Vancomycin-resistant Enterococcus: Risk factors, surveillance, infections, and treatment

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Vancomycin-Resistant Enterococcus: Risk Factors, Surveillance, Infections, and Treatment*

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Abstract

Background: The use of vancomycin has continued to expand because of the increasing number of patients infected or colonized with methicillin-resistant Staphylococcus aureus, causing an increase in the prevalence of vancomycin-resistant Enterococcus (VRE).

Methods: Review of the pertinent English language literature.

Results: Vancomycin-resistant Enterococcus spp. are being identified more often in nosocomial infections of surgical patients. The biology of resistance, modes of transmission, patient risk factors, and current treatment strategies are discussed.

Conclusions: The reservoir of resistance in enterococci looms as a major threat for genetic transfer and the emergence of increasing numbers of vancomycin-resistant S. aureus.

Overview

Enterococcus spp. are part of the normal human intestinal flora. Enterococcus faecalis and E. faecium account for most human infections with enterococci. Enterococcus faecalis infections tend to be observed in patients who have not had extensive exposure to antibiotics, whereas E. faecium infections are more common in patients heavily treated with antibiotics, particularly in an ICU setting.

Enterococcus infections are inherently difficult to treat because of both intrinsic and acquired resistance to many antibiotics. These organisms are intrinsically resistant to trimethoprim-sulfamethoxazole, many penicillins other than selected aminopenicillins and ureidopenicillins, and all cephalosporins with the possible exception of cefotiboprole and ceftaroline, currently undergoing clinical evaluation. In addition, enterococci have acquired resistance to many other classes of antibiotics, to which the organisms are not intrinsically resistant, including tetracyclines, macrolides, lincomamines, fluoroquinolones, aminoglycosides, and penicillins. Many strains of E. faecalis are susceptible to certain penicillins, carbapenems, and fluoroquinolones; however, virtually all strains of E. faecium are resistant to these agents [2].

Resistance of enterococci to vancomycin was first reported in Europe in 1986; the first case report in the United States followed the next year. Since that time, VRE has been identified worldwide. Although fewer than 10% of E. faecalis isolates from ICU patients with enterococcal infections are vancomycin-resistant, 70% of the E. faecium isolates are resistant [3].

Resistance is attributable to a series of transposable genetic elements collectively termed the van gene complexes. These elements also confer resistance to teicoplanin and, to variable degrees, other glycopeptides. They alter the binding target for vancomycin in the synthesis of bacterial cell wall precursors. Six van gene complexes have been described, of which vanA and vanB are the most relevant clinically. The vanA gene complex confers high-level resistance to vancomycin and teicoplanin, whereas vanB confers moderate to high-level resistance to vancomycin only [2].

*Presented at the 27th annual meeting of the Surgical Infection Society, Toronto, Ontario, Canada, April 21, 2007.
The potential transmission of vancomycin resistance to staphylococci is of great concern. It has been estimated that 9.5%–19% of patients colonized with VRE also are colonized with methicillin-resistant Staphylococcus aureus (MRSA) [4–6]. Specifically, one study of ICU patients at two academic medical centers identified 3% of patients as being co-colonized, with 40% of those being colonized at the same perirectal site [5]. Thus, opportunities for transmission of genetic information seem relatively common. There have been reports of such transmission, the first case being reported in 2003 [7]. The frequency of this transmission, and the capacity of these staphylococci to colonize and spread to other individuals, is not known. However, widespread emergence of staphylococci with high-level resistance to vancomycin and other glycopeptides would have a major impact on management of infections attributable to these organisms.

### Acquisition of VRE

The primary reservoirs from which patients acquire VRE are other patients already colonized with the organism. In addition, the healthcare environment, where the organism can survive as long as 7 days, probably plays a reservoir role as well. In some European countries, animal reservoirs have proved to be a source of VRE transmission to individuals outside the healthcare setting. The use of avoparcin, a glycopeptide antibiotic, as a growth promoter in animal husbandry was implicated in the maintenance of VRE in these animal sources [8].

Colonization with VRE appears to require not only exposure to the organism but also the presence of a susceptible host [8,9] (Table 1). The patients most likely to be colonized are elderly, severely ill individuals with multiple co-morbidities. These patients tend to be housed for long periods of time in areas of the hospital, such as ICUs, where VRE endemicity is highest.

An additional risk factor for VRE acquisition is exposure to antibiotics. Several agents have been implicated, but use of vancomycin and third-generation cephalosporins appears to be associated most commonly with the spread of this organism. Two studies suggested that altering antibiotic choice may influence the spread of VRE. In these studies, lower rates of VRE colonization were identified after the substitution of piperacillin/tazobactam, an antibiotic with anti-enterococcal activity, for ceftazidime or ticarcillin/clavulanic acid, antibiotics that lack such activity [10,11].

Although the emphasis on recognizing hosts susceptible to VRE is of some importance, one cannot overlook the fact that these patients have to acquire VRE from a source [8]. Thus, the proximity and duration of exposure to patients or environmental reservoirs of VRE probably is the most important risk factor for acquisition of VRE. This was clearly demonstrated by Byers et al., who identified proximity to an unisolated VRE case as a highly significant risk factor for colonization with VRE, outweighing all other risk factors [12]. Thus, high rates of colonization within an institutional setting lead to perpetuation of the epidemic.

Vancomycin-resistant enterococci can be transmitted readily between patients on the hands of healthcare workers. One study showed that VRE could be recovered from the hands of 13–43% of workers who were caring for colonized patients [13]. Thus, healthcare workers may help perpetuate an epidemic once VRE has gained a foothold within the institution.

### VRE Surveillance

In order to prevent further spread of VRE, rigorous infection control measures must be employed. Active surveillance and isolation are the primary tools. Active surveillance, which involves screening of asymptomatic patients at risk for carrying the organism, is necessary because only a small fraction of the patients colonized with VRE are identified from positive cultures. The efficacy of this approach has been demonstrated in The Netherlands, where a nationwide program of active surveillance and isolation has led to very low rates of VRE acquisition; fewer than 2% of enterococcal isolates in The Netherlands are resistant to vancomycin [3].

There are many issues to be considered in screening. Screening of all patients likely would be cost prohibitive, but selected screening of patients admitted to wards where the prevalence of VRE is greater than 20% has been proposed [8]. Other issues include the frequency with which screening should be undertaken, the patient site(s) to be utilized, and the specific laboratory method used. For instance, stool cultures are considered the gold standard for detecting VRE, but most screening involves rectal or perirectal sampling. Detection at that site is a function of the concentration of VRE in the stool, as well as the current exposure of the patient to antibiotics, potentially decreasing the sensitivity of detection [14,15].

Once a patient is identified as being colonized with VRE, contact isolation procedures should be initiated. An unresolved question is how long such patients need to remain isolated. Many of the chronically ill patients colonized with VRE can be expected to be rehospitalized. Unfortunately, VRE carriage appears to be prolonged, if not permanent. In one study, 43% of pediatric oncology patients colonized with VRE remained persistent carriers, with VRE being excreted for a median of 112 days [16]. In another study, 61% of adult oncology patients were still colonized with VRE on re-admission to the hospital, with the sicker patients more likely

### Table 1: Risk Factors for Colonization with Vancomycin-Resistant Enterococci

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<tr>
<th>Risk Factor</th>
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<td>Advanced age</td>
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<td>Severe underlying illness</td>
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<td>Inter-hospital transfer</td>
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<td>Nursing home residency</td>
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<td>Extended hospitalization</td>
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<td>Specialized nutritional support</td>
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<td>Central venous catheterization</td>
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<td>Hematologic malignant tumor</td>
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<td>Solid organ allograft</td>
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<td>Chronic hemodialysis</td>
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<td>Antibiotic exposure:</td>
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<td>Vancomycin</td>
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<tr>
<td>Third-generation cephalosporins</td>
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<td>Metronidazole</td>
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<td>Anti-anaerobic antibiotics</td>
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<td>Multiple antibiotics</td>
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<td>Long duration of antibiotic therapy</td>
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From reference 8.
to remain colonized [17]. Thus, there is no specific answer as to when patients colonized with VRE can be removed from isolation. The current recommendation from the U.S. Centers for Disease Control and Prevention (CDC) are that “stringent criteria might be appropriate, such as VRE-nega-
tive results on at least three consecutive occasions (≥ 1 week apart) for all cultures from multiple body sites . . .”

Nonetheless, active surveillance and isolation for VRE re-
main controversial [19]. Proponents note the success of in-
fection control programs in the control of disease processes
such as tuberculosis, smallpox, and, more recently, severe
acute respiratory syndrome (SARS). They also point to the
potential risk that dissemination of VRE will lead inevitably
to wider development of glycopeptide-resistant staphylococci. However, opponents question the value of these pro-
grams, noting that infections caused by VRE are relatively
uncommon, and tend to occur in patients who typically will
acquire infections with resistant pathogens in any case. Some
also believe that colonization is already too widespread in
the healthcare environment, and that infection control efforts
may result only in the near-universal isolation of all hospi-
talized patients, which may be deleterious to care as a result
of decreased patient contact with healthcare providers. Fi-
nally, despite numerous opportunities for transmission of
vanA to staphylococci, vancomycin-resistant staphylococci
continue to be rare. Thus, at present, there is no consensus
on whether active surveillance and isolation for VRE is a
worthwhile pursuit.

Infections Caused by VRE

Infections develop in patients who have already been col-
onized with VRE [9]. The types of infections are similar to
those seen with typical enterococci, with intra-abdominal,
skin and soft tissue, urinary tract, and blood stream infec-
tion and endocarditis being the most common. Three per-
cent of patients with VRE bacteremia reportedly develop en-
docarditis [20]. Vancomycin-resistant enterococcal infections
of the central nervous system are uncommon, and respira-
atory infections are rare.

Vancomycin-resistant enterococcal infections are most
common in immunocompromised patients [9]. The patients
at highest risk are those with hematologic malignant tumors,
particular those treated with bone marrow transplants. Pa-
ients with solid organ allografts also represent a group at
higher risk for VRE infections. Patients with liver transplants
may develop VRE infections related to the biliary tract, prob-
ably because of the innate capacity of enterococci to survive
in an environment where there are high concentrations of
bile salts.

The implication of an infection by VRE remains uncertain.
A meta-analysis of 13 studies of patients with vancomycin-
resistant vs. vancomycin-sensitive enterococcal bacteremias
suggested a higher risk of death related to infection by VRE
(RR = 2.57; 95% confidence interval [CI], 2.27–2.91). The
mortality rate attributable to infection with the vancomycin-
resistant strain was estimated at 17%. The hospital stay was
2.9 to 27 days longer in patients with infections caused by
VRE [21]. Another study focused on patients with liver
allografts who developed infections with VRE. In these 19
patients, VRE was cultured from the blood in 35% of pa-
ients, the peritoneal fluid in 20%, bile in 20%, and urine in
14%. The survival of patients with VRE infections was 52%,
compared with 82% in matched patients without this infec-
tion [22].

Nonetheless, some authorities believe that the high mor-
tality rates observed in patients with VRE infections reflect
their complicated medical conditions, and are not attribut-
able specifically to VRE. They point out to the inherent dif-
ficulty of attributing death in these patients to a VRE infec-
tion when there are so many other medical co-morbidities.
Further, they point out that many of the studies showing
high mortality rates from VRE infections took place before
more effective therapy for VRE was available [23,24].

Antibiotics for VRE Infections

A number of agents are potentially useful in the treatment
of infections caused by VRE (Table 2). Certain older agents
can be used. Some aminopenicillins and ureidopenicillins
(such as ampicillin and piperacillin) have activity against the
occasional strain of vancomycin-resistant E. faecalis [9,25].
However, virtually all strains of E. faecium are resistant, so
these agents are not useful for the majority of VRE infections.

Older tetracyclines, such as doxycycline and minocycline,
have been used. However, a report on urinary isolates of
vancomycin-resistant E. faecium indicated that only 60% of
strains were fully sensitive to doxycycline [26]. In addition,
many authorities would question the use of these agents for
VRE bacteremia, as they are considered bacteriostatic rather
than bactericidal.

Chloramphenicol has been successful for the treatment of
VRE infections. In the survey of urinary isolates of vanco-
mycin-resistant E. faecium, nearly all strains were susceptible
to this drug [26]. However, additional reports now indicate
emergence of strains of VRE resistant to chloramphenicol,
particularly as its use has increased [27].

Among newer agents, quinupristin/dalfopristin has been
useful in the treatment of infections caused by VRE. Of note,
this agent is useful only for E. faecium infections, because E.
faecalis has intrinsic resistance [9,25]. Clinical response rates
of 71–83% have been reported when this agent has been used
to treat patients with VRE infections. However, quin-
upristin/dalfopristin has been reported to be associated with
relatively high rates of side effects, especially arthralgias
(33% of treated patients) and myalgias (47% of treated pa-
tients). In addition, this antibiotic generally must be admin-
istered through a central venous catheter [25,28] because of
the high incidence of phlebitis. Resistance to quinupristin/
dalfopristin has been reported in 1.3–2.4% of patients with
vancomycin-resistant E. faecium [26,29].

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<tr>
<th>Table 2. Antibiotics for Treatment of Infections Caused by Vancomycin-Resistant Enterococci</th>
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<tr>
<td>Selected aminopenicillins, ureidopenicillins, and carbapenems <em>(E. faecalis strains only)</em></td>
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<tr>
<td>Doxycycline, minocycline</td>
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<tr>
<td>Chloramphenicol</td>
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<td>Quinupristin-dalfopristin <em>(E. faecium strains only)</em></td>
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<td>Linezolid</td>
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<td>Daptomycin</td>
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<td>Tigecycline</td>
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Linezolid probably is the agent used most often for the treatment of VRE infections with the exception of bacteremia. Clinical response rates of 67–81% have been reported [25,28]. In solid organ allograft recipients, mortality rates of 33% for all patients and 42% for liver transplant patients were reported when linezolid was used to treat VRE infections. These rates were substantially decreased relative to the 53–83% rates in historical controls [30]. A randomized controlled trial in 40 cancer patients with vancomycin-resistant *E. faecium* infections compared linezolid with quinupristin/dalfopristin; the clinical response rates were 58% for linezolid and 43% quinupristin/dalfopristin [31]. Nonetheless, resistance of VRE to linezolid has surfaced, as with most other antibiotics. In a report from the M.D. Anderson Cancer Center, susceptibility of vancomycin-resistant *E. faecium* to linezolid decreased to 83% six months after inclusion of linezolid on the hospital formulary [32]. Although linezolid generally has been safe, development of thrombocytopenia or other evidence of bone marrow suppression may be an important limiting side effect, particularly in immunosuppressed or cancer patients [29].

Daptomycin also has good in vitro activity against VRE. This agent is bactericidal rapidly, and theoretically might be preferred for patients with VRE bacteremia or endocarditis [29]. However, experience in the treatment of VRE is relatively limited. In one series of eleven patients with VRE bacteremia, treatment success was noted in five [33]. In another series of neutropenic patients with bacteremia, four of nine patients were treated successfully [34]. As with other antibiotics, resistance of VRE to daptomycin has emerged [9,29].

Tigecycline, a recently released glycycline, has good in vitro activity against VRE. However, there are few published data regarding treatment of VRE infections with this agent. Because it is bacteriostatic and achieves relatively low serum concentrations, it may not be ideal for patients with bacteremia. Its utility in patients with VRE resistant to older tetracyclines such as minocycline has yet to be determined [9,28,29].

Conclusions

Colonization of hospitalized patients with VRE has become common throughout the world. Colonization is most common in the critically ill patient, whose concurrent illness and exposure to antimicrobial therapy facilitates acquisition of resistant organisms, and who is housed in a healthcare setting where exposure to previously colonized individuals and environmental sources is facilitated. Active surveillance for VRE and isolation of colonized patients may decrease the spread of this organism. The typical patient who develops an overt infection attributable to VRE is immunosuppressed and has been colonized previously with the organism. Although several antibiotics have activity against VRE, the mortality rate in patients with infections caused by VRE remains high.

The development of larger numbers of infections caused by VRE is a major clinical problem, particularly for the critically ill or immunosuppressed patient. However, dissemination of this resistant organism is of further concern because of the potential for transfer of the vancomycin resistance genetic trait to *S. aureus*. This event has been documented clinically, and the frequent co-colonization of patients with both MRSA and VRE suggests that such transfer may occur with increasing frequency in the future. This prospect of widespread development of vancomycin-resistant *S. aureus* also argues for continued diligence in efforts to control VRE.

Author Disclosure Statement

Dr. John E. Mazuski has served as speaker, consultant, and/or on advisory boards for Merck & Co., Ortho-McNeil Pharmaceuticals, Pfizer, Inc., Schering-Plough Corp., and Wyeth Pharmaceuticals, and has received research support for clinical studies from Pfizer, Inc.

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