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Invasive infections due to vancomycin-resistant enterococci in adult patients

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Since 1990, vancomycin-resistant enterococci have emerged as important nosocomial pathogens. Invasive infections caused by these organisms have challenged most physicians because they are resistant to multiple antibiotics. We analyzed the clinical characteristics of adult patients with invasive vancomycin-resistant enterococci infections in the National Taiwan University Hospital from January 1993 through December 2000. A total of 11 adult patients were identified, 9 of whom had bacteremia (7 caused by vancomycin-resistant *Enterococcus faecalis* and 2 by vancomycin-resistant *Enterococcus faecium*) and one each had thoracic empyema (vancomycin-resistant *E. faecium*) and peritonitis (vancomycin-resistant *E. faecium*). Five patients had rectal swab cultures positive for vancomycin-resistant enterococci; 4 of them had underlying malignancies. The majority (91%) of these patients had prolonged hospitalization and prior long-term use of broad-spectrum cephalosporins (ceftriaxone, ceftazidime, or cefepime) or anti-anaerobic agents (clindamycin or metronidazole). The crude mortality rate was 64%. In conclusion, invasive infection caused by vancomycin-resistant enterococci is an emerging problem among hospitalized patients in Taiwan, particularly those with severe underlying diseases and exposure to multiple antibiotics.

Key words: Invasive infection, vancomycin-resistant enterococci

Vancomycin-resistant enterococci (VRE), first described in 1988, have emerged in the 1990s as major nosocomial pathogens [1-3]. Their resistance to environmental conditions such as heat and desiccation allows prolonged survival, and poor compliance with hand-washing procedures by healthcare workers has resulted in rapid spread of enterococci in hospitals [4-6]. Enterococci, particularly *Enterococcus faecium*, have intrinsic and/or acquired resistance to many clinically important antimicrobial agents, notably ampicillin, penicillinase-resistant penicillin, cephalosporin, aminoglycoside, clindamycin, and vancomycin [7,8]. From 1989 through 1993, the percentage of nosocomial enterococcal pathogens that were resistant to vancomycin increased 26-fold according to data from the National Nosocomial Infections Surveillance (NNIS) System [9]. Data from the NNIS System indicated that enterococci were the third most commonly isolated pathogens among nosocomial bloodstream infections from 1990 through 1992 [10]. In 1989, less than 0.4% of the enterococci were resistant to vancomycin in general hospital wards and intensive care units (ICUs). Eight years later, 15% of enterococcal isolated in general hospital wards and 23% in ICUs were resistant to vancomycin [11]. Efforts to prevent colonization using universal precautions and restricted vancomycin use at centers where VRE is endemic have been largely unsuccessful [4,12].

The pathogenicity of VRE, although solidly affirmed among cases of meningitis and endocarditis, has been difficult to establish among bloodstream infections. This is because these infections are often polymicrobial (especially among infections caused by vancomycin-susceptible enterococci) [3] and most are present in severely ill patients [3,4,14-16]. Data concerning patients with invasive VRE infections, however, are lacking in Taiwan.

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In Taiwan, the first clinical isolate of VRE was described in 1995 from a patient with bacteremic pneumonia [17]. Since then, increasing incidence of isolation of these organisms has been documented in many hospitals [18-20]. In this study, clinical and microbiological features of 11 patients with invasive VRE infections seen at hospital were analyzed.

Materials and Methods

From January 1993 through December 2000, all patients who had cultures positive for VRE from clinical specimens at the National Taiwan University Hospital were enrolled into this study. The medical charts of these patients were reviewed regarding their clinical characteristics including demographic information (age, sex), admission and discharge diagnosis, invasive devices use, duration of hospitalization (at general wards and ICU, respectively), exposure to antimicrobial agents, and outcomes. Patients with invasive VRE infections were defined as those identified with VRE from sterile body sites (such as blood, pleural effusion, and ascites) or from tips of central access (with confluent colony forming units). To evaluate the percentage of ICU-hospitalized cases invaded by or colonized with VRE flora, the total number of these patients was also calculated.

Exposure to antimicrobials was evaluated from the date of admission through the date of initial VRE isolation from blood, central vascular catheter, pleural effusion, or ascites. The exposed antibacterial antibiotics were classified into broad-spectrum cephalosporins, vancomycin, metronidazole, clindamycin, and others (including fluoroquinolones, antipseudomonal penicillins, β-lactam/β-lactamase inhibitors, and imipenem). Results of each antibiotic used daily in all individuals with invasive VRE infections were calculated using a sum of one specific anti-microbial agent multiplied by the duration (days in unit) of its administration. With respect to the outcome, the duration from admission to mortality or survival 2 months after invasive VRE events were recorded.

Enterococci were identified based on the following characteristics: growth on sheep blood agar, growth on bile-esculin agar and sodium chloride 6.5%, growth at 45°C, lack of gas production from glucose, hydrolysis of pyrrolidonly-B-naphthylamide, and identified to species level using the standard methods. Antimicrobial susceptibility testing of these isolates was performed initially using the standard disc diffusion method [21]. Vancomycin resistance was defined as a minimum inhibitory concentration (MIC) of ≥64 μg/mL. Rectal swabs were obtained for further identification of VRE colonization within gastrointestinal tract for all patients who had positive VRE cultures from other body sites.

Results

The clinical characteristics of 11 adult patients (5 men and 6 women) with invasive VRE infections are shown in Table 1. Their ages ranged from 43 to 77 years (mean, 64 years). Four (36%) patients had solid-organ malignancies (including cancers of esophagus, breast, and ovary). Seven (64%) patients had pneumonia when they acquired invasive VRE infections during hospitalization. Six of them had spent their hospitalization in ICUs. One female patient (Patient 8) was admitted because of secondary mediastinitis (after esophageal intubation). She underwent surgical debridement and intrapleural irrigation followed by chest tube implantation. Vancomycin-resistant *E. faecium*, oxacillin-resistant *Staphylococcus aureus* (ORSA), and *Candida albicans* were concomitantly isolated from her pleural effusion. Patient 11 was admitted monthly for regular chemotherapy for ovarian cancer. Duration of each hospitalization was short (<7 days), and she received only 4 days of cefazolin therapy within 2 months before VRE (*E. faecium*) was cultured from her ascetic fluid. Four patients (Patients 3, 7, 8, and 11) had VRE colonization during their ICU stay.

One patient (Patient 7) was transferred from a local hospital and his previous hospitalization course was not clear. The total hospitalization duration (before events of invasive VRE infections) for the 10 patients ranged from 5 to 67 days (mean, 43 days). Four (40%) of these 10 patients were not admitted to ICUs before acquisition of invasive VRE infections. Five patients acquired *E. faecium* and the other 6 acquired *E. faecalis* infections. Vancomycin-resistant *E. faecium* was isolated from both the blood sample and tip of central venous access in only one (Patient 2) of 10 patients who had central vascular lines (including 2 patients with port-A catheter) implanted.

Ten (91%) patients received broad-spectrum cephalosporins and/or ciprofloxacin before the acquisitions of VRE infections. Only 6 (55%) patients were prescribed vancomycin. All but one patient were given active agents against anaerobes (eg, β-lactam/β-lactamase inhibitors, cephamycin, antipseudomonal penicillins, imipenem, clindamycin, and metronidazole). These 11 patients received antibiotics for 4 to 111 days (mean, 61 days).

The overall crude mortality rate was 64%. Four patients died on the day when they were infected with the VRE. Four patients survived more than 2 months after acquisition of the VRE infections; of them, 2

Table 1. Clinical characteristics of 11 patients with invasive vancomycin-resistant enterococcal infections

Patient no.	Age/ sex	Clinical demographic characteristics				Exposure of antimicrobial agents				Outcome
		Underlying disease	Hospitalization in general wards/ ICU, day	Enterococcus species	Specimen(s) recovering VRE	Broad-spectrum cephalosporins (day)	Vancomycin (day)	Others (day)	Antibiotic, day	
1	76/F	Pneumonia Old pulmonary TB DM	36/16	*E. faecium*	Blood Pressure sore Uriine Anal swab	Cefepime (13)	+ (14)	Imipenem (12) Ciprofloxacin (11)	64	Survived
2	77/M	Esophageal cancer DM	52/Nil	*E. faecium*	Blood CVP tip Anal swab	Ceftriaxone (6) Ceftazidime (8)	+ (2)	Imipenem (2) Ciprofloxacin (4) Amox/clavulanate (2) Amp/sulbactam (4)	44	Died
3	73/M	Pneumonia Liver cirrhosis Heart failure	12/19	*E. faecium*	Blood Anal swab	Ceftazidime (14)	Nil	Clindamycin (14)	40	Died
4	45/F	Breast cancer Pneumonia	46/Nil	*E. faecium*	Blood	Ceftazidime (2)	Nil	Imipenem (14) Cefmetazole (4)	41	Died
5	40/F	Breast cancer In febrile neutropenia	35/19	*E. faecium*	Blood Vaginal discharge	Ceftazidime (14)	+ (17)	Imipenem (19) Ciprofloxacin (14)	97	Died
6	73/M	ICH Pneumonia	39/21	*E. faecium*	Blood Urine Anal swab	Ceftriaxone (1) Ceftazidime (13)	+ (42)	Imipenem (3) Ciprofloxacin (7) Cefmetazole (6) Metronidazole (13)	97	Survived
7	76/F	COPD Pneumonia	?/12	*E. faecium*	Blood	Ceftazidime (9)	Nil	Amox/clavulanate (2)	19	Survived
8	61/F	Mediastinitis ESRD	Nil/37	*E. faecium*	Pleural effusion Anal swab	Ceftazidime (8)	+ (23)	Imipenem (6) Ciprofloxacin (19) Amp/sulbactam (2) Metronidazole (2)	81	Survived
9	63/M	Pneumonia CAD Adrenal insufficiency	19/48	*E. faecium*	Blood	Ceftazidime (5)	+ (32)	Imipenem (25) Ciprofloxacin (19) Amp/sulbactam (5) Clindamycin (2) Metronidazole (5)	111	Died
10	73/M	COPD Cor pulmonale Pneumonia	26/Nil	*E. faecium*	Blood	Ceftriaxone (12) Ceftazidime (6)	Nil	Imipenem (2) Ciprofloxacin (7) Amp/sulbactam (6) Metronidazole (7)	71	Died
11	43/F	Ovarian cancer	5/Nil	*E. faecium*	Ascites	Nil	Nil	Nil	4	Died

Abbreviations: ICU = intensive care unit; VRE = vancomycin-resistant enterococci; TB = tuberculosis; DM = diabetes mellitus; ICH = intracranial hemorrhage; COPD = chronic obstructive pulmonary disease; ESRD = end-stage renal disease; CAD = coronary artery disease; CVP = central venous pressure

received intravenous teicoplanin therapy and the other 2 (Patients 1 and 6) did not receive effective antimicrobial agents. Three patients (Patients 2, 9, and 11) died within 2 months after acquisition of VRE infections, one (Patient 9) was prescribed inadequate doses of ampicillin (500 mg every 6 h intravenously) for treatment of VRE bacteremia. The MIC results of VRE isolates from blood and tip of central venous access (Patient 2) showed that these 2 VRE isolates were susceptible only to tetracycline.

Discussion

According to previous studies, many factors seemed to be associated with the emergence of invasive VRE infections, including prolonged hospital stays, central venous access (with or without hyperalimentation), exposure to metronidazole, and underlying immunocompromised conditions (such as neutropenia or acquired immunodeficiency syndrome) [3,15,16]. In the 11 adult patients, 3 of 4 patients with solid organ malignancies had not stayed in ICUs before they

acquired invasive VRE infections. In contrast, one of the 7 patients without malignancy had not stayed in an ICU before invasive VRE infections. Only 3 (27%) patients were younger than 60 years. These findings suggested that more than one factor including underlying immunodeficient illness, ICU hospitalization, and older chronological age may increase the risk for hosts susceptibility to invasive VRE sepsis or infections.

Central venous catheters may be the actual conduit through which the bacteremia is established, or they may simply be markers of debilitation and prolonged hospitalization, with other sources of bloodstream infection predominating. There is a well-documented conclusion that VRE line-related bacteremias and surgical sites (including abscesses) could be managed by catheter removal and surgical debridement or drainage, respectively [22]. Only one patient, who had underlying esophageal cancer and diabetes mellitus, was definitely considered to have central catheter-originated VRE sepsis. This patient died 21 days after the occurrence of VRE sepsis, even though the catheter was removed 5 days before VRE bloodstream infection occurred. Underlying diseases and probably high score in acute physiologic and chronic health evaluation (APACHE) II (data not shown) might be ascribed to his death.

Of the 9 adult patients with VRE bacteremias, only one (11%) was considered polymicrobial (ORSA and VRE). These results were similar to those of previous studies [3,23]. With the exception of 2 patients reported to have VRE bacteremia discovered at autopsy, at least 4 (57%) of the remaining 7 adult VRE bacteremic patients were proved (using rectal swabs) to have VRE colonization within the gastrointestinal tract. In view of the low polymicrobial incidence for VRE patients, some experts suggested that VRE bacteremia may emerge in the setting of prolonged gastrointestinal colonization as an isolated breakthrough event in antimicrobial coverage [3,16]. Two patients experienced extravascular (pleural effusion and ascites) VRE infections. One patient had mediastinitis after surgical intervention and chest tube insertion. *Enterococcus faecium* (in combination with ORSA and *C. albicans*) was isolated from her pleural effusion after a 37-day ICU stay. The other patient had postoperative ovarian cancer and received monthly chemotherapy. She did not spend more than 5 days for each hospitalization, nor was she exposed to multiple antimicrobial agents before acquisition of intraabdominal VRE infection. Whether short consecutive hospitalizations (of general ward) alone predisposes patients to acquiring VRE infections remains to be clarified.

With respect to pharmaceutical exposure, not all patients with invasive VRE infections had undergone vancomycin therapy. Instead, a high percentage of cases were prescribed broad-spectrum antibacterial antimicrobials (91%) and/or anti-anaerobic antimicrobial(s) (91%) during hospitalization. Except for one patient (Patient 7) who was referred from a nearby hospital acquired VRE bacteremia on the twelfth day of hospitalization, all 8 patients received at least 40 days of antibiotic treatment immediately before they were infected with VRE bacteremias. All of them received broad-spectrum cephalosporins. However, only 4 (36%) patients were prescribed metronidazole and 2 (18%) were prescribed clindamycin before invasive VRE infections. Either β-lactam/β-lactamase inhibitors or imipenem (or both agents) were administered to most (73%) patients. Based on their findings, Edmond and colleagues [16] hypothesized that agents with significant anaerobic activity increased the likelihood of VRE colonization in the lower gastrointestinal tract. 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 increased the frequency of translocation into mesenteric lymph nodes [24-26]. It has been argued that broad-spectrum antimicrobials that were inactive against enterococci (cephalosporins) also increased the risk for patients to experience enterococcus-associated bloodstream infections by creating a selective milieu for an enterococcal superinfection [27,28]. Thus, patients who are colonized with VRE within their gastrointestinal tract should be considered at risk for bacteremia, especially if anti-anaerobic antibiotics are concurrently administered.

Data from previous studies have provided evidence that invasive VRE infections seem to serve as a hallmark indicative of a severe, life-threatening disease processes [29]. Of the 11 patients with invasive VRE infections, 4 (36%) died immediately after invasion of VRE, and 3 (27%) died within 2 months of being infected with VRE. However, 4 patients survived more than 2 months after these infections. None of the 4 survivors had any underlying malignancy, although all of them had prolonged hospitalization and had received antibiotics for many days. In addition, 2 of the surviving patients (Patients 7 and 8) were prescribed parenteral teicoplanin because of the relatively low MIC results, but the remaining 2 survivors (Patients 1 and 6) were under strict isolation maneuvers without effective antibiotic therapy. Other unknown factors may have exerted important impact on their survival.

This study enrolled only 11 patients, and analysis

of the critical predictors for survival was difficult because of the limited case number. Fewer patients hospitalized in the ICU in this study experienced VRE infections than those in other hospitals [11]. Whether the enormous quantities of antibiotics employed in the agricultural and animal husbandry industries or the different microbiological strains had a more decisive role in the incidence of VRE infections and patient mortality needs more investigation.

In conclusion, many factors are considered to determine a patient's susceptibility to invasive VRE infections. Among a variety of enterococcal species, *E. faecalis* and *E. faecium* accounted for all VRE strains in this study. In addition to metronidazole and clindamycin, the use of broad-spectrum cephalosporins and other anti-anaerobic agents (β-lactam combined with β-lactamase inhibitor, imipenem) were documented in patients with invasive VRE infections. Translocation of these VRE pathogens within the gastrointestinal tract after overgrowth would probably led to bacteremia and extravascular infections. The association between the ban of antimicrobial use in the animal husbandry industry and fewer invasive VRE infections in the ICU patients needs more investigation.

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