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

John E. Mazuski

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.*

Vancomycin-resistant *Enterococcus* (VRE) is an increasing problem worldwide. Approximately 30% of enterococci isolated from patients in intensive care units (ICUs) in the United States carry this resistance trait [1]. Bacteremia and endocarditis caused by these organisms are being reported with increasing frequency, and these organisms also can be involved in urinary tract, intra-abdominal, and skin and soft tissue infections. However, of potentially greater importance, the transfer of vancomycin resistance to other gram-positive organisms, particularly staphylococci, remains a threat. In this paper, the epidemiology and risk factors for colonization with VRE are reviewed, as are measures to prevent the spread of VRE colonization. In addition, antibiotic therapy for infections attributable to VRE is discussed.

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 ceftobiprole 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, lincosamines, 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].

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 organisms. 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

Advanced age
Severe underlying illness
Inter-hospital transfer
Nursing home residency
Extended hospitalization
Specialized nutritional support
Central venous catheterization
Hematologic malignant tumor
Solid organ allograft
Chronic hemodialysis
Antibiotic exposure:
   Vancomycin
   Third-generation cephalosporins
   Metronidazole
   Anti-anaerobic antibiotics
   Multiple antibiotics
   Long duration of antibiotic therapy

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-negative results on at least three consecutive occasions (≥ 1 week apart) for all cultures from multiple body sites . . . "

Nonetheless, active surveillance and isolation for VRE remain controversial [19]. Proponents note the success of infection 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 programs, 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 hospitalized patients, which may be deleterious to care as a result of decreased patient contact with healthcare providers. Finally, 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 colonized 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 infection and endocarditis being the most common. Three percent of patients with VRE bacteremia reportedly develop endocarditis [20]. Vancomycin-resistant enterococcal infections of the central nervous system are uncommon, and respiratory 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. Patients 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, probably 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 patients, 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 infection [22].

Nonetheless, some authorities believe that the high mortality rates observed in patients with VRE infections reflect their complicated medical conditions, and are not attributable specifically to VRE. They point out to the inherent difficulty of attributing death in these patients to a VRE infection 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 vancomycin-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, quinupristin/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 patients). In addition, this antibiotic generally must be administered 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].

TABLE 2. ANTIBIOTICS FOR TREATMENT OF INFECTIONS CAUSED BY VANCOMYCIN-RESISTANT ENTEROCOCCI

Selected aminopenicillins, ureidopenicillins, and
  carbapenems (*E. faecalis* strains only)
Doxycycline, minocycline
Chloramphenicol
Quinupristin-dalfopristin (*E. faecium* strains only)
Linezolid
Daptomycin
Tigecycline

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 glycylcycline, 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

References

1. National Nosocomial Infections Surveillance System. National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control 2004;32:470–485.
2. Linden PK. Optimizing therapy for vancomycin-resistant enterococci (VRE). Semin Respir Crit Care Med 2007;28:632–645.
3. Tenover FC, McDonald LC. Vancomycin-resistant staphylococci and enterococci: Epidemiology and control. Curr Opin Infect Dis 2005:18;300–305.
4. Franchi D, Climo MW, Wong AH, et al. Seeking vancomycin-resistant *Staphylococcus aureus* among patients with vancomycin-resistant enterococci. Clin Infect Dis 1999;29:1566–1568.
5. Warren DK, Nitin A, Hill C, et al. Occurrence of co-colonization or co-infection with vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus* in a medical intensive care unit. Infect Control Hosp Epidemiol 2004;25:99–104.
6. Furuno JP, Perencevich EN, Johnson JA, et al. Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci co-colonization. Emerg Infect Dis 2005;11:1539–1144.
7. Chang S, Sievert DM, Hageman JC, et al. Infection with vancomycin-resistant *Staphylococcus aureus* containing the *vanA* resistance gene. N Engl J Med 2003;342:1342–1347.
8. DeLisle S, Perl TM. Vancomycin-resistant enterococci: A road map on how to prevent the emergence and transmission of antimicrobial resistance. Chest 2003;123:504S-518S.
9. Zirakzadeh A, Patel R. Vancomycin-resistant enterococci: Colonization, infection, detection, and treatment. Mayo Clin Proc 2006;8:529–536.
10. Bradley SJ, Wilson AL, Allen MC, et al. The control of hyperendemic glycopeptide-resistant *Enterococcus* spp. on a haematology unit by changing antibiotic usage. J Antimicrob Chemother 1999;43:261–266.
11. Winston LG, Charlebois ED, Pang S, et al. Impact of a formulary switch from ticarcillin-clavulanate to piperacillin-tazobactam on colonization with vancomycin-resistant enterococci. Am J Infect Control 2004;32:462–469.
12. Byers KE, Anglim AM, Anneski CJ, et al. A hospital epidemic of vancomycin-resistant *Enterococcus*: Risk factors and control. Infect Control Hosp Epidemiol 2001;22:140–147.
13. Bonilla HF, Zervos MA, Lyons MJ, et al. Colonization with vancomycin-resistant *Enterococcus faecium*: Comparison of a long-term-care unit with an acute-care hospital. Infect Control Hosp Epidemiol 1997;18:333–339.
14. Weinstein JW, Tallapragada S, Farrel P, Dembry LM. Comparison of rectal and perirectal swabs for detection of colo-

nization with vancomycin-resistant enterococci. J Clin Microbiol 1996;34:210–212.

15. D'Agata EM, Gautam S, Green WK, Tang YW. High rate of false-negative results of the rectal swab culture method in detection of gastrointestinal colonization with vancomycin-resistant enterococci. Clin Infect Dis 2002;34:167–172.

16. Henning KJ, Delencastre H, Eagan J, et al. Vancomycin-resistant *Enterococcus faecium* on a pediatric oncology ward: Duration of stool shedding and incidence of clinical infection. Pediatr Infect Dis J 1996;15:848–854.

17. Montecalvo MA, de Lencastre H, Carraher M, et al. Natural history of colonization with vancomycin-resistant *Enterococcus faecium*. Infect Control Hosp Epidemiol 1995;16:680–685.

18. Hospital Infection Control Practices Advisory Committee. Recommendations for preventing the spread of vancomycin resistance. Hospital Infection Control Practices Advisory Committee (HICPAC). Infect Control Hosp Epidemiol 1995;16:105–113.

19. Farr BM. What to think if the results of the National Institutes of Health randomized trial of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* control measures are negative (and other advice to young epidemiologists): A review and an au revoir. Infect Control Hosp Epidemiol 2006;27:1096–1106.

20. Vergis EN, Hayden MK, Chow JW, et al. Determinants of vancomycin resistance and mortality rates in enterococcal bacteremia: A prospective multicenter study. Ann Intern Med 2001;135:484–492.

21. Salgado CD, Farr BM. Outcomes associated with vancomycin-resistant enterococci: A meta-analysis. Infect Control Hosp Epidemiol 2003;24:690–698.

22. Gearhart M, Martin J, Thomas M, et al. Consequences of vancomycin-resistant *Enterococcus* in liver transplant recipients: A matched control study. Clin Transplant 2005;19:711–716.

23. Patel R. Clinical impact of vancomycin-resistant enterococci. J Antimicrob Chemother 2003;51(Suppl S3):iii13–iii21.

24. Mascini EM, Bonten MJM. Vancomycin-resistant enterococci: Consequences for therapy and infection control. Clin Microb Infect 2005;11(Suppl 4):43–56.

25. Linden PK. Treatment options for vancomycin-resistant enterococcal infections. Drugs 2002;62:425–441.

26. Nichol KA, Sill M, Laing NM, et al. Molecular epidemiology of urinary tract isolates of vancomycin-resistant *Enterococcus faecium* from North America. Int J Antimicrob Agents 2006;27:392–396.

27. Lautenbach E, Gould CV, LaRosa LA, et al. Emergence of resistance to chloramphenicol among vancomycin-resistant enterococcal (VRE) bloodstream isolates. Int J Antimicrob Agents 2004;23:200–203.

28. Torres-Viera C, Dembry LM. Approach to vancomycin-resistant enterococci. Curr Opin Infect Dis 2004;17:541–547.

29. Linden PK. Optimizing therapy for vancomycin-resistant enterococci (VRE). Semin Respir Crit Care Med 2007;28:632–645.

30. El Khoury J, Fishman JA. Linezolid in the treatment of vancomycin-resistant *Enterococcus faecium* in solid organ transplant recipients: Report of a multicenter compassionate-use trial. Transpl Infect Dis 2003;5:121–125.

31. Raad I, Hachem R, Hanna H, et al. Prospective, randomized study comparing quinupristin-dalfopristin with linezolid in the treatment of vancomycin-resistant *Enterococcus faecium* infections. J Antimicrob Chemother 2004;53:646–649.

32. Raad II, Hanna HA, Hachem RY, et al. Clinical-use-associated decrease in susceptibility of vancomycin-resistant *Enterococcus faecium* to linezolid: A comparison with quinupristin-dalfopristin. Antimicrob Agents Chemother 2004;48:3583–3585.

33. Segreti JA, Crank CW, Finney MS. Daptomycin for the treatment of gram-positive bacteremia and infective endocarditis: A retrospective case series of 31 patients. Pharmacotherapy 2006;26:347–352.

34. Poutsiaka DD, Skiffington S, Miller KB, et al. Daptomycin in the treatment of vancomycin-resistant *Enterococcus faecium* bacteremia in neutropenic patients. J Infect 2007;54:567–571.

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