

Vancomycin-resistant *Enterococcus* – A Review From a Singapore Perspective

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Abstract

Introduction: Vancomycin-resistant enterococcus (VRE) can cause serious infections in vulnerable, immunocompromised patients. **Materials and Methods:** In this article, we summarise current data on epidemiology, detection, treatment and prevention of VRE. **Results:** VRE was first isolated in Singapore in 1994 and until 2004 was only sporadically encountered in our public hospitals. After 2 outbreaks in 2004 and in 2005, VRE has become established in our healthcare institutions. Multiple studies have shown that VRE spreads mainly via contaminated hands, cloths and portable equipment carried by healthcare workers. **Conclusions:** Only a comprehensive programme (consisting of active surveillance, isolation of colonised/infected patients, strict adherence to proper infection control practices and anti-microbial stewardship) can limit the spread of these organisms. In addition to monitoring the compliance with traditional infection control measures, new strategies that merit consideration include pre-emptive isolation of patients in high-risk units and molecular techniques for the detection of VRE.

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Introduction

The first isolates of high-level vancomycin-resistant enterococci (VRE) were reported from the United Kingdom in the late 1980s. Since then rates of VRE infection and colonisation have been steadily rising. Recent surveillance study showed that in the United States of America (USA), 28.5% of enterococcal isolates were resistant to vancomycin. Prevalence of VRE in Singapore is markedly lower than in other developed countries but the rates of VRE infection and colonisation have risen in the last few years. In 2006, VRE constituted 0.8% of all enterococci isolated in our public hospitals.

In this article, we summarise current data on colonisation, infection, detection, treatment and prevention of VRE. We also describe in detail local epidemiology of VRE and suggest infection control interventions that can help to limit the spread of VRE in Singapore.

The Organism

Enterococci constitute an integral part of bowel flora of humans and the majority of animals.¹

Enterococci are very hardy organisms. They are able to grow in 6.5% NaCl, and in a wide range of pH and temperatures (between 10°C and 45°C).² They can survive on inanimate objects for weeks – the feature that allows them to adapt well to any environment and contribute to their nosocomial transmission.^{3,4}

Enterococci, including VRE, are clearly less virulent as opposed to other common pathogenic bacteria such as *Staphylococcus aureus* or *Streptococcus pyogenes*.⁵ They do not produce exotoxins or superantigens. They can adhere to the epithelium of urinary tract and heart valves and occasionally cause urinary tract infection and endocarditis.

Enterococci are commonly found in cultures of intra-abdominal and pelvic infections. However, their role in these infections is not clear.⁵ VRE can cause serious infections in vulnerable, immunocompromised patients.⁶ Several studies have evaluated the impact of vancomycin resistance on mortality. The results of these studies are in conflict, with some suggesting higher mortality^{7,8} in VRE than in vancomycin-sensitive enterococcus (VSE)

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infections, and others showing no such association.^{9–12} It is often difficult to determine whether increased mortality in some of these studies is due to host factors (i.e. VRE affecting sicker patients) or increased virulence of VRE.¹³

Mechanisms of Resistance

Vancomycin inhibits enterococci by binding to the D-alanyl-D-alanine terminus of the cell wall precursors, compromising the synthesis of the bacterial cell wall. If the amino-acid composition of such terminus is altered, vancomycin binds to it with much lower affinity. Resistance to vancomycin is encoded by different clusters of genes referred to as the vancomycin resistance gene clusters (e.g. *vanA*, *vanB* and *vanC*). Both high and low level vancomycin resistance can occur in enterococci. Low level vancomycin resistance (*vanC*) is limited to 2 relatively non-virulent species: *E. gallinarum* and *E. casseliflavus*. High-level resistance (encoded by *vanA* and *vanB* genes) is more problematic because it is frequently associated with resistance to multiple classes of antibiotics. The major phenotypes (referred to as VanA and VanB) can be differentiated by the level of vancomycin resistance and susceptibility to teicoplanin.⁵

VanA is the most common type of vancomycin resistance in Europe and the USA.¹⁴ In contrast, a vast majority of VRE isolates in Australia^{15,16} and Singapore¹⁷ belong to *VanB* phenotype.

Transfer of vancomycin resistance gene clusters in the form of plasmids or transposons can occur between different strains of enterococci or even between enterococci and other bacterial species. *VanA* cluster has disseminated to other bacterial species including methicillin-resistant *S. aureus* (MRSA).¹⁸ In 2003, physicians in the USA reported the first case of vancomycin-resistant *S. aureus* (VRSA) in a patient with a chronic wound colonised by both VRE and MRSA.¹⁹ To date, 6 other cases of VRSA isolates have been identified in the USA. Of note, 5 of 7 cases were reported in Michigan.²⁰ The first 4 reported patients had multiple medical problems, prolonged hospital stay and received long courses of vancomycin. VRE have been isolated from 3 of the 4 VRSA patients, and in-vivo transfer of the *VanA* resistance gene is thought to underlie the development of vancomycin resistance.²¹

Epidemiology

High-level resistance to glycopeptide antimicrobials, vancomycin and teicoplanin, was first reported in Europe in 1986²² and in the US in 1987.²³ Since then VRE have been isolated in multiple countries on several continents and its prevalence is on the rise.²⁴ Between 1989 and 1993, the rate of vancomycin resistance reported in the USA by

the National Nosocomial Infections Surveillance (NNIS) system increased from 0.3% to 7.9%.²⁵ The most recent NNIS system report showed that in 2003, 28.5% of enterococcal isolates were resistant to vancomycin – an increase of 12% compared with data averaged for the years between 1998 and 2002.²⁶ The first VRE was isolated in Singapore in 1994²⁷ and after 2 consecutive outbreaks in 2004²⁸ and 2005,²⁹ it has slowly become established in several of our hospitals. According to the Network for Antimicrobial Resistance Surveillance (Singapore) (NARSS) in 2006, VRE constituted 0.8% of all enterococci isolated in our public hospitals.³⁰ Local incidence of VRE is still markedly lower than in other developed countries but the experience of these countries shows that the incidence rates increase sharply unless comprehensive infection control measures are introduced.

In the USA, VRE is found mainly in patients exposed to healthcare settings. Studies conducted in the USA in the 1990s failed to detect VRE among farm animals.^{31,32} The situation is different in Europe where a glycopeptide called avoparcin was used as a growth promoter in the animal industry until 1997.³³ That led to a high rate of VRE colonisation in animals and, subsequently, in healthy human beings via the food chain, either by direct contact or by eating contaminated products.³⁴ Fortunately, the prevalence of VRE in farm animals decreased significantly after avoparcin was withdrawn.^{35,36} In South East Asia, the situation may be similar since avoparcin has been used in animal industry in several Asian countries.^{37,38} In fact, there are several reports describing isolation of VRE from food and farm animals in Asia.^{39,40}

Risk Factors for Nosocomial Acquisition of VRE

There are numerous risk factors for nosocomial colonisation and infection with VRE. These risk factors include advanced age, renal and hepatic failure, haematological malignancy, severity of illness, invasive procedures and devices, gastrointestinal surgery, transplantation, proximity to another VRE-positive patient and antimicrobial therapy. Affected patients are usually ill, with prolonged hospital stay and who had received long courses of broad-spectrum antibiotics.^{5,41,42} Solid organ transplant recipients, patients in ICU, haematology units or long-term care facilities are all at high risk of VRE infection and colonisation.^{3,10,13,43–58}

As pointed out in an extensive review by Safdar and Maki,⁵⁹ there is a remarkable commonality of risk factors for infection and colonisation with several nosocomial pathogens such as VRE, MRSA, *Clostridium difficile*, extended-spectrum beta-lactamase (ESBL) producing gram-negative bacteria and *Candida* sp.

Antibiotic exposure has been consistently identified as a

risk factor for VRE positivity. It facilitates VRE transmission by 2 mechanisms: a) it suppresses normal competing bowel flora providing selective advantage for VRE and b) it increases concentration of VRE in stool of previously colonised patients rendering them more contagious.⁶⁰

VRE colonisation has been associated with multiple classes of antibiotics including glycopeptides, second and third generation of cephalosporins and other antibiotics with prominent anti-anaerobic activity.⁶⁰ The association of vancomycin with VRE remains controversial as several studies showed no effect.⁵⁴⁻⁵⁶

The common design problem in studies evaluating risk factors for antibiotic resistance is the failure to select an appropriate control group.⁶¹ If a study evaluating risk factors for VRE uses patients infected with VSE as a control group, it introduces selection bias. Patients infected with VSE are unlikely to be exposed to vancomycin in the past and therefore exposure to vancomycin may be erroneously ascribed as a risk.⁶²

Risk factors for VRE colonisation were also evaluated locally, during the VRE outbreak in 2005. The results of this study were slightly different from the results of the studies mentioned above and showed that hospitalisation in a crowded communal ward was the strongest predictor of VRE carriage (OR, 2.75; 95% CI, 1.60 to 4.74). Other significant predictors of VRE carriage included: age >65 years, female gender, history of diabetes mellitus and prolonged hospital stay. The influence of recent antibiotic usage on VRE carriage status was not examined in this study.²⁹

Mechanism of Transmission

Multiple studies have shown that VRE spreads mainly via contaminated hands, cloths and portable equipment carried by healthcare workers (HCWs), such as stethoscopes, tourniquets, sphygmomanometers, cuffs, otoscopes and papers of HCWs.^{63,64}

Environmental surfaces such as furniture or floors can harbour VRE and may play a role in transmission especially since VRE can persist on dry environmental surfaces for days to months (range, 7 days to 4 months).^{3,4,65}

Treatment

The significance of clinical cultures yielding VRE should be critically evaluated prior to initiating the therapy. Majority of urine cultures yielding VRE represent colonisation or asymptomatic bacteruria and in such cases, antibiotic therapy is not required.⁶⁶ Wound infections may also resolve without specific therapy.⁶⁷ On the other hand, VRE bacteraemia increases hospital length of stay by an average of 2 weeks^{68,69} and has an attributable mortality approaching 30%.⁶⁸⁻⁷¹ Antimicrobial therapy is clearly indicated for

endocarditis, meningitis and bacteraemia caused by VRE. Several antibiotics are now available for the treatment of infections caused by VRE.^{5,72,73}

VRE infections are more difficult to treat than those caused by VSE. Antibiotics active against VRE are more expensive and with the notable exception of linezolid, can only be administered intravenously.⁷³ It is one of the reasons why VRE infections are associated with high cost and prolonged hospital stay.

The first antibiotic approved for VRE infection was quinapristin/dalfopristin (Synercid). Its use was largely abandoned⁷⁴ due to narrow spectrum (active only against *E. faecium* but not *E. faecalis*) and frequent side-effects, especially myalgia, arthralgia and inflammation at the infusion site.⁷⁵

Most experts recommend linezolid as a drug of choice in the therapy of serious infections caused by VRE.^{73,76} It penetrates well to various tissues (including CSF) and is available in oral form. On the other hand, linezolid is expensive and can cause bone marrow suppression after prolonged use. There are several reports of the serotonin syndrome caused by linezolid especially when used in combination with other medications.⁷⁷ Other antibiotics with anti-VRE activity include daptomycin and tigecycline.⁷⁸

Preventing the Spread of VRE

Detailed discussion of all preventive strategies and interventions is beyond the scope of this article. Several professional organisations issued practice guidelines on prevention and control of VRE. The most widely applied guidelines were prepared by the Hospital Infection Control Practices Advisory Committee (HICPAC)⁷⁹ and the Society for Healthcare Epidemiology of America (SHEA).⁶⁴ These guidelines constitute the best reference for infection control practitioners.

Safdar and Maki⁵⁹ pointed out that “infection-control programmes that focus on 1 organism or only 1 antimicrobial agent are unlikely to succeed. For maximum benefit, we believe that infection-control programmes must apply global strategies aimed at all resistant organisms”.

A comprehensive programme (consisting of active surveillance, isolation or cohorting of colonised/infected patients, strict adherence to proper infection control practices and antimicrobial stewardship) should therefore reduce not only rates of VRE but also other antibiotic-resistance organisms.

Active Surveillance

Active surveillance is an important part of a comprehensive VRE control programme.⁸⁰⁻⁸² For each patient with VRE infection there are many others who are

asymptomatic.^{6,56,83} They may remain colonised for a prolonged period serving as reservoirs of transmission of VRE to other patients. Only surveillance cultures can identify these asymptomatic carriers allowing early institution of appropriate precautions in order to prevent the spread of VRE. Surveillance cultures were also shown to be cost-effective.⁸⁴

Several microbiological screening methods have been developed for detecting VRE using stool specimens, rectal swabs or perirectal swabs. Isolation rates of VRE from stool specimens are generally higher than those from rectal swabs.⁸⁵ Detection can be optimised by inoculating faecal samples or swabs in broth enrichment (such as Enterococcosel broth),⁸⁶⁻⁸⁸ followed by sub-culture on agar plates containing vancomycin. Molecular techniques can shorten turnaround time but specificity and positive predictive value are low.^{89,90}

Numerous questions remain about the most appropriate method of VRE surveillance. More research is required to determine optimal frequency of sampling, site of specimen collection (faecal or rectal) or microbiological assay used for VRE identification (culture or molecular assay).⁹¹ Detailed discussion of these controversial points is beyond the scope of this article.

Infection Control Processes

Standard infection control measures such as hand hygiene, use of gowns and gloves and proper cleaning and disinfection of environmental surfaces and hospital equipment are extremely important in preventing VRE transmission. These interventions have to be integral aspects of infection control programmes.⁶⁴

In many institutions, contact precautions are instituted only after clinical or surveillance cultures confirm the presence of VRE. The delay in turnaround times for cultures may result in cross-transmission. PCR techniques may overcome this delay but their usefulness is limited by the high rate of false positive results due to the detection of vancomycin resistance genes in other non-enterococcal intestinal bacteria.⁸⁹

Mathematical models have shown that instituting barrier precautions for all patients upon entry to high-risk units would be more effective.⁹² This strategy is often called “pre-emptive or protective isolation”. Studies have shown that it is highly effective in preventing the spread of multi-resistant organisms, in an epidemic setting and amongst high-risk populations.^{93,94} Although such approach has not been specifically studied as a VRE control measure, there are reasons to believe that it should also be effective as a tool to contain the spread of this organism.

Antimicrobial Stewardship

Indiscriminate use of antibiotics is one of the main

reasons for the current crisis in antimicrobial resistance.⁹⁵⁻⁹⁸ Studies indicate that up to 50% of hospitalised patients may receive inappropriate antibiotics⁹⁹ or receive antimicrobial therapy even though there is no evidence of infection or clear indication for antibiotics.^{100,101}

Several studies have shown that an antimicrobial stewardship programme can result in the recovery of antimicrobial susceptibilities among drug-resistant pathogens.¹⁰²⁻¹⁰⁷ However, the evidence that antimicrobial control can decrease rates of vancomycin resistance among enterococci is limited.¹⁰⁸ Nevertheless, antimicrobial stewardship should be a part of any comprehensive infection control programme.

The available armamentarium of interventions include institutional guidelines for antimicrobial use, educational programmes, and restriction of formulary or automatic stop orders for surgical prophylaxis.¹⁰⁹⁻¹¹¹ However, computer-assisted prescribing may be the most innovative and promising approach to limiting inappropriate use of antibiotics in the future.¹¹²⁻¹¹⁴

The Role of Information Management

Patients may remain colonised with VRE for months^{83,115,116} and antimicrobial agents cannot reliably eradicate VRE from the gastrointestinal tract.¹¹⁷⁻¹¹⁹ Negative stool cultures in former VRE carriers may just reflect low bacterial burden rather than permanent clearance.¹²⁰ Administration of broad-spectrum antibiotics may increase the concentration of VRE in stool rendering these patients contagious.¹²¹

Electronic tagging of these patients in the hospital database allows early identification and isolation upon re-admission in order to prevent re-introduction of VRE by known carriers.⁶⁴ On the other hand, indefinite tagging may strain limited resources, especially isolation rooms.^{83,122} It remains controversial when electronic tagging of VRE carriers can be safely discontinued. HICPAC guidelines recommend that a previously colonised patient can be considered to be cleared after 3 consecutive negative cultures obtained with at least a 1-week interval.⁷⁹ However, even this approach does not guarantee complete eradication of VRE.^{83,121} Further research is required to determine whether innovative strategies such as a combination of a risk scoring system and negative surveillance stool cultures can safely exclude persistent VRE carriage.

Local Situation

1994-2004

In Singapore, VRE was isolated for the first time in March 1994 from the wound of a 4-year-old boy hospitalised in the Burns Centre of Singapore General Hospital (SGH). Prior to the isolation of VRE, he spent 34 days in hospital, receiving multiple broad-spectrum antibiotics.²⁷

In 1995, 2 more isolates were obtained from urinary specimens of 2 patients managed in Tan Tock Seng Hospital. One of these patients was not hospitalised and received no antibiotics prior to isolation of VRE. Both strains were determined to be *Enterococcus faecalis* and were phenotypically VanB. VRE bacteriuria in both cases was transient and resolved without antimicrobial therapy.¹²³

In the following years, 2 epidemiological studies were completed in order to investigate local prevalence of VRE. In the first study performed in 1997 at the National University Hospital (NUH), 299 consecutive stool specimens were tested for VRE. This survey showed that 35 patients carried enterococci with reduced susceptibility to vancomycin (MIC >4 mg/mL). However, only 2 (0.7%) VRE isolates (both VanB) demonstrated a high level of vancomycin resistance. Both patients were immunocompromised, had prolonged hospital stay and received long courses of antibiotics (although only 1 of them was treated with vancomycin).¹²⁴

The second survey (Dr Ling Moi Lin, personal communication, 2005) was conducted in the SGH among haematology and renal in-patients between 1999 and 2001. Three hundred and twenty-seven patients had stool cultures performed on admission and then weekly as long as they remained hospitalised. VRE had not been isolated.

For the next few years, the incidence of VRE in Singapore remained very low. Between 1999 and 2002, VRE was not isolated from any clinical specimen in the microbiology laboratory of NUH. There was only 1 VRE isolate in 2003 and 4 VRE isolates in 2004. Each case was investigated, contact traced and found to be epidemiologically unrelated. All 5 patients had recently been in other hospitals, either overseas or local. Strict isolation was applied. Microbiological investigation suggested that local spread at NUH was unlikely.¹²⁵ In the same period (1998-2003), only sporadic isolates (no more than 4 per year) were detected in SGH.¹⁷

The First Outbreak

In April 2004, VRE was isolated within the same week from the blood of 2 haematology in-patients hospitalised in the same ward.²⁸ Both patients suffered from haematological malignancies and received prolonged courses of broad-spectrum antibiotics for several weeks prior to the development of VRE bacteraemia.

The affected ward was closed, and strict infection control measures were applied. Contact tracing identified 136 patients [13 in intensive care unit (ICU) and 123 in haematology ward] who were hospitalised together with the 2 index patients. Four of these patients had faecal or rectal cultures positive for VRE. All 6 isolates were identified as *Enterococcus faecium* and multiplex PCR for

van genes confirmed the VanB phenotype. All isolates had almost identical PFGE patterns suggesting that the outbreak was caused by a single clone of VRE. All patients from the affected ward were gradually discharged and the affected ward was re-opened 5 weeks later. No further new cases were detected in the next 6 months.

The Second Outbreak

The situation changed dramatically the following year. In March 2005, VRE was isolated from wound samples of 2 patients from different wards in SGH. Index patients were isolated and all neighbouring contacts were screened. Despite these enhanced infection control measures by end March 2005, a further 43 isolates from several different wards were detected.^{29,126} The following measures were applied to eradicate a hospital-wide outbreak of VRE:

(1) formation of a VRE task force; (2) hospitalwide screening; (3) isolation of carriers; (4) physical segregation of contacts; (5) surveillance of high-risk groups; (6) increased cleaning; (8) electronic tagging of VRE status; and (7) education and audits. These strict measures were based on measures that led to successful eradication of large VRE outbreak in the Royal Perth Hospital.¹⁶ Active VRE screening of all inpatients and physical segregation of carriers, contacts and newly admitted patients (considered “clean” or “unknown”) was instituted on 3 April 2005. The task was enormous. There were 1086 in-patients in SGH on the day segregation and cohorting of patients was introduced. Patients were classified as contacts and were moved to pre-designated cubicles usually to one side of each ward to facilitate new admissions (unknown or clean) to the other side. Bed management systems were stressed by the need to segregate patients according to the different outbreak categories while keeping to their class status. Elective surgical admissions were cancelled for 1 week to facilitate this process.

The cancellations of surgical electives to facilitate patient segregation movements affected cost and inconvenienced patients. To facilitate appropriate patient placement, long delays in admissions from the emergency department ensued.

Active screening posed even bigger challenges. Using outbreak definitions, 19,574 contacts were identified as eligible for active screening. Screening was done in phases over 2 weeks in order to allow the microbiology laboratory to cope with the increased number of specimens. At least 2 negative stool or rectal swab cultures or PCR tests collected at least 1 day apart were required before any patient could be transferred to a clean section of the ward. By end June, a total of 147 carriers and 4 clinical cases were detected. The outbreak appeared to spare haematology, oncology, and ICU patients. The majority of affected patients were

hospitalised in crowded, subsidised medical and surgical wards.²⁹

In summary, a multi-pronged strategy orchestrated by a central task force helped curb the outbreak at the expense of bed management systems, loss of revenue and inconveniences to patients. Eradicating VRE was hampered by large hospital size, heterogeneous population mix of patients with lots of in-patient movements and communal wards.

It is important to note that just 1 year after the first outbreak, several new clones of VRE were detected in SGH. The 2004 outbreak was caused by a single clone. In 2005, 4 major clones were detected in addition to several sporadic VRE isolates. Only 1 of these clones (the smallest) resembled the 2004 clone by the pulsed field gel electrophoresis (PFGE) criteria.¹⁷

There are a few possible explanations for this phenomenon. It is possible that these VRE clones were already present in SGH but limited surveillance, performed at that time, did not detect them. Introduction of the new selective culture media in early 2005 could have contributed to an improved rate of VRE detection. The presence of the multiple clones of VRE could also be caused by the recurrent introduction of new VRE strains from other healthcare facilities. Both index patients with VRE in 2004 and in 2005 had been previously hospitalised in other countries suggesting that they could have brought VRE from overseas.¹⁷

Another interesting theory was recently presented by Willems et al. They observed that new genetic lineage of enterococcus has spread globally over the last 20 years. This new complex of related enterococcal strains evolved through recombination events and mutations in response to ongoing antimicrobial use in healthcare facilities. It can be characterised by enhanced antimicrobial resistance, virulence and ability to spread.¹²⁷ Such gradual evolution of enterococcus through recurrent recombination events and mutations could also explain the emergence and co-existence of several seemingly different VRE clones in Singapore.

Local Situation after Second Outbreak.

Following the second VRE outbreak, VRE surveillance was enhanced in restructured hospitals. According to recently published data, 31 strains of VRE were isolated in six restructured hospitals in 2006, which constituted 0.8% of all isolated enterococci in the same period.³⁰

In addition, active VRE surveillance was introduced in NUH in 2005. High-risk patients in selected wards have been screened on admission with rectal cultures. In 2005, 371 specimens were tested, followed by 379 specimens in 2006 and 866 specimens in 2007. There were 11 positive cultures in 2005, only 1 positive culture in 2006, and 21

positive cultures in 2007. In these 3 years, VRE was also detected in clinical specimens (3 in 2005, 1 in 2006 and 4 in 2007) (Dr Dale Fisher, personal communication, 2008).

These results show that an active surveillance programme can help to detect previously unknown VRE carriers in high-risk wards. It also shows that active surveillance is an important part of an infection control programme as it helps to estimate the true prevalence of VRE among vulnerable patients.

Conclusions

The prevalence of VRE in Singapore remains low but there is no reason to believe that it will not increase in the same way it did in other countries. Infection control efforts must be more comprehensive in order to slow down the spread of antimicrobial resistance among nosocomial pathogens, including VRE. Universal, active VRE surveillance may not be justified at this point but should be considered in high-risk units (ICU or haematology) or among high-risk patients (e.g. those transferred from overseas hospitals).^{58,128}

In addition to monitoring compliance with the traditional infection control measures, new strategies that merit consideration include pre-emptive isolation of patients in high-risk units and molecular techniques for the detection of VRE. It is also high time to introduce antimicrobial stewardship programmes in our hospitals.

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