Unusual Increase of Vancomycin-resistant *Enterococcus faecium* but not *Enterococcus faecalis* at a University Hospital in Taiwan

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Background: Enterococcal infections at the Chang Gung Memorial Hospital, Taiwan, have increased significantly in recent years, accompanied by a significant growth of vancomycin resistance from < 1% to 3.8%. However, the significant increase in vancomycin resistance was only found in *Enterococcus faecium* (from 0.5% to 17.4%).

Methods: A total of 172 patients infected with vancomycin-resistant enterococci (85 *E. faecium* and 87 *E. faecalis*) during 1998-2004 were retrospectively studied. Clinical and laboratory features were analyzed using Stata for Windows (version 8.2). Genotypes of the isolates were determined by infrequent-restriction-site polymerase chain reaction.

Results: Multivariate analysis revealed that prior use of imipenem (odds ratio [OR], 30.1; 95% confidence interval [CI], 4.2-215.9) or clindamycin (OR, 6.5; 95% CI, 1.5-28.1), positive urine cultures (OR, 6.1; 95% CI, 2.1-17.8) and penicillin resistance (OR, 55.9; 95% CI, 18.5-168.3) were significantly associated with the infections caused by vancomycin-resistant *E. faecium*. Genotyping analysis demonstrated a predominant genotype in 71 (83.5%) of the *E. faecium* isolates, while diverse genotypes were found among the *E. faecalis* isolates. No apparent correlation between genotype and any specific ward was found. Up to the end of 2005, primary efforts to restrict imipenem usage and reinforce infection control measures have reduced by half the infections caused by vancomycin-resistant *E. faecium*.

Conclusion: Multiple factors were associated with the unusual increase of vancomycin-resistant *E. faecium* infections in this hospital. Continuous monitoring of appropriate antimicrobial usage and stringent compliance to infection control measures are required to control the increase of such infections.

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Key words: vancomycin-resistant enterococcus, molecular epidemiology, infection control

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Enterococci are a part of the intestinal flora of humans and animals. They may also colonize many body sites of otherwise healthy individuals and, when possible, cause a wide spectrum of infections. Among the more than one dozen species of *Enterococcus, E. faecalis* and *E. faecium* are the two most predominant enterococci, accounting for approximately 85%-90% and 5%-10% of human enterococcal infections, respectively.[1] Enterococci are intrinsically resistant to a variety of antibiotics. They are also capable of acquiring antimicrobial resistance efficiently by mutations or the acquisition of foreign resistant genes, and express resistance to many other antibiotics.[1] These characteristics allow enterococci to survive in an environment, such as a hospital, where antimicrobial agents are heavily used. Their natural neighbors in the gastrointestinal tract, other Gram-negative rods or anaerobes, are usually readily killed by these antibiotics, thus providing resistant enterococci the opportunity to propagate adequately.

Vancomycin is the drug of choice for infections caused by resistant enterococci.[2] However, following the first detection of vancomycin-resistant enterococci (VRE) in 1986,[3] the prevalence of VRE has increased rapidly in many countries.[4-6] The increasing incidence of VRE is accompanied with several problems. VRE infections are associated with higher treatment costs, and greater morbidity and mortality.[6-10] Vancomycin resistance genes can be transferred to other more virulent or multi-resistant pathogens, such as *Staphylococcus aureus*, in a laboratory model.[2,6] In fact, clinical isolates of vancomycin-resistant *S. aureus* have recently been reported.[11,12]

The clinical impact of VRE has many facets. Understanding the epidemiology of these troublesome organisms should be very helpful in the management of VRE infections. The prevalence of enterococcal infections at the Chang Gung Memorial Hospital (CGMH), Taoyuan, Taiwan, increased significantly from 2,608 in 1998 to 4,055 in 2004 ($p < 0.0001$), accompanied with a significant growth of vancomycin resistance from less than 1.0% to 3.8% ($p < 0.0001$). However, the significant increase in vancomycin resistance was only found in *E. faecium* (from 0.5% to 17.4%; $p < 0.0001$). The present study was conducted to reveal possible explanations for the unusual increase.

METHODS

Setting

CGMH is a 4071-bed university-affiliated medical center located in northern Taiwan. To serve patients with different clinical needs, the hospital consists of 13 disease-orientated departments, which include 26 intensive care units (ICUs) and 73 ordinary wards. The Clinical Microbiology Laboratory in the Department of Clinical Pathology provides a routine service for isolation/identification and antimicrobial susceptibility testing of microbiological pathogens for the whole hospital. Records of these culture results have been incorporated into the centralized computer system of the CGMH since 1998. Each year, data on the number of isolates and their antimicrobial susceptibility patterns are summarized and posted in the intranet system of the hospital to be used as a reference guide for empirical antimicrobial therapy.

Clinical epidemiology

Records of VRE isolates between 1998 and 2004 were retrospectively retrieved from the computer system and analyzed. Records of isolates from all surveillance cultures were excluded. Consecutive isolates with the same antimicrobial susceptibilities obtained within 30 days from the same body site of the same patient were regarded as repetitive and removed from the statistical analysis. To elucidate the correlation between the annual consumption of certain antibiotics and the prevalence of VRE, antimicrobial consumption was calculated as defined daily doses (DDD) per 1000 patient-days.

For each patient from whom at least one VRE isolate was available, only the first isolate was included for further molecular investigation. For these patients, all clinical features, including demographic characteristics, underlying diseases, recent surgeries or procedures received, location and length of hospitalization, including ICU stay, and antibiotics used within 30 days prior to the VRE isolation were collected and analyzed.

Bacterial culture and antimicrobial susceptibility testing

All clinical isolates of enterococci were cultured and identified by standard methods.[13] No major

changes in methods for the identification of enterococci were made during the study period. Antimicrobial susceptibility was tested and interpreted according to the criteria suggested by the National Committee for Clinical Laboratory Standards.[14,15] Isolates in the intermediate category were deemed resistant in this study. The antimicrobial agents examined included ampicillin, gentamicin (high level, 500 μg/mL), linezolid, penicillin, teicoplanin and vancomycin. For selected VRE isolates, the minimum inhibition concentrations (MICs) of the abovementioned antimicrobial agents, and chloramphenicol, erythromycin, amikacin (high level, 1000 μg/mL), quinupristin/dalfopristin, rifampin and tetracycline, were either examined by a broth microdilution method or E-test strips according to the manufacturer's instructions.

Molecular study

Resistance to vancomycin is encoded by *van* genes, including *vanA, vanB, vanC1, vanC2* and *vanC3*. To determine the associated *van* genes in VRE isolates, a multiplex polymerase chain reaction (PCR) assay was used as reported previously.[16]

Genotyping of bacterial isolates provides information on the genetic relatedness of the isolates studied. For this purpose, VRE isolates were analyzed by a previously described molecular typing method, infrequent-restriction-site PCR (IRS-PCR).[17] Banding patterns with more than four-band differences were arbitrarily categorized as different genotypes.

Statistical analysis

Univariate analysis of all categorical variables was performed with simple logistic regression analysis, while continuous variables were analyzed using a two-tailed Student's *t*-test. A difference was considered statistically significant when the *p* value was less than 0.05. In order to control for possible confounding factors and fit a predictive model, multivariate stepwise analysis (both manual and automatic) with forward selection and backward selection rechecking was performed for those significant variables identified in the above univariate analysis. All statistical analyses were performed using the computer program Stata for Windows, version 8.2. Continuous data were expressed as mean ± standard deviation unless stated otherwise.

RESULTS

Increasing prevalence of VRE infections

A total of 394 VRE isolates were identified during 1998-2004 at CGMH. The annual number of VRE isolates increased significantly from less than 30 before 2001 to 156 in 2004 (Fig. 1). Compared to the total number of enterococcal isolates in the CGMH laboratory, the proportion of VRE isolates increased significantly from less than 1.0% to 3.8% during the study period ($p < 0.0001$). When different VRE species were further analyzed, a significant increase was observed only in *E. faecium* (< 1.0% before 2001, 11.5% during 2002-2003 and 17.4% in 2004; $p < 0.0001$). In contrast, the proportion of *E. faecalis* remained relatively constant at a range of 0.5%-1.2% during the study period. Since 2002, *E. faecium* (from 5.4% to 67.2%) has replaced *E. faecalis* (from 74.9% to 24.5%) to become the most prevalent VRE species. When different wards were compared, the sudden increase in vancomycin-resistant *E. faecium* in 2002 was more likely to occur in ICUs than in general wards (23.7% vs. 7.4%; $p < 0.0001$). However, the rate of vancomycin-resistant *E. faecium* increased continuously in non-ICU areas

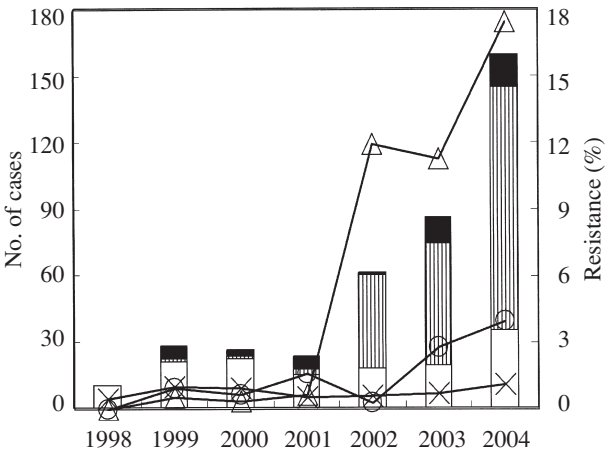

Fig. 1 Trends in the annual number of cases of vancomycin-resistant *E. faecalis* (column in white), *E. faecium* (column in vertical lines) and other Enterococcus species (column in black), and the respective proportion (%) when compared with the total population of each species (△, *E. faecium*; ×, *E. faecalis*; ○, *Enterococcus* species) at Chang Gung Memorial Hospital, Taiwan, 2000-4.

and reached similar levels to those in ICUs (both 17.4%) in 2004.

Vancomycin-resistant *E. faecium* and *E. faecalis*

A total of 172 patients who had been infected with VRE, including 85 *E. faecium* and 87 *E. faecalis*, during the study period were retrospectively studied. The epidemiological characteristics and underlying diseases/conditions of the patients are shown in Table 1. The percentage of male patients was similar in all VRE or either species group. The age of the patients was significantly higher in the *E. faecium* group but the proportion was similar to that observed among the vancomycin-susceptible enterococcal isolates (data not shown). The most common underlying illness was diabetes mellitus; the only significant difference was found in sepsis (with other bacteria), which was more prevalent in patients with *E. faecium* infections.

VRE infections caused by *E. faecium* were more likely to be associated with the hospital; the infection occurred much later, by an average of 13 days, compared to that caused by *E. faecalis* but the difference was not significant. The total hospitalization period was longer, by about 14 days, in patients with hospital-associated *E. faecium* VRE infections compared with those with *E. faecalis* but the difference was also not significant. Approximately 28% of the VRE infections occurred in ICUs, and *E. faecium* was significantly more common than *E. faecalis*. At the onset of the VRE infection, 42% of the patients had indwelling urinary catheters and the rate was significantly higher for those infected by *E. faecium*. Before the VRE infection, various antimicrobial agents had been used on the patients. Significant differences were found in penicillins, extended-spectrum β-lactams, imipenem, ciprofloxacin, clindamycin and teicoplanin; all were more frequently used in patients subsequently infected by *E. faecium*.

Comparisons of microbiological features between the two VRE species are summarized in Table 2. The majority (82.5%) of VRE species were isolated from pus/wound and urine; *E. faecium* was more likely to be recovered from urine, while *E. faecalis* was more likely to be recovered from pus/wound. Polymicrobial infection with one to four kinds of other bacterial species was found in one-third of the patients.

When the MICs of various antimicrobial agents were examined, the highest resistance rate (90%) was found for erythromycin, while linezolid, with a resistant rate of 33%, remained the most susceptible agent among the VRE isolates. *E. faecium* showed a significantly higher resistance to some antimicrobial agents, such as ampicillin and penicillin, but *E. faecalis* was more resistant to other antimicrobial agents, including newer drugs such as linezolid and quinupristin/dalfopristin. Two-thirds of the VRE isolates belonged to the VanA phenotype, the majority of which were *E. faecium*. However, 96.5% of the VRE isolates had a *vanA* gene, resulting in 32% of the isolates being associated with a unique VanB phenotype-*vanA* genotype, more of which were found in *E. faecalis*.

Despite many variables being found to be significantly different between the two VRE species, only four retained significant association with *E. faecium* after multivariate analysis: prior use of imipenem ($p < 0.005$; odds ratio [OR], 30.06; 95% confidence interval [CI], 4.19-215.90) or clindamycin ($p < 0.05$; OR, 6.50; 95% CI, 1.50-28.13), positive urine cultures ($p < 0.005$; OR, 6.07; 95% CI, 2.07-17.77) and penicillin resistance ($p < 0.0005$; OR, 55.85; 95% CI, 18.54-168.25).

Molecular typing analysis of the VRE isolates revealed a total of 65 genotypes among the 87 *E. faecalis* isolates, while only 15 genotypes were found in the 85 *E. faecium* isolates. A predominant genotype was found in 71 (83.5%) isolates of the vancomycin-resistant *E. faecium*. The clone has been present in this hospital since the first VRE, an *E. faecium* isolate, was found in June 1997. The highest prevalence of this predominant clone was 6 isolates found in two medical ICUs and 5 isolates found in one surgical ICU and a medical ward; the number of this clone was below 3 in other ICUs and wards throughout the study period. There was no apparent correlation between distribution of genotypes and the location of any specific ward or ICU.

Annual consumption of clindamycin and imipenem

The annual consumption of clindamycin and imipenem during 2000-2004 is shown in Figure 2. A significant increase in imipenem consumption was observed in 2002 and paralleled the increase of vancomycin resistance in *E. faecium* (Fig. 1). An increasing consumption of clindamycin was also

Table 1. Epidemiological Characteristics of Patients with Vancomycin-Resistant *E. faecium* or *E. faecalis* Enterococci Infections

Characteristic	Mean ±SD (range) or number (%) of patients		*p*-value*	Odds ratio (95% CI)
	E. faecium (n = 85)	*E. faecalis* (n = 87)		
Male	41 (48.2%)	44 (50.6%)	NS	0.91 (0.50-1.66)
Age (yr)	64.6 ±17.6 (20-93)	56.2 ±20.7 (4-89)	< 0.005	N/A (2.60-14.23)
Underlying disease†				
Diabetes mellitus	33 (38.8%)	23 (26.4%)	NS	1.77 (0.93-3.37)
Sepsis	24 (28.2%)	7 (8.0%)	< 0.005	4.50 (1.82-11.12)
Brain dysfunction or head injury	18 (21.2%)	9 (10.3%)	NS	2.33 (0.98-5.53)
Malignancy	9 (10.6%)	11 (12.6%)	NS	0.82 (0.32-2.09)
Spinal diseases	3 (3.5%)	7 (8.0%)	NS	0.42 (0.10-1.67)
Liver cirrhosis	6 (7.1%)	2 (2.3%)	NS	3.23 (0.63-16.46)
Bedsore	1 (1.2%)	6 (6.9%)	NS	0.16 (0.02-1.36)
Burn	3 (3.5%)	1 (1.1%)	NS	3.15 (0.32-30.86)
Pregnancy	0 (0%)	2 (2.3%)	NS	0.00 (0.00-1.96)
Any	68 (80.0%)	54 (62.1%)	< 0.01	2.44 (1.17-5.15)
Recent surgery				
Abdomen	14 (16.5%)	19 (21.8%)	NS	0.71 (0.33-1.52)
Limbs	9 (10.6%)	17 (19.5%)	NS	0.49 (0.20-1.16)
Head	3 (3.5%)	7 (8.0%)	NS	0.42 (0.10-1.67)
Chest	3 (3.5%)	5 (5.7%)	NS	0.60 (0.14-2.59)
Any	28 (32.9%)	47 (54.0%)	< 0.01	0.42 (0.23-0.78)
Hospital-associated infection	62 (72.9%)	50 (57.5%)	< 0.05	1.99 (1.05-3.78)
Length of hospital stay before the infection	38.9 ±46.8 (0-298)	25.6 ±44.6 (0-291)	NS	N/A (-1.62-28.20)
Hospital-associated only	46.2 ±47.7 (5-298)	36.8 ±50.2 (4-291)	NS	N/A (-9.14-27.88)
Community-associated only	0.9 ±1.0 (0-3)	1.1 ±1.0 (0-3)	NS	N/A (-0.91-0.57)
Total hospitalization days	63.3 ±54.5 (5-301)	46.7 ±52.1 (4-319)	NS	N/A (-1.27-34.60)
Hospital-associated only	71.3 ±55.6 (10-301)	57.7 ±59.6 (4-319)	NS	N/A (-8.93-36.16)
Community-associated only	21.5 ±15.5 (5-48)	23.2 ±12.1 (4-44)	NS	N/A (-12.97-9.60)
ICU stay at onset of the infection	32 (37.6%)	16 (18.4%)	< 0.01	2.68 (1.33-5.38)
Use of indwelling urinary catheter at onset of infection	51 (60.0%)	21 (24.1%)	< 0.0001	4.71 (2.45-9.08)
Prior antibiotic use				
Penicillins (including ampicillin, oxacillin, piperacillin)	30 (35.3%)	14 (16.1%)	< 0.01	2.84 (1.38-5.87)
Amoxicillin-clavulanate	4 (4.7%)	3 (3.4%)	NS	1.38 (0.30-6.37)
Cefazolin	17 (20.0%)	19 (21.8%)	NS	0.89 (0.43-1.87)
Cefuroxime	14 (16.5%)	6 (6.9%)	NS	2.66 (0.97-7.29)
Extended-spectrum β-lactams (including ceftazidime and ceftriaxone)	27 (31.8%)	5 (5.7%)	< 0.0005	7.63 (2.78-21.00)
Aztreonam	2 (2.4%)	5 (5.7%)	NS	0.40 (0.07-2.10)
Imipenem	16 (18.8%)	10 (2.3%)	< 0.005	9.86 (2.19-44.34)
Aminoglycosides (including gentamicin and amikacin)	27 (31.0%)	24 (28.2%)	NS	1.22 (0.63-2.35)
Ciprofloxacin	20 (23.5%)	7 (8.0%)	< 0.01	3.52 (1.40-8.83)
Clindamycin	21 (24.7%)	7 (8.0%)	< 0.005	3.75 (1.50-9.38)
Teicoplanin	16 (18.8%)	4 (4.6%)	< 0.01	4.81 (1.54-15.06)
Vancomycin	15 (17.6%)	14 (16.1%)	NS	1.12 (0.50-2.48)
Metronidazole	10 (11.8%)	6 (6.9%)	NS	1.80 (0.62-5.19)
Fluconazole	5 (5.9%)	3 (3.4%)	NS	1.75 (0.40-7.56)

Abbreviations: SD: standard deviation; CI: confidence interval; NS: not statistically significant; N/A: not applicable; ICU: intensive care unit; *: Simple logistic regression and two-tailed Student's *t*-test were used for statistical analysis of the differences between isolates of *E. faecium* and *E. faecalis*. A difference was considered statistically significant with a *p* value of less than 0.05; †: Some patients had no underlying diseases or more than one underlying disease.

Table 2. Microbiological Features of the 172 Vancomycin-Resistant Enterococci Isolates

Characteristic	*E. faecium* (n = 85)	*E. faecalis* (n = 87)	*p*-value*	Odds ratio (95% CI)
Source of specimen				
Pus	23 (27.1%)	51 (58.6%)	< 0.0001	0.26 (0.14-0.50)
Urine	49 (57.6%)	19 (21.8%)	< 0.0001	4.87 (2.50-9.48)
Body fluids (including blood)	9 (10.6%)	13 (14.9%)	NS	0.67 (0.27-1.67)
Other	4 (4.7%)	4 (4.6%)	NS	1.02 (0.25-4.24)
Polymicrobial infection				
VRE only	63 (74.1%)	53 (60.9%)	NS	1.84 (0.96-6.52)
VRE + other bacteria	22 (25.9%)	34 (39.1%)	NS	0.54 (0.27-1.09)
Non-glucose-fermenting bacilli	11 (12.9%)	21 (24.1%)	NS	0.47 (0.21-1.04)
Enterobacteriaceae	9 (10.6%)	20 (23.0%)	< 0.05	0.40 (0.17-0.93)
Gram-positive cocci	3 (3.5%)	7 (8.0%)	NS	0.42 (0.10-1.67)
Anaerobes	1 (1.2%)	4 (4.6%)	NS	0.25 (0.03-2.26)
Candida albicans	7 (8.2%)	4 (4.6%)	NS	1.86 (0.52-6.61)
Antimicrobial resistance, number of resistant isolates (%) [MIC_{50}/MIC_{90}, μg/mL]				
Penicillin	70 (82.4%) [>16/>16]	11 (12.6%) [4/>16]	< 0.0001	32.24 (13.88-74.91)
Ampicillin	69 (81.2%) [>16/>16]	10 (11.5%) [1/>16]	< 0.0001	33.21 (14.13-78.02)
Gentamicin, high level	61 (71.8%) [>500/>500]	44 (50.6%) [>500/>500]	< 0.005	2.48 (1.32-4.67)
Amikacin, high level	22 (25.9%) [1000/>1000]	55 (63.2%) [>1000/>1000]	< 0.0001	0.20 (0.11-0.39)
Tetracycline	26 (30.6%) [0.5/>16]	69 (79.3%) [>16/>16]	< 0.0001	0.11 (0.06-0.23)
Erythromycin	74 (87.1%) [>16/>16]	81 (93.1%) [>16/>16]	NS	0.50 (0.18-1.41)
Vancomycin (≥ 32 μg/mL)	80 (94.1%) [256/>256]	85 (97.7%) [>256/>256]	NS	0.38 (0.07-2.00)
Teicoplanin	64 (75.3%) [24/>256]	42 (48.3%) [12/>256]	< 0.0005	3.24 (1.67-6.28)
Chloramphenicol	19 (22.4%) [8/>32]	51 (58.6%) [32/>32]	< 0.0001	0.20 (0.10-0.40)
Rifampin	70 (82.4%) [>8/>8]	56 (64.4%) [4/>8]	< 0.01	2.58 (1.27-5.25)
Linezolid	12 (14.1%) [2/3]	44 (50.6%) [3/>256]	< 0.0001	0.20 (0.10-0.39)
Quinupristin/dalfopristin	18 (21.2%) [0.5/>32]	70 (80.5%) [>32/>32]	< 0.0001	0.06 (0.03-0.13)
Van phenotypes				
VanA	66 (77.7%)	45 (51.7%)	< 0.0005	3.24 (1.67-6.28)
VanB	19 (22.3%)	42 (48.3%)	< 0.0005	0.31 (0.16-0.60)
Van genotypes				
vanA	81 (95.3%)	85 (97.7%)	NS	0.48 (0.08-2.67)
vanB	3 (3.5%)	2 (2.3%)	NS	1.55 (0.25-9.55)
vanC1	1 (1.2%)	0 (0%)	NS	0.00 (0.00-17.06)
VanB phenotype-VanA genotype	15 (17.6%)	40 (46.0%)	< 0.0001	0.25 (0.13-0.51)

Abbreviations: CI: confidence interval; NS: not statistically significant; VRE: vancomycin-resistant enterococci; MIC: minimum inhibitory concentration; *: Simple logistic regression and two-tailed Student's *t*-test were used for statistical analysis of the differences between isolates of *E. faecium* and *E. faecalis*. A difference was considered statistically significant with a *p* value of less than 0.05.

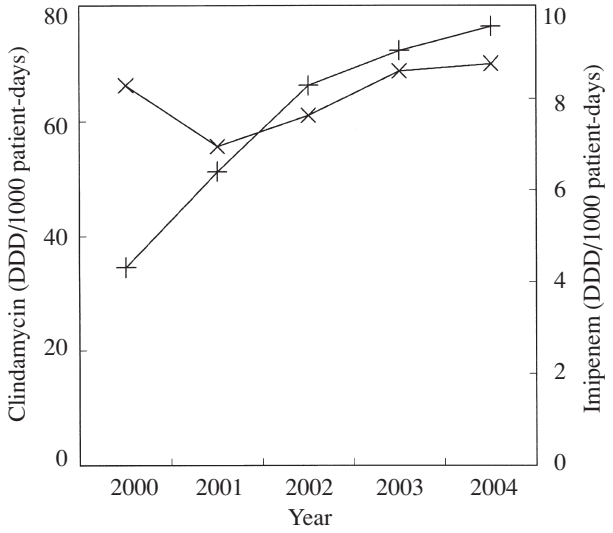

Fig. 2 Annual consumption of imipenem (+) and clindamycin (×) at Chang Gung Memorial Hospital, Taiwan, 2000-4.

found during the same period.

Follow-up observation

Although no particular inappropriateness in the daily care of patients with VRE infections was found, the finding of an endemic clone of vancomycin-resistant *E. faecium* was a reminder to the medical personnel to maintain a more stringent compliance to the infection control policy. Figure 3 shows the seasonal trend of VRE isolates among various species since the beginning of this investigation in January 2004. The number of VRE isolates, *E. faecium* in particular, has reduced since the third quarter of 2004. Furthermore, the study coincided with a hospital-wide, computerized antibiotic controlling program started in October 2004. Although clindamycin was not included in the program, the use of imipenem was controlled and reduced substantially thereafter (data not shown). Thus, the number of VRE isolates continued to decrease and by 2005 reached about half of the peak amount of VRE isolates in the second quarter of 2004.

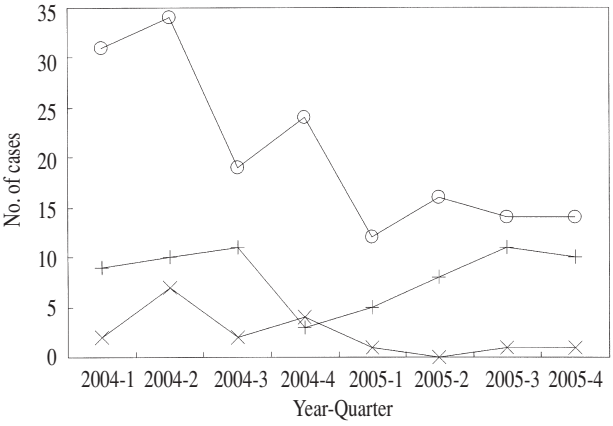

Fig. 3 Seasonal trends of vancomycin-resistant *E. faecium* (○), *E. faecalis* (+) and other *Enterococcus* species (×) at Chang Gung Memorial Hospital, Taiwan, 2004-5.

DISCUSSION

An unusual increase of vancomycin-resistant *E. faecium* infections was discovered in this retrospective study, despite infection control measures for VRE infections that have remained the same since the first isolation of VRE in 1997 in CGMH. Traditionally, *E. faecalis* is the most predominant enterococcus among clinical isolates but *E. faecium* has been the most prevalent among the VRE.[1,2] An ultimate example is shown by a recent report that demonstrated vancomycin resistance in 50% of *E. faecium* and 3% of *E. faecalis*.[18] The explanation for such a significant difference, however, remains unclear. In CGMH, the rate of vancomycin resistance of *E. faecium* increased significantly to 17.4% during the study period (Fig. 1). Although the rate is not as high as those found in western countries, effective measures have to be implemented to prevent a continuous increase. To reveal the possible explanations for the unusual increase of vancomycin-resistant *E. faecium* infections, the current study was designed to assess the difference between infections caused by vancomycin-resistant *E. faecium* and vancomycin-resistant *E. faecalis* from both clinical and laboratory viewpoints. Although the individuals in each group were not purposely matched, the non-significant difference between the characteristics of patients in the two groups indicates the appropriateness of the cases for comparison purposes.

Although many significant factors were found in the univariate model, only four independent factors remained significant after multivariate analyses, including prior use of imipenem and clindamycin. Gastrointestinal colonization with VRE is generally

considered to precede VRE infections.[19,20] Previous studies have also identified a variety of antimicrobial exposures as risk factors for the establishment of gastrointestinal colonization or infections with VRE. The associated antibiotics include glycopeptides,[21-25] cephalosporins[26,27] and antianaerobic drugs, such as metronidazole,[19,28] clindamycin[19,29] and imipenem.[19] To obtain the associated risk factors, these studies usually compared patients with VRE infections and those with their vancomycin-susceptible counterparts.[19,21,23,24,27,28] Thus, the current study differs from previous reports in providing a statistical analysis between infections caused by the two VRE species. By univariate analyses, a significant difference was found in prior use of several antibiotics but only imipenem and clindamycin remained significant in the multivariate model. The increasing consumption of these two antibiotics at CGMH provides further evidence, suggesting that the use of the two drugs might have contributed to the increase of vancomycin-resistant *E. faecium* infections. Similar findings have been shown in previous reports, which showed a significant correlation between the use of clindamycin and the prevalence of VRE.[29,30] Although these drugs may suppress the growth of other Gram-negative rods or anaerobes and, in turn, provide VRE a better opportunity for propagation, it remains unclear why the situation only favored vancomycin-resistant *E. faecium*. Whether the high prevalence of the specific clone of the bacterium played a role in this regard requires further investigation. Previous reports have indicated that manipulation of antimicrobial formulary had a great effect on controlling the prevalence of VRE infections.[31] To prevent the continuous increase of vancomycin-resistant *E. faecium* observed in our institution, restriction of the use of or establishing a better utilization program for imipenem and clindamycin appears inevitable. Indeed, interim data have already demonstrated the significant decrease of VRE isolates, especially *E. faecium*.

Previous reports have demonstrated that the presence of dominant VRE clones in hospitals may indicate a possibility of intrahospital spread and could be an important factor in establishing endemicity.[32] In the present study, nosocomial transmission is suggested by the high clonality found among the vancomycin-resistant *E. faecium* isolates. The fact that the increase of vancomycin-resistant *E. faecium* infections occurred earlier in the ICUs and subsequently spread into the non-ICU areas further indicates the role of nosocomial spread in the sudden increase of vancomycin-resistant *E. faecium* infections. Furthermore, positive urine cultures are identified as one of the independently significant factors, implying that urine of patients infected with vancomycin-resistant *E. faecium* may have served as the reservoir for the subsequent intrahospital spread. Consistent with this observation, vancomycin-resistant *E. faecium* in the present study was more likely to be related to hospital-associated infections, longer hospital stay before the onset of the VRE infection, and the use of indwelling urinary catheters and/or stay in an ICU at the onset of the infection. All these factors provide a better environment or opportunity for the nosocomial dissemination of vancomycin-resistant *E. faecium*, thus resulting in the vast number of associated infections. Although the route of transmission requires further clarification, reinforcement of the infection control policy in the management of urinary tract infections and daily care of indwelling urinary catheters may be warranted to reduce possible cross-contamination by vancomycin-resistant *E. faecium*.

Although it may be difficult to completely eliminate VRE from a clinical setting, a comprehensive control strategy may still help to control the problems associated with resistant organisms. As the significant increase of VRE infections was only found with *E. faecium*, the original infection control policy established in this institution may be sufficient in this regard. Preliminary efforts to control the few significant factors discovered in the current study have demonstrated a significant success in the eradication of the apparent endemic strain of vancomycin-resistant *E. faecium*. Continuous monitoring of appropriate antimicrobial usage and stringent compliance to infection control measures are required to control the increase of such infections.

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台灣一家大學附設醫院中萬古黴素抗藥性 *Enterococcus faecium*，但非 *Enterococcus faecalis*，感染的異常增加調查

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背 景： 近幾年腸球菌感染件數在長庚醫院有明顯地增加，同時我們也發現此類細菌對萬古黴素的抗藥性從之前的小於 1% 快速增加到近年的 3.8%。然而此一抗藥性的增加，卻明顯集中於 *Enerococcus faecium* (從 0.5% 增加到 17.4%)，其他腸球菌則沒有類似的情形。

方 法： 我們回溯性地收集了 1998 年至 2004 年之間共 172 株萬古黴素抗藥性腸球菌進行研究，其中包括 85 株 *E. faecium* 及 87 株 *E. faecalis*。臨床資料及實驗結果均以統計方法進行分析，使用的程式是 Stata 視窗系統 8.2 版。細菌的基因型則以低頻切位酶鏈鎖反應進行分析。

結 果： 多變項分析結果顯示下列幾項因素明顯與萬古黴素抗藥性 *E. faecium* 造成的感染相關：感染前曾使用 imipenem (勝算比，30.1；95% 信賴區間，4.2-215.9) 或 clindamycin (勝算比，6.5；95% 信賴區間，1.5-28.1)，尿道感染 (勝算比，6.1；95% 信賴區間，2.1-17.8)，及 penicillin 抗藥性 (勝算比，55.9；95% 信賴區間，18.5-168.3)。基因型分析顯示，有 71 株 (83.5%) *E. faecium* 屬於同一種主要基因型，而 *E. faecalis* 的基因型則比較多樣性，沒有類似的集中現象；基因型的分布與感染發生的病房區也沒有明顯關聯性。截至 2005 年底爲止，針對 imipenem 的限制使用及感控措施的再加強等初步的努力，已經使萬古黴素抗藥性 *E. faecium* 造成的感染減少至高峰期的一半以下。

結 論： 此一萬古黴素抗藥性 *E. faecium* 感染的異常增加與多種因素有關。若欲有效控制此種感染的增加，必須仰賴抗生素藥物適當使用的持續監控，以及感控相關措施的確實執行。

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關鍵詞： 萬古黴素抗藥性腸球菌，分子流行病學，感染管制

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