

Vancomycin-Resistant Enterococcal Infections in Korea

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Enterococci recently became the second-to-third most commonly isolated organism from nosocomial infections. Enterococci are intrinsically more resistant to many antimicrobial agents and often show acquired resistance to many antimicrobial agents including high-level aminoglycosides. With the increased use of vancomycin, vancomycin-resistant enterococci (VRE) has become an important nosocomial pathogen. In Korea, the proportion of VRE among all enterococcal isolates in most tertiary care hospitals has remained around 1% or less, but the rate of carriage of VRE is no longer low in some settings and recent observations of a sudden increase of VRE isolation in several hospitals in Korea suggests that VRE infection may become a serious problem in the near future. The most important considerations are that vancomycin-resistant genes may spread to other highly virulent genera, such as MRSA, and that there are no approved and convincingly effective antibiotics for the treatment of VRE. Therefore, current efforts have concentrated on limiting the spread of these organisms within the hospital environment. Prudent use of antimicrobial agents and strict adherence to preventive measures such as aggressive communication, education, and infection control practices are essential to control the spread of this organism. However, hospital infection control protocols and the laboratory support they require are costly in terms of space and supplies, as well as in personnel resources. These factors add further pressure to already stretched hospital budgets. Nevertheless, policies or programs defining and managing VRE infection or colonization should be established and now is the time to enforce an overall management strategy against VRE.

Key Words: Vancomycin-resistant enterococci, VRE, Korea

Enterococci are normal flora in the gastrointestinal tract (Gin and Zhanel, 1996), colonizing the bowels of over 90% of healthy humans and are found in counts of up to 10^7 cfu/g of stool (French, 1998). Enterococcal infection was not previously prevalent, however enterococci became the second-to-third most commonly isolated organism from nosocomial infections. Among the 17 recognized species, *E. faecalis*

and *E. faecium* have been the predominant species, accounting for 85% to 90% of clinical enterococcal isolates.

Enterococci are intrinsically more resistant to many antimicrobial agents compared to streptococci, with which the organisms were previously classified. The MICs of penicillins are 2–8 $\mu\text{g}/\text{mL}$ for *E. faecalis* and 16–32 $\mu\text{g}/\text{mL}$ for *E. faecium*. Enterococci are also intrinsically resistant to low levels of aminoglycosides. Therefore, serious enterococcal infections are usually treated with aminobenzyl penicillin in combination with an aminoglycoside. However, enterococci often show acquired resistance to many antimicrobial agents including high-level aminoglycosides by chromosomal mutation or by acquisition of plasmids encoding aminoglycoside-

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modifying enzymes (French, 1998). Synergistic effects cannot be obtained when the infecting strain is resistant to β -lactams or to high-level aminoglycosides.

Vancomycin has been used increasingly to treat infections due to *Clostridium difficile*, β -lactam-resistant enterococci, and methicillin-resistant staphylococci. Vancomycin is also used to treat infected patients who have hypersensitivity to β -lactams. Vancomycin-resistant enterococci (VRE) were first reported in 1988 in the United Kingdom and France (Leclercq *et al.* 1988; Uttley AHC *et al.* 1988). With the increased use of vancomycin, glycopeptide-resistant enterococci became an important nosocomial pathogen. The purpose of this article was to present the status of vancomycin-resistant enterococcal infection in Korea and to discuss the difficulties in the treatment and prevention of VRE infection.

Prevalence and characteristics of VRE in Korea

There have only been a few studies on the prevalence and characteristics of VRE in Korea. In 1992, Park *et al.* tested 287 strains of enterococci

isolated from routine clinical specimens and detected one strain of VRE, which was *E. durans* rather than the common *E. faecium* or *E. faecalis*. It was the first VRE reported in Korea. The patient had underlying disease of acute myelogenous leukemia, but since the source was the oral cavity, the isolate was possibly not clinically significant. Thereafter, 4 strains of vancomycin-resistant *E. casseliflavus* were reported (Kim *et al.* 1995), but it was later revealed that the species of all 4 strains was *E. faecium*. In 1996, one strain each of vancomycin-resistant *E. faecalis* and *E. faecium* were isolated from a patient transferred from the United States, and it was suspected that the patient carried the organism from previous hospitalization (Jeong *et al.* 1996). In most tertiary care hospitals, the proportion of VRE among all enterococcal isolates has remained around 1% or less.

VRE is much more prevalent in the United States, where the proportion among nosocomial isolates increased from 0.3% in 1989 to 7.9% in 1993. Among the strains isolated from intensive-care units, the proportion increased by 34-fold from 0.4% in

Table 1. Prevalence and characteristics of vancomycin-resistant enterococci reported in Korea

Reference	No. of specimens studied	No. (%) of VRE	Isolate (No.) by:		
			Species	Site	Genotype
Park <i>et al.</i> 1992	287	1 (0.3)	<i>E. durans</i> (1)	O (1)	<i>vanA</i> (1)
Kim <i>et al.</i> 1995	NM	4*	<i>E. faecium</i> (4)	W (2), B (1), U (1)	<i>vanA</i> (4)
Jeong <i>et al.</i> 1996	NM	2*	<i>E. faecalis</i> (1)	U (1)	<i>vanB</i> (1)
			<i>E. faecium</i> (1)	W (1)	<i>vanB</i> (1)
Peck <i>et al.</i> 1996	74	6 (8.1)	<i>E. faecium</i> (1)	Stool [†]	<i>vanA</i> (1)
			<i>E. faecalis</i> (2)		<i>vanA</i> (2)
			<i>E. casseliflavus</i> (3)		<i>vanC</i> (3)
Cheong <i>et al.</i> 1998	202	2 (1.0)	<i>E. faecium</i> (2)	U (1), W (1)	<i>vanA</i> (2)
Lee <i>et al.</i> 1998	790	36 (4.6)	<i>E. faecium</i> (12)	U (7), W (3), B (1), PF (1)	<i>vanB</i> (10)
			<i>E. faecalis</i> (2)	B (1), Bi (1)	NT
			<i>E. gallinarum</i> (7)	U (2), W (1), B (1), Bi (2), C (1)	<i>vanC</i> (7)
			<i>E. casseliflavus</i> (3)	B (2), Bi (1)	<i>vanC</i> (3)
			<i>Enterococcus</i> sp. (12)	U (2), W (5), B (3), PF (1), C (1)	<i>vanB</i> (3)
Jeong <i>et al.</i> 1998	172	6 (3.5)	<i>E. faecium</i> (4)	Stool [†]	<i>vanA</i> (4)
			<i>E. avium</i> (1)		<i>vanA</i> (1)
			<i>Enterococcus</i> sp. (1)		<i>vanA</i> (1)

*: Case report.

†: Intestinal colonization survey.

B, blood; Bi, bile; C, catheter; O, oral cavity; PF, peritoneal fluid; U, urine; W, wound; NM, not mentioned; NT, not tested.

1989 to 13.6% in 1993 (Centers for Disease Control and Prevention, 1993).

A determination of carriage of VRE by culturing stool specimens from 80 inpatients showed six (8.1%) of 74 isolates of enterococci were VRE: one *E. faecium*, two *E. faecalis* and three *E. casseliflavus* (Peck *et al.* 1996). In a test with 202 clinical isolates of enterococci, only two strains (1.0%) of vancomycin-resistant *E. faecium* were detected (Cheong *et al.* 1998), while in another study 36 isolates (4.6%) of VRE were detected among 790 clinical isolates of enterococci (Lee *et al.* 1998). Another surveillance (Table 1) showed that 6 (3.5%) of 172 isolates of enterococci in 303 patients were VRE (Jeong *et al.* 1998).

Among four types vancomycin resistance, VanA and VanB types are clinically more significant. Recent determination by PCR of the genotypes of VRE strains isolated in five university hospitals in Korea showed that among the 42 isolates which included 21 isolates of *E. faecium*, 13 *E. casseliflavus*, 6 *E. faecalis*, and 2 *E. avium*, 14 (33%) were VanA type, 7 (17%) VanB type, and 21 (50%) VanC type (Kim *et al.* 1998). It is noteworthy that 50% of the VRE were VanC type, which is the type found in the intrinsically vancomycin-resistant species with questionable pathogenicity. They also determined the plasmid profiles and PFGE patterns and suggested intrahospital spreads of the same clones in three hospitals. It is known (Murray, 1998) that when VRE from patients in a given hospital have been examined, particularly after initial recovery of VRE,

evidence is often found of a single or predominant strain. However, when VRE has been present in a hospital for some time a diverse clone may be present.

Available data suggest that VRE infection is rare in Korea at the moment, but that the rate of carriage is no longer low in some settings, indicating a possible increase of VRE infection in the near future. In our hospital, the proportion of VRE was less than 1% until 1997, but from January to August, 1998, VRE were isolated in 43 patients (Fig. 1). This sudden increase may indicate nosocomial spread. Among the VRE, 36 isolates were *E. faecium* and 7 were *E. faecalis*. Most patients with VRE have been in hospital for a prolonged duration and have been exposed to many kinds of antimicrobials, including vancomycin and cephalosporins. It has been known that a long duration of hospitalization and previous exposure to vancomycin or broad-spectrum antimicrobials are the major risk factors for the emergence of VRE (Boyce, 1997; Leclercq and Courvalin, 1997; Noskin, 1997).

Species identification and susceptibility testing of enterococci

Antimicrobial resistant patterns may be different depending on enterococcal species and also depending on the strains among the species. Therefore, both accurate identification of enterococcal species and determination of antimicrobial resistance are necessary for the appropriate treatment and control of the infection. *E. faecalis* accounts for about 90% of enterococcal isolates in clinical specimens, but in recent years *E. faecium* has become more common, probably because of its greater resistance (French, 1998).

There are 17 species of enterococci, which is difficult to identify either by conventional methods or by commercial systems. A previous misidentification of vancomycin-resistant *E. faecium* as *E. casseliflavus* was such an instance. Most VRE are either *E. faecium* or *E. faecalis*. As *E. casseliflavus*, *E. gallinarum* and *E. flavescens* are intrinsically vancomycin-resistant and rarely cause infection, misidentification of the species may result in improper treatment or failure to treat patients or to take control measures.

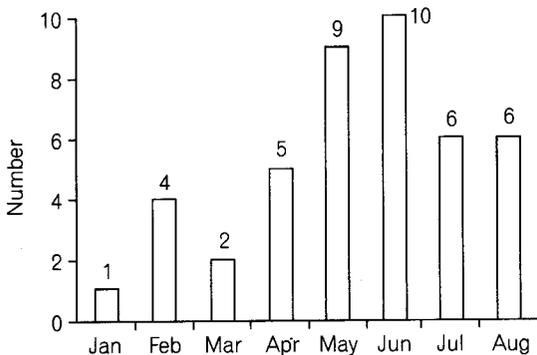


Fig. 1. Monthly reports for VRE-isolated patients at Severance Hospital from January through August 1998.

In order to determine the optimum treatment regimen for an enterococcal infection, an in vitro susceptibility test became necessary as resistant strains are very prevalent. For isolates from serious infection, tests are required for susceptibilities to ampicillin or penicillin, high-level gentamicin or streptomycin, and vancomycin or teicoplanin (NCCLS, 1998).

Detection of VRE is not easy either by the disk diffusion method or by rapid commercial system, therefore requiring special attention. A recent report showed that a rapid commercial system, Vitek GPSSA card, resulted in 7% very major error (Kohner *et al.* 1997).

Treatment of VRE infection

Enterococci cause various infections. For the last two decades enterococci have been the third most common cause of hospital-acquired infections after *E. coli* and *S. aureus*, and ahead of *P. aeruginosa* (French, 1998). Nosocomial infection surveillance in the United States during 1986–1997 showed that enterococci were the most common organism isolated from surgical site infection and the third most common organism from both bloodstream and urinary tract infections (NNIS, 1997). Enterococci are responsible for 10–12% of all hospital-acquired infection, 10–20% of hospital-acquired urinary tract infections and 5–10% of hospital-acquired bacte-

remias (French, 1998). Urine was the most frequent source from which VRE was isolated in a Korean university hospital (Fig. 2). However, the proportions of VRE isolated from blood and spinal fluid were not low, 9.3% and 2.3%, respectively. Some enterococcal infections such as endocarditis, meningitis, and osteomyelitis are the infections particularly difficult to cure.

As some enterococcal infections such as endocarditis is difficult to cure, β -lactams and aminoglycosides are administered together to obtain a synergistic effect. However, many isolates of *E. faecium* acquired high-level resistance to ampicillin (French,

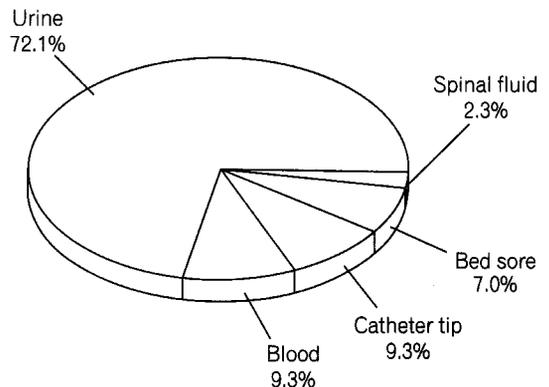


Fig. 2. Frequency (%) of body sites from which VRE were recovered at Severance Hospital, 1998.

Table 2. Suggested regimens for treatment of enterococcal endocarditis

Susceptibility of the strain	Antimicrobial agents	Dosage	Duration (weeks)
Vancomycin and high level gentamicin susceptible Penicillin resistant (MIC >8 $\mu\text{g/mL}$) by PBP change	Vancomycin + Gentamicin	30 mg/kg/day in 2 divided doses 1 mg/kg IV or IM q48h	4–6
	Ampicillin/ sulbactam + Gentamicin	175 mg/kg/day in divided doses 1 mg/kg IV or IM q48h	4–6
Penicillin resistant (MIC >8 $\mu\text{g/mL}$) by β -lactamase production	Vancomycin + Gentamicin	30 mg/kg/day in 2 divided doses 1 mg/kg IV or IM q48h	4–6
Multiply high level aminoglycoside resistant	Ampicillin	>200 mg/kg/day in divided doses or by continuous infusion	≥ 8

Modified from Wilson, 1998.

Perform killing curves with multiple drug regimens and use most effective combination of agents.

1998). Also, some strains of *E. faecalis* were reported to produce β -lactamase. Although ampicillin-resistant *E. faecalis* has not been reported in Korea, ampicillin-resistant *E. faecium* became very prevalent. In a hospital in Korea, 93% of *E. faecium* isolated in 1997 was reported to be resistant to ampicillin, while none of *E. faecalis* was. High-level aminoglycoside-resistant enterococci became very prevalent.

If the enterococci isolated from endocarditis is resistant to ampicillin but susceptible to gentamicin, streptomycin and vancomycin, then vancomycin and one of the aminoglycosides can be used for treatment. It is a problem when the enterococci are resistant to multiple drugs (Wilson, 1998). In patients with multiple high-level aminoglycoside resistance, prolonged therapy of 8 weeks or longer with ampicillin or amoxicillin is recommended (Table 2).

For the treatment of serious infections with high-level aminoglycoside resistance or resistance to all cell-wall active antibiotics, alternative therapy is necessary (Nicoletti and Stefani, 1995). These investigators reported that against 6 strains of high-level aminoglycoside resistant *E. faecalis*, ciprofloxacin-vancomycin was synergistic in none of them and antagonistic in 33%, while ciprofloxacin-teicoplanin was synergistic in 33% of strains and antagonistic in none of them.

In cases with high-level resistance to penicillin and vancomycin, triple combination therapy with ampicillin, vancomycin, and gentamicin was reported to be effective (Fraitow *et al.* 1992; Whitman *et al.* 1993). There were other combinations, such as imipenem and ampicillin, β -lactam and vancomycin, high dose ampicillin/sulbactam and gentamicin, ciprofloxacin and netilmicin, or ciprofloxacin and ampicillin, reported to be effective (Caron *et al.* 1995; Mekoene *et al.* 1995). It was reported recently that clinafloxacin was significantly more active than ciprofloxacin and markedly synergistic when combined with the cationic peptide (Cho *et al.* 1998).

In cases of enterococcal bacteremia on a liver transplant service, vancomycin resistance, shock, and liver failure were independent risk factors for enterococcus-associated mortality (Linden *et al.* 1996). Higher rates of refractory infection, serious morbidity, and attributable death were reported in the vancomycin-resistant *E. faecium* cohort and were

partly mediated by the lack of effective antimicrobial therapy.

With the increase of VRE, we have come to need new antimicrobials active against them. Quinupristin-dalfopristin is active against vancomycin-resistant *E. faecium*, but not against *E. faecalis*. Also, the emergence of resistant *E. faecium* to quinupristin-dalfopristin has been reported. It was considered that drug susceptibility, high inoculum, organism growth phase and penetration barrier could increase clinical resistance (Aeschlimann *et al.* 1998). Oxazolidinone compounds, eperezolid and linezolid demonstrated good in vitro inhibitory activity against both vancomycin-susceptible and -resistant enterococci, but both were bacteriostatic in action (Rybak *et al.* 1998).

Prevention of VRE infection

The reservoir for enterococci is the bowel and most infections are endogenous. Thus, the increasing isolation rate for enterococci is usually caused by multiple endogenous strains rather than outbreaks of cross-infection (French, 1998). Nevertheless organisms are probably spread from patient to patient on the hands of hospital staff. After experimental inoculation, VSE and VRE survive on the fingers for about 30 minutes. Washing with soap and water fails to remove these organisms. Aqueous chlorhexidine and povidone iodine are also unreliable agents, but alcohol and alcoholic chlorhexidine are effective. Hospital staff are notoriously poor at hand washing (French, 1998). The natural ability of enterococci to readily acquire, accumulate, and share extrachromosomal elements encoding virulent traits or antibiotic-resistant genes renders them advantages to their survival in the hospital environment and in part explains their increasing importance as nosocomial pathogens (Jett *et al.* 1994)

In a Korean hospital, the Departments of Neurosurgery (16 patients) and Rehabilitation (7 patients) had the largest number of VRE-positive patients compared to other departments because these patients usually have chronic complicated diseases, have received many kinds of antimicrobials, and have stayed in ICU for a prolonged period. VRE-infected patients are now being seen with increasing frequency among patients with chronic renal failure

or under renal replacement therapy (hemodialysis or continuous ambulatory peritoneal dialysis) and malignancies, those with organ transplants, and others who receive immunosuppressants.

It is important to prevent VRE infection because the infection is difficult to treat. The recommended guidelines by the Hospital Infection Control Practice Advisory Committee (HICPAC) of the CDC in the United States include the importance of education about the significance of VRE infection, prudent use of vancomycin and other antimicrobials, detection of VRE-infected patients, and prevention and control of nosocomial transmission of VRE (Centers for Disease Control and Prevention, 1995). The high prevalence of VRE infection in the United States suggests that VRE nosocomial infection is difficult to control. We may have to confront serious VRE problems in the near future because the quality of our hospital environment is lower than that in the United States and we have limited capabilities to control nosocomial infection.

In conclusion, enterococci became frequently isolated from various specimens including the blood of inpatients. Infection and carriage of VRE in Korean patients have been much less frequent compared to patients in the United States. However, recent observation of a sudden increase of VRE isolation in a Korean hospital suggests that VRE infection may become a serious problem in the near future. As it is difficult to cure some of the infections caused by VRE, it is now time to enforce preventive measures such as aggressive communication, education, and infection control practice. Policies or programs defining and managing VRE infection and colonization as well as clinical eradication should be established as critical in the overall management strategy.

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