogens. This study was conducted to clarify the clinical features and outcome of patients with vancomycin-resistant enterococcal bacteremia.

Methods: Patients with vancomycin-resistant enterococcal bacteremia treated at a medical center in northern Taiwan between November 1998 and July 2006 were reviewed. Clinical and bacteriological characteristics of *Enterococcus faecium* and *Enterococcus faecalis* were compared.

Results: Twelve patients (6 males and 6 females) were included for analyses. The mean age was 69.3 years (range, 40 to 86 years), and 8 cases (66.7%) were older than 65 years. All patients had underlying disease. Two patients received total hip replacement before development of VRE bacteremia. Twelve patients had prior exposure to broad-spectrum antimicrobial therapy. Ten patients had prior intensive care unit stay and prior mechanical ventilation before VRE bacteremia. All of the patients (n = 12) had an intravascular catheter in place. Bacteremia was caused by *E. faecalis* in 4 patients and by *E. faecium* in eight. The portals of entry included urinary tract (8.3%), skin, soft tissue and bone (41.7%) and unknown sources (50.0%). *E. faecium* showed a higher rate of resistance to ampicillin and teicoplanin than *E. faecalis* (87.5% vs 0.0%, p=0.01). The 60-day mortality rate was higher in patients with *E. faecium* bacteremia than *E. faecalis* bacteremia (62.5% vs 0.0%), although statistical significance was not obtained (p=0.08).

Conclusions: VRE bacteremia may have an impact on the mortality and morbidity of hospitalized patients. Patients with bacteremia caused by vancomycin-resistant *E. faecium* had a grave prognosis, especially immunosuppressed patients. The prudent use of antibiotics and strict enforcement of infection control may prevent further emergence and spread of VRE.

Key words: Bacteremia; *Enterococcus faecalis*; *Enterococcus faecium*; Vancomycin resistance

Introduction

Enterococci are now firmly established as major nosocomial pathogens. Bacteria of the genus *Enterococcus* are the fourth most common cause of hospital-acquired infection and the third most common cause of bacteremia in the United States [1,2]. Of the genus *Enterococcus*, *Enterococcus faecalis* and *Enterococcus faecium* are the most commonly encountered species [3]. Enterococci, particularly *E. faecium*, have intrinsic and/or acquired resistance to many clinically important antimicrobial agents, such as ampicillin, penicillinase-resistant penicillin, cephalosporins, aminoglycosides, clindamycin and vancomycin [4]. Infections with vancomycin-resistant enterococci (VRE) have bee associated with increased morbidity, mortality and costs. We hypothesized that *E. faecalis* was more susceptible to ampicillin than *E. faecium*, and hence the difference in ampicillin susceptibility may impact on the clinical outcome of

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VRE bacteremia. In this study, the clinical features and outcome of patients with VRE bacteremia due to *E. faecalis* and *E. faecium* were compared.

Methods

Records of patients with VRE bacteremia treated at a medical center in northern Taiwan between November 1998 and July 2006 were reviewed. Data and information including demographic characteristics, underlying diseases, possible primary infection foci, invasive device use, laboratory findings, culture and susceptibility results, antimicrobial therapy and clinical outcome were obtained from the medical records.

Patients with VRE bacteremia were defined as having isolation of VRE from the blood culture. Antimicrobial susceptibility was determined by both broth microdilution and disk diffusion tests according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI; formerly National Committee for Clinical Laboratory Standards [NCCLS]) [5,6]. Tested antibiotics included ampicillin, gentamicin, vancomycin and teicoplanin. The minimal inhibitory concentration (MIC) of each antimicrobial agent was defined as the lowest concentration that inhibited visible growth of the organism. Vancomycin resistance was defined as an MIC ≥32 μg/mL.

Invasive device use was defined as having in place an intravascular catheter, such as a central venous catheter, Permcath, double lumen catheter and Swan-Ganz catheter. Prior broad-spectrum antimicrobial therapy from the date of admission to the date of VRE bacteremia was recorded.

The broad-spectrum antibiotics were classified into broad-spectrum cephalosporins, clindamycin, metronidazole, vancomycin, teicoplanin, fluoroquinolones, anti-pseudomonas penicillin, beta-lactam/beta-lactamase inhibitors, and imipenem.

Fever was defined as body temperature >38°C, leukocytosis as white blood cell count >12,000/μL, leucopenia as white blood cell count <4000/μL, and thrombocytopenia as platelet count <80,000/μL.

Sepsis syndrome was defined as a systemic response to infection and was indicated by the presence of ≥2 of the following conditions: (1) a temperature >38°C or <36°C; (2) a heart rate >90 beats per min; (3) a respiratory rate >20 breaths per min or partial pressure of carbon dioxide <32 Torr; and (4) a white blood cell count >12,000/μL or <4000/μL or the presence of >10% immature (band) forms in peripheral blood.

The statistical differences between *E. faecium* bacteremia and *E. faecalis* bacteremia were analyzed by using Fisher's exact test.

Results

During the 9-year study period, a total of 12 patients with VRE bacteremia were identified. There were 6 males and 6 females. The mean age was 69.3 years (range, 40 to 86 years), and 8 cases (66.7%) were older than 65 years. All of them had underlying disease, including hypertensive cardiovascular disease (n = 8), type 2 diabetes mellitus (n = 7), chronic renal insufficiency (n = 6), carcinoma of breast (n = 2), coronary artery disease (n = 1), sick sinus syndrome post-pacemaker implantation (n = 1), idiopathic pulmonary fibrosis (n = 1), chronic obstructive pulmonary disease (n = 2) and acute lymphocytic leukemia (n = 1).

The demographic and clinical data of the patients are summarized in Table 1. Two patients received total hip replacement before VRE bacteremia. Twelve patients had prior broad-spectrum antimicrobial therapy and ten patients had prior intensive care unit stay before VRE bacteremia. Ten patients experienced with prior mechanical ventilation before VRE bacteremia. Twelve patients had an intravascular catheter in place, including central venous catheter (n = 11), Permcath (n = 2), double lumen catheter (n = 1) and Swan-Ganz catheter (n = 1).

Nine patients had VRE colonization, obtained from rectal swab (n = 7, 58.3%), urine (n = 1, 8.3%), wound discharge (n = 4, 33.3%) and tissue (n = 1, 8.3%) before VRE bacteremia.

The clinical characteristics and outcome of patients with VRE bacteremia are shown in Table 2. The most common findings associated with the onset of VRE bacteremia were fever and leukocytosis. Clinical sepsis was evident in ten patients (83.3%). Three patients presented with disseminated intravascular coagulation. The mean Acute Physiology And Chronic Health Evaluation II score was higher in patients colonized with *E. faecium* than *E. faecalis* (26.3 vs 18.8), but statistical significance was not obtained. The 14-day mortality rate in the *E. faecium* and *E. faecalis* group was 37.5% and 0.0%, respectively (p>0.05). The 30-day mortality rate in was 50.0% and 0.0% (p>0.05) and the 60-day mortality rate was 62.5% and 0.0% (p=0.08).

Among the 12 patients with VRE bacteremia, four were caused by *E. faecalis* and eight were *E. faecium*.

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Table 1. Demographics, underlying diseases and predisposing conditions of 12 patients with vancomycin-resistant enterococcal bacteremia

Variable	*Enterococcus faecium* (n = 8) No. (%)	*Enterococcus faecalis* (n = 4) No. (%)	*p*
Age (years; mean) [range]	67.8 (46-82)	72.3 (40-86)	NS
Gender			
Male	4 (40.0)	2 (50.0)	
Female	4 (40.0)	2 (50.0)	
Underlying disease			
Type 2 diabetes mellitus	4 (50.0)	3 (75.0)	NS
Hypertensive cardiovascular disease	5 (62.5)	3 (75.0)	NS
Chronic renal insufficiency	5 (62.5)	1 (25.0)	NS
Carcinoma of breast	1 (12.5)	1 (25.0)	NS
Coronary artery disease	0 (0.0)	1 (25.0)	NS
Sick sinus syndrome post-pacemaker implantation	1 (12.5)	0 (0.0)	NS
Idiopathic pulmonary fibrosis	1 (12.5)	0 (0.0)	NS
Chronic obstructive pulmonary disease	1 (12.5)	1 (25.0)	NS
Acute lymphocytic leukemia	1 (12.5)	0 (0.0)	NS
Predisposing condition			NS
Total hip replacement	1 (12.5)	1 (25.0)	NS
Prior broad-spectrum antimicrobial therapy	8 (100.0)	4 (100.0)	NS
Prior ICU admission	6 (75.0)	4 (100.0)	NS
Length of ICU stay prior to bacteremia (days; mean) [range]	22.3 (0-73)	16.0 (3-34)	NS
Mechanical ventilation prior to bacteremia	7 (87.5)	3 (75.0)	NS
Mechanical ventilation prior to bacteremia (days; mean) [range]	19.0 (0-65)	34.3 (0-92)	0.06
Central venous catheter in place	8 (100.0)	4 (100.0)	NS

Abbreviations: ICU = intensive care unit; NS = not significant

The portals of entry for VRE bacteremia were urinary tract (8.3%), skin, soft tissue and bone (41.7%) and unknown source (50.0%).

One patient received total hip replacement and developed osteomyelitis caused by *E. faecalis* and methicillin-resistant *Staphylococcus aureus*. He received numerous courses of debridement and broad-spectrum antibiotic treatment. Prior long-term VRE colonizations were demonstrated on the rectal swab, central venous catheter tip and surgical wound.

The results of antimicrobial susceptibility testing are shown in Table 3. *E. faecium* showed higher rates of resistance to ampicillin and teicoplanin than *E. faecalis* (87.5% vs 0.0%, p=0.01). Six patients (50.0%) were prescribed vancomycin when the preliminary blood cultures grew Gram-positive cocci, and only two of them received appropriate antimicrobial therapy after the final report.

Only two patients with *E. faecium* bacteremia received appropriate antimicrobial therapy. One was a 77-year-old male with underlying idiopathic pulmonary fibrosis with acute exacerbation and type 2 diabetes mellitus. Vancomycin was prescribed, as the preliminary blood culture report showed Gram-positive cocci. He received quinupristin-dalfopristin treatment after the final blood culture report disclosed *E. faecium* that was resistant to all of the tested antimicrobial agents. He died sixty days after developing VRE bacteremia. The cause of death may not have been VRE bacteremia. Another 71-year-old male patient with underlying type 2 diabetes mellitus was admitted due to acute cholecystitis and developed gastric ulcer with bleeding during hospitalization. He also received vancomycin therapy when the preliminary blood culture report disclosed Gram-positive cocci. He received broad-spectrum penicillinase-resistant penicillin treatment after the final blood culture disclosed *E. faecium* that was susceptible to ampicillin. He died 25 days after developing VRE bacteremia due to sepsis with multiple organ failure.

Discussion

The prevalence of infections related to VRE continues to increase annually. In the United States, Song et al reported that 316 patients developed 345 episodes of nosocomial VRE bacteremia in the Johns Hopkins Hospital within 7 years [7]. In our study, the prevalence of VRE bacteremia was 0.0036 per 1000 patient-days.

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Table 2. Clinical characteristics and outcome of 12 patients with vancomycin-resistant enterococcal bacteremia

Variable	*Enterococcus faecium* (n = 8) No. (%)	*Enterococcus faecalis* (n = 4) No. (%)	*p*
Clinical and laboratory findings			
Fever (>38°C)	5 (62.5)	2 (50.0)	NS
Leukocytosis (>12,000/μL)	5 (62.5)	3 (75.0)	NS
Leukopenia (<4000/μL)	2 (25.0)	0 (0.0)	NS
Thrombocytopenia (<80,000/μL)	3 (37.5)	0 (0.0)	NS
Sepsis	8 (100.0)	2 (50.0)	0.09
DIC	1 (12.5)	2 (50.0)	NS
Source of bacteremia			
Urinary tract	1 (12.5)	0 (0.0)	NS
Skin, soft tissue and bone	3 (37.5)	2 (50.0)	NS
Unknown source	4 (50.0)	2 (50.0)	NS
APACHE II score (mean) [range]	26.3 (19-38)	18.8 (4-33)	NS
Mortality			
14-day	3 (37.5)	0 (0.0)	NS
30-day	4 (50.0)	0 (0.0)	NS
60-day	5 (62.5)	0 (0.0)	0.08

Abbreviations: DIC = disseminated intravascular coagulation; APACHE = Acute Physiology And Chronic Health Evaluation; NS = not significant

Jean et al described 9 cases with VRE bacteremia in the National Taiwan University Hospital within 7 years [4]. Previous studies demonstrated that many factors seemed to be associated with the emergence of VRE bacteremia, including prolonged hospital stays, presence of a central venous catheter (with or without hyperalimentation), exposure to broad-spectrum antibiotics, and underlying immunocompromised conditions (such as neutropenia or acquired immunodeficiency syndrome) [8-10].

Approximately 36.3% of patients who die have mortality attributed to VRE bloodstream infections regardless of underlying causes, compared with 16.4% mortality among patients with bloodstream infections from vancomycin-sensitive enterococci [11].

Two of 8 patients in the *E. faecium* group who had solid tumor and hematologic malignancy, respectively, received chemotherapy. They developed neutropenic fever after chemotherapy and rapidly developed *E. faecium* bacteremia with sepsis. Both died within 3 days after the preliminary blood culture result showed Gram-positive cocci. Host factors, such as comorbidities and presence of serious underlying medical conditions (for example, immunosuppression, malignancy, chronic or hepatic failure), are important predisposing conditions [12,13].

In our study, the *E. faecium* group was highly resistant to ampicillin and teicoplanin compared with the *E. faecalis* group (p=0.01). High-level vancomycin resistance with teicoplanin susceptibility is generally referred to as Van-B type resistance, and is normally associated with the *van*B-resistance gene [14,15]. Noskin demonstrated that *E. faecium* is the strain most frequently resistant to vancomycin [16], and can result in high mortality. We suggested that immunocompromised patients with vancomycin-resistant *E. faecium* bacteremia should not receive vancomycin treatment. Quinupristin-dalfopristin, linezolid, daptomycin and tigecycline have been suggested as drugs of choice

Table 3. Susceptibilities of 12 isolates of vancomycin-resistant enterococci

Antibiotic	*Enterococcus faecium* (n = 8)[a] No. (%)	*Enterococcus faecalis* (n = 4)[a] No. (%)	*p*
Ampicillin	1 (12.5)	4 (100.0)	0.01
Gentamicin	1 (12.5)	1 (25.0)	NS
Vancomycin	0 (0.0)	0 (0.0)	NS
Teicoplanin	1 (12.5)	4 (100.0)	0.01

Abbreviation: NS = not significant

[a]Vancomycin minimal inhibitory concentration ≥256 μg/mL.

to treat vancomycin-resistant *E. faecium* bacteremia [17]. Based on our study results, ampicillin and teicoplanin could be the preferred treatment in patients with vancomycin-resistant *E. faecalis* bacteremia.

Many factors can increase the risk of colonization or infection with VRE. They can be divided into factors related to the host, the hospital, invasive procedures, the environment, and antibiotic use. These include prior antibiotic therapy, the number and duration of antibiotics received, prolonged hospitalization, hospitalization in an intensive care unit, concomitant serious illness, exposure to equipment or devices contaminated with VRE, and exposure to other patients who are colonized or infected with VRE [16,18].

Previous study demonstrated that patients with prolonged hospital stays, a central venous catheter in place, prior exposure to broad-spectrum antibiotics and underlying immunocompromised conditions were at high risk for VRE bacteremia. If these patients have prior VRE colonization and develop Gram-positive bacteremia, we suggest that vancomycin may be not the drug of choice and quinupristin/dalfopristin, linezolid, daptomycin or tigecycline should be considered.

Because vancomycin may contribute to the occurrence of VRE, its prudent use is essential [19]. Ena et al applied criteria to determine whether vancomycin use was indicated. They found that 33% of cases of vancomycin use were empiric, 33% of cases were prophylactic, and only 34% of cases were appropriate [20]. In fact, vancomycin use was frankly inappropriate in 10% of reviewed charts, and its use inappropriately monitored in 60% of cases [21]. Animal models suggested that disruption of anaerobic flora by some antibiotics (especially metronidazole) promoted overgrowth of enterococcal species in the gastrointestinal tract as well as increasing the frequency of translocation into mesenteric lymph nodes [21-23]. Therefore, appropriate vancomycin use needs to be promoted.

Broad-spectrum antibiotics such as cephalosporins have long been known to increase enterococcal infections, and many infections with VRE resolve with nonspecific therapy [16]. However, Quale et al restricted the use of third-generation cephalosporins, clindamycin, and vancomycin and noted a dramatic decrease in VRE prevalence, from 47% to 15% [24].

VRE bacteremia may have a major impact on the mortality and morbidity of hospitalized patients, especially in imunosuppressed hosts. The prudent use of antibiotics and strict enforcement of infection control may prevent further emergence and spread of VRE.

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