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Vancomycin-Resistant Enterococci: Mechanisms and Clinical Observations

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Enterococci are not generally regarded as highly virulent bacterial pathogens. However, resistance to many antimicrobial drugs complicates treatment of enterococcal infections. Acquired resistance to high concentrations of glycopeptide antibiotics, specifically vancomycin, has exacerbated this problem. This article seeks to concisely review the mechanisms of that resistance and its effects on clinical management of enterococcal infections, as well as clinical microbiology and infection control.

Enterococcus gallinarum and *Enterococcus casseliflavus* are relatively infrequent causes of human infection. As a result, the intrinsic resistance to low concentrations of vancomycin (MICs as high as 32 μg/mL) that is a characteristic of these species was little more than a curiosity to infectious diseases clinicians. In contrast, *Enterococcus faecalis* and *Enterococcus faecium* cause the great majority of enterococcal infections. When clinical isolates of these enterococcal species with acquired vancomycin resistance began to appear in the late 1980s, it prompted significant changes in testing of enterococci in the clinical microbiology laboratory, infection control of enterococci, and treatment of enterococcal infections [1].

Enterococci are normal inhabitants of the alimentary canal and cause urinary tract infections, bacteremia, and endocarditis. They are also commonly recovered from infections of the abdomen, the pelvis, the biliary tract, and wounds, settings in which polymicrobial flora are common. Enterococci less frequently cause infections of other sites, for example, bone, joints, and the meninges. *E. faecalis* causes the majority of enterococcal infections overall. *E. faecium* causes a substantial proportion of enterococcal infections, particularly infections acquired in the hospital setting. Data collected by the National Nosocomial Infections Surveillance System on infections in patients in intensive care units from 1989 through 1998 showed that enterococci were the third most common bloodstream isolate, the third most common urinary isolate, the most common isolate from surgical site infections, and the fourth most common isolate from all sites [2]. Enterococci are primarily opportunistic pathogens. The increasing severity of illness in hospitalized patients has contributed to the ascendance of enterococci as nosocomial pathogens. Progress in medical technology and treatment, such as the use of various intravascular access devices, implanted prosthetic devices, cytotoxic chemotherapy, and immunosuppression, has magnified the impact of organisms of relatively low virulence, such as enterococci. Of critical import is the intensive use of relatively broad-spectrum antibiotics in the hospital, which provides selective pressure favoring the growth of intrinsically drug-resistant commensal organisms such as enterococci.

Resistance to a number of antimicrobial drugs is a characteristic of the genus *Enterococcus* (table 1) [3], although some species (e.g., *E. faecium*) are more intrinsically resistant than others. Enterococci obtained from antibiotic-naive populations in the Solomon Islands demonstrated resistance to penicillinase-resistant penicillins, cephalosporins, clindamycin, and low levels of both penicillins and aminoglycosides [4]. *E. faecium* carries *aac(6′)-Ii,* a chromosomal gene encoding an aminoglycoside-modifying enzyme that prevents synergy between cell wall–active agents and the aminoglycosides tobramycin, kanamycin, and netilmicin [5]. Although the combination of trimethoprim and sulfamethoxazole may appear to be active against enterococci in vitro, the microorganisms are presumed to be clinically resistant by virtue of their ability to use exogenous folate, thus circumventing the mechanism of action of those drugs [6]. Tolerance is the ability of the organism to

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Table 1. Intrinsic and acquired antimicrobial drug resistance in enterococci.

Type of resistance, antimicrobial drug
Intrinsic
β-Lactams (particularly cephalosporins and penicillinase-resistant penicillins)
Low concentrations of aminoglycosides
Clindamycin
Fluoroquinolones
Trimethoprim-sulfamethoxazole (in vivo)
Acquired
High concentrations of β-lactams (via penicillin-binding proteins or β-lactamase)
High concentrations of aminoglycosides
Glycopeptides (vancomycin and teicoplanin)
Tetracycline
Erythromycin
Fluoroquinolones
Rifampin
Chloramphenicol
Fusidic acid
Nitrofurantoin

NOTE. Reproduced, with modifications, from [3].

survive levels of drugs well in excess of the MIC. Tolerance to cell wall–active drugs (e.g., penicillin and vancomycin) is common among clinical isolates of enterococci and was thought to be intrinsic until nontolerant isolates of *E. faecalis* were obtained from an antimicrobial drug–naive population. It was subsequently demonstrated that these strains could be made tolerant by exposure to pulsed doses of penicillin [7].

Through mutation and transfer of resistance genes from other species (and in some cases between enterococcal species), enterococci have acquired additional resistance determinants (table 1). *E. faecium* often (>60%) displays acquired resistance to concentrations of penicillin that are substantially higher than the microorganism is intrinsically able to resist, mediated by increased expression of low-affinity penicillin-binding protein 5 (PBP5) or mutations in PBP5 that produce progressively lower affinity for penicillin in the most resistant strains [8]. Production of a β-lactamase essentially identical to the one that is found in *Staphylococcus aureus* causes penicillin resistance in rare isolates of *E. faecalis* [9]. High-level aminoglycoside resistance, typically mediated by aminoglycoside-modifying enzymes, has been found in ~25%–50% of enterococcal isolates in a number of studies [10]. Resistance to fluoroquinolones, in excess of the modest intrinsic resistance found in many enterococci, is mediated by alterations in enzymes involved in DNA replication [11]. Other common acquired genetic determinants confer resistance to macrolides, tetracycline, and chloramphenicol. Chromosomal mutations may occur that produce resistance to rifampin and fusidic acid, among others. Because of all of the problems with drug resistance outlined above, vancomycin was a reliable and critically important antimicrobial for the treatment of enterococcal infections.

PHENOTYPES, GENOTYPES, AND MECHANISMS OF GLYCOPEPTIDE RESISTANCE IN ENTEROCOCCI

The first report of enterococci resistant to high concentrations of glycopeptide antibiotics (vancomycin and teicoplanin) was published in 1988, when Uttley et al. [1] reported the occurrence of an outbreak of vancomycin-resistant *E. faecium* infecting patients in a hospital renal unit. At that time, use of vancomycin and teicoplanin (the latter has not been approved for use in the United States) had been growing rapidly, in part because of the increasing use of intravascular devices combined with the high prevalence of methicillin resistance among staphylococci. Also, orally administered vancomycin was a widely used treatment for *Clostridium difficile* colitis. Consumption of huge quantities of glycopeptides was also occurring in an entirely different population; specifically, avoparcin (another glycopeptide drug) was being used as a growth promoter in food animals. This use of a glycopeptide at subtherapeutic concentrations in animals may have played a role in the development of acquired vancomycin resistance in enterococci [12].

Various types of vancomycin-resistant enterococci (VRE) have been characterized on phenotypic and genotypic bases, as summarized in table 2 [13]. VanA enterococci are resistant to high levels of vancomycin (MIC, ⩾64 μg/mL) and teicoplanin (MIC, ⩾8 μg/mL). Resistance is induced by the presence of either drug [14]. VanB organisms are resistant to a range of vancomycin concentrations, from 4 to >1024 μg/mL. They typically retain susceptibility to teicoplanin, which has not been seen to induce resistance [15]. *vanA* and *vanB* clusters have been found primarily in *E. faecalis* and *E. faecium*. *vanA* and *vanB* have been found less commonly in other enterococcal species. Evidence of transfer of these resistance genes beyond the genus *Enterococcus* includes the finding of several gram-positive species carrying *vanA* and a stool isolate of *Streptococcus bovis* carrying *vanB* [16]. The ability of these genes to be expressed in diverse hosts was demonstrated by the experimental laboratory transfer of *vanA* to *S. aureus* and other gram-positive organisms [17, 18]. Fortunately, we are as yet unaware of any transfer of these genes to *S. aureus* in nature. Less common phenotypes of acquired glycopeptide resistance include VanD, which has been described in several isolates of *E. faecium* that were resistant to modest levels of vancomycin (MIC, 64–128 μg/mL) and teicoplanin (MIC, 4 μg/mL), and one isolate of VanE *E. faecalis* that was resistant to a low concentration of vancomycin (MIC, 16 μg/mL) but susceptible to

Table 2. Characteristics of phenotypes of glycopeptide-resistant enterococci in the majority of reported isolates.

Variable	VanA	VanB	VanC	VanD	VanE
Vancomycin MIC, μg/mL	64–>1000	4–1024	2–32	64–256	16
Teicoplanin MIC, μg/mL	16–512	≤0.5	≤0.5	4–32	0.5
Most frequent *Enterococcus* spp.	*Enterococcus faecium*	*Enterococcus faecalis*	*Enterococcus gallinarum*	*E. faecium*	*E. faecalis*
	E. faecalis	*E. faecium*	*Enterococcus casseliflavus*	—	—
Genetic determinant	*vanA* cluster; acquired	*vanB* cluster; acquired	*vanC1, vanC2* cluster; intrinsic	*vanD* cluster; acquired	*vanE* cluster; acquired
Transferability	Yes	Yes	No	ND	ND

NOTE. ND, not demonstrated.

teicoplanin [19, 20]. The vancomycin-dependent enterococci are another unusual phenotype of VRE. These are progeny of the standard VanA and VanB VRE that develop mutations that prevent them from growing in the absence of glycopeptides [21]. *E. gallinarum* and *E. casseliflavus,* the VanC enterococci, are intrinsically resistant to vancomycin at concentrations typically lower than or equal to 32 μg/mL, although these species may acquire additional Van determinants, resulting in higher MICs.

The mechanism of acquired glycopeptide resistance in VanA and VanB enterococci was found to be a cluster of genes encoding an alternate biosynthetic pathway for the production of cell wall precursors that bind vancomycin poorly (figure 1) [22, 23]. Unlike the normal peptidoglycan (PG) precursors, which have D-alanyl–D-alanine (D-Ala–D-Ala) dipeptide termini, those of enterococci with acquired vancomycin resistance (except VanE types) end with the depsipeptide D-alanyl–D-lactate (D-Ala–D-Lac). Vancomycin binds to these altered molecules at .001 times the affinity with which it binds to native PG precursor [24]. This alteration of the target site for glycopeptide antibiotics is accomplished by several proteins that sense the presence of the drug (or an effect of the drug), produce a drug-resistant target, and eliminate the drug-susceptible target in a coordinated manner. In VanA enterococci, for example, the VanR protein (the response regulator), and the VanS protein (a histidine kinase sensor) form a 2-component regulatory system [14]. The presence of vancomycin, teicoplanin (and several other compounds), or perhaps more likely some perturbation of cell wall precursors elicited by these drugs causes the VanS protein to autophosphorylate, then in turn to phosphorylate VanR. In addition to increasing expression of *vanR* and *vanS,* phosphorylated VanR protein binds to the promoter region for *vanHAX,* driving transcription of these genes that encode the essential structural molecules of the gene cluster—that is, the system is induced by the presence of vancomycin or teicoplanin [25]. The VanH protein converts pyruvate into D-lactate, which is combined with D-alanine by the VanA ligase to create D-Ala–D-Lac. The VanX dipeptidase hydrolyzes D-Ala–D-Ala (the product of the native D-Ala:D-Ala ligase), thereby reducing the pool of D-Ala–D-Ala available to make the vancomycin-susceptible PG precursor. VanY is an accessory structural protein that removes the terminal D-Ala residue from the PG precursor. This carboxypeptidase augments glycopeptide resistance by removing residual vancomycin binding sites. The function of the VanZ protein is not understood, but it contributes to teicoplanin resistance. Like the native PG precursors, these modified precursors are polymerized into functional cell wall.

The *vanB* cluster is functionally similar to the *vanA* cluster, but it differs in its regulation [15, 25]. In VanB enterococci, vancomycin, but not teicoplanin, induces resistance to varying concentrations of vancomycin. Mutational studies indicate that this specificity of induction is a characteristic of $VanS_B$. In addition to homologues of *vanRS,* the *vanB* cluster contains genes that are homologous to *vanHAX.* A VanY homologue (carboxypeptidase) is present in some strains, but the function of an additional protein, VanW, is unknown. VanD enterococci have a mechanism of glycopeptide resistance similar to VanA and VanB microorganisms—that is, the formation of D-Ala–D-Lac–terminated PG precursors mediated by a cluster of genes with homology to *vanRS, vanY,* and *vanHAX* [26, 27].

Infection and colonization caused by vancomycin-dependent enterococci have been described [28]. The mechanism for this phenomenon is the loss of a functional pathway for production of native PG precursors and the consequent requirement for glycopeptides to be present to induce the alternative pathway [21].

The source of these vancomycin-resistance genes is not known, but the *vanHAX* genes have an arrangement identical to and significant predicted amino acid–sequence similarity to those of genes found in *Streptomyces toyocaensis* and *Amycolatopsis orientalis,* actinomycetes that produce glycopeptide antibiotics [29]. Substantial differences between the G + C (guanine + cytosine) content of these 2 groups of homologous genes suggest that a recent transfer of vancomycin-resistance genes from these antibiotic producers to enterococci has not occurred. Another, more closely related group of *vanHAX* homologues (on the basis of deduced amino acid–sequence homology and G + C content) was found in the vancomycin-

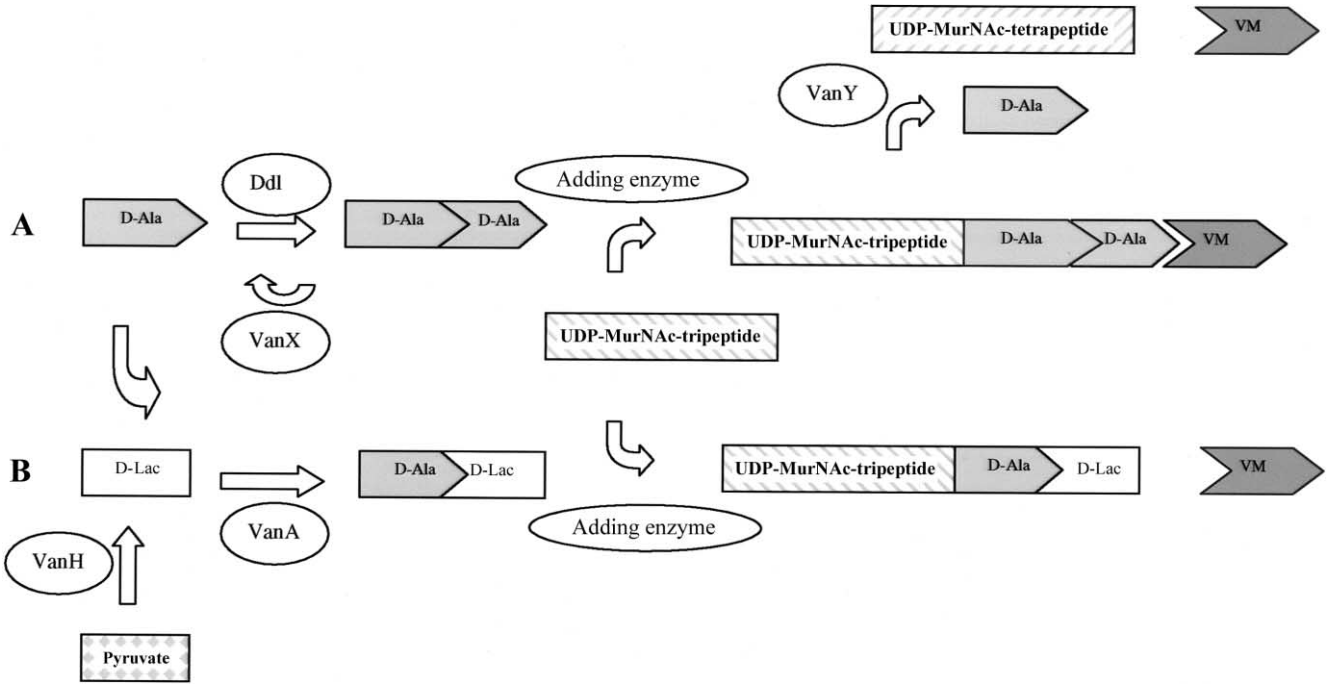

Figure 1. Simplified schematic representation of the 2 pathways for synthesis of peptidoglycan (PG) precursors present in a VanA enterococcus. The upper pathway *(A)* produces the native PG precursor that is the target for vancomycin. The altered PG precursor produced by the lower pathway *(B)* binds vancomycin poorly. VanY, encoded by the *vanA* gene cluster, modifies the finished native PG precursor. D-Ala, D-alanine; D-Ala–D-Ala, D-alanyl–D-alanine; D-Ala–D-Lac, D-alanyl–D-lactate; Ddl, D-Ala:D-Ala ligase; D-Lac, D-lactate; UDP-MurNAc, uridine diphosphate-*N*-acetyl muramyl; VM, vancomycin. Modified from [22].

resistant biopesticide *Paenibacillus popilliae* [30]. The evolutionary lineage of these groups of homologous genes is not clear, but they may have a common, remote ancestor. Several intrinsically vancomycin-resistant, gram-positive organisms, including *Pediococcus* species, *Leuconostoc* species, and some lactobacilli, also produce PG precursors that terminate in D-Lac. However, the D-Ala:D-Lac ligases found in these organisms are only distantly related to the VanA, VanB, and VanD ligases [31]. Because of differences in G + C content, it has been hypothesized that the regulatory genes (*vanR* and *vanS*) and the accessory genes (*vanY* and *vanZ*) may be derived from a different source than the essential structural genes (*vanHAX*). The regulatory genes of the *vanA* and *vanB* clusters show substantially lesser homology to each other than *vanHAX* does to $vanH_B$ BX_B.

The *vanA* and *vanB* glycopeptide resistance gene clusters are carried on transposons. The best known *vanA* transposon, Tn*1546,* is a 10.8-kilobase nonconjugative transposon that has been localized to plasmids and chromosomal DNA [32]. The *vanB* cluster also may be present on the chromosome or plasmid DNA and thus far has been found in 2 different transposons, Tn*1547* and Tn*5382* [33, 34]. Tn*5382* has been reported to be part of a larger element that carries PBP5 (mediating high-level penicillin resistance), along with the *vanB* cluster. A number of geographically diverse VanB-type isolates were shown to cotransfer vancomycin resistance and resistance to high concentrations of ampicillin [35].

VanC enterococci have 2 different pathways for the synthesis of PG precursors [36]. One pathway produces precursors with D-Ala–D-Ala termini. *vanC* gene clusters mediate the other pathway, producing PG precursors with D-alanyl–D-serine termini that bind vancomycin poorly and are the source of the intrinsic vancomycin resistance of *E. gallinarum* and *E. casseliflavus* [37]. A single isolate of *E. faecalis* has been described that uses the same mechanism of resistance, namely the production of PG precursors that terminate with D-alanyl–D-serine, resulting in a phenotype similar to VanC, designated VanE [20].

CLINICAL AND MOLECULAR EPIDEMIOLOGY OF VRE

The spread of glycopeptide resistance among enterococci is an epidemic of genes that are mobile to varying degrees and an epidemic of clones carrying those resistance determinants. A recent study suggested that an epidemic clone of VRE carrying a putative virulence determinant was present in outbreaks on 3 continents [38]. As individual strains of VRE are identified by use of pulsed-field gel electrophoresis (PFGE), the gene clusters themselves can be analyzed and tracked by DNA-based

techniques [39, 40]. Almost 18% of nosocomial enterococcal bloodstream isolates in a 1997 study were vancomycin resistant, including fully 50% of *E. faecium* isolates [41]. In 1999, 25.2% of enterococci associated with nosocomial infections in intensive care unit patients were vancomycin resistant [42]. Studies of the molecular epidemiology of VanA and VanB VRE, typically based on PFGE, have yielded interesting and varied results [43]. Some nosocomial outbreaks are monoclonal or oligoclonal, whereas other analyses show multiple clones. Single clones have been noted in multiple medical centers in a given city and, in some cases, in different states, but overall, VRE isolates in the United States are genetically diverse [44]. The molecular epidemiology of VRE within an institution may change over time, with certain clones establishing themselves as vancomycin resistance becomes endemic.

Colonization or infection with VRE has been associated with a variety of factors, including length of hospital stay, underlying disease (particularly renal failure and neutropenia), liver transplantation, severity of illness, and the presence of feeding tubes [43]. Proximity to infected or colonized patients has been identified as a risk factor because it is thought that the organisms are transferred via the hands of health care workers, as well as on fomites such as thermometers, physical therapy equipment, and hospital beds. Antibiotic exposure, in particular intense antibiotic treatment and treatment with certain antibiotics (e.g., cephalosporins, drugs with activity against anaerobic bacteria, and orally and parenterally administered vancomycin), is an often-cited risk factor for VRE colonization or infection. Epidemiological studies have not yielded uniform results in this regard, and some authors have concluded that, after statistically controlling for length of hospital stay, exposure to vancomycin is not a risk factor for nosocomial VRE [45]. A prospective study of stool colonization in health care–associated patients revealed that antibiotics with activity against anaerobic bacteria promoted high-density VRE colonization. Furthermore, the authors found that high-density colonization, as opposed to low-density colonization, was associated with contamination of the environment with VRE when patients were incontinent of stool [46].

Patients who are colonized with VRE typically carry the organism in their bowel flora and may be colonized for extended periods of time (colonization for >2 years has been documented). In general, patients who develop infections with VRE are among the most severely ill in the hospital. This complicates measurement of the rate of mortality associated with VRE infection that is directly attributable to vancomycin resistance. The literature on this issue is divided as to whether vancomycin resistance is an independent predictor of death among patients with enterococcal infections or—perhaps more likely—is a marker of severe illness [47, 48].

An intriguing feature of the epidemiology of VRE is the discrepancy between North America and Europe. Veterinary use of huge quantities of the glycopeptide antibiotic avoparcin in Europe (now banned) was associated with the presence of VanA VRE in farm animals and meat products available to consumers [12]. People who live in farming communities in Europe have been found to carry VanA VRE, in some cases of the same PFGE type as was found in the farm animals. Notably, hospital infection rates in Europe are relatively low. However, the opposite is true in North America, where VRE have not been isolated from environments outside of the hospital and nosocomial VRE infection is a significant problem. Differences in antibiotic prescribing practices in Europe and the United States may contribute to this paradox.

VRE AND THE CLINICAL MICROBIOLOGY LABORATORY

Clinical isolates of enterococci should be screened for vancomycin resistance. Agar screening plates (6 μg/mL of vancomycin in brain-heart infusion agar) provide a simple, sensitive test for vancomycin resistance and are recommended by the National Committee for Clinical Laboratory Standards [49, 50]. Resistance to moderate and high concentrations of vancomycin is easily detected by standard susceptibility testing procedures. Modifications have improved the detection of low-level vancomycin resistance (typically VanB enterococci), which had been problematic for some automated systems. Similarly, a 24-h incubation and the use of strong transmitted light to read the plates have improved the accuracy of the disk diffusion method. The E-test method is an accurate alternative for the detection of vancomycin resistance [50].

It is useful to speciate vancomycin-resistant enterococcal isolates, in part to distinguish the VanC organisms, because that distinction has implications for treatment and infection control (as is discussed later). Research laboratories have developed genetic tests for the presence of vancomycin-resistance genes, usually based on PCR, but these are not commercially available at this time in the United States [51]. Clinically significant VRE isolates should be tested for susceptibility to all potentially active commercially available drugs (e.g., ampicillin, quinupristin-dalfopristin, linezolid, chloramphenicol, tetracycline, fluoroquinolones, and, for urinary isolates, nitrofurantoin, and possibly fosfomycin). Where teicoplanin is available for clinical use, it should be tested. *E. faecalis* isolates causing significant infections should be assessed for β-lactamase activity by the nitrocefin (a chromogenic substrate) test, although β-lactamase activity has remained a rare mechanism of resistance. Enterococcal isolates from patients with endocarditis and meningitis, if not all isolates from sterile spaces, should undergo screening for high-level aminoglycoside resistance.

TREATMENT OPTIONS AND THE EFFECT OF GLYCOPEPTIDE RESISTANCE ON CLINICAL DECISION-MAKING

Intrinsic and acquired drug resistance complicates treatment of enterococcal infections. Careful review of in vitro susceptibility data is required to treat infections caused by multidrug-resistant *E. faecium,* the most commonly found group of VRE. Empiric therapy for enterococcal infections should be guided by local patterns of drug resistance. It is a general rule of infectious diseases that foci of infection that are amenable to drainage should be drained, and infected foreign bodies, such as central venous catheters, should be removed. This is particularly critical when dealing with VRE and may be at least as important as the choice of antimicrobial therapy [52]. The established treatment of serious enterococcal infections, particularly endocarditis and the rare case of enterococcal meningitis, pairs a cell wall–active agent such as a β-lactam (typically ampicillin or penicillin) or vancomycin and an aminoglycoside (typically gentamicin or streptomycin) to produce a synergistic bactericidal effect [53]. High-level resistance to either agent will abrogate this synergy. Infrequently, isolates of VRE, almost exclusively *E. faecalis,* are susceptible to aminoglycosides and ampicillin (which is typically one 2-fold dilution more active than penicillin). In this situation, those drugs can and should be used. The precise MIC of penicillin at which synergy is lost for isolates of *E. faecium* that are susceptible to high concentrations of aminoglycosides has not been well defined, although high-dose ampicillin is likely to have some activity against isolates with ampicillin MICs $\leqslant$64 μg/mL, but not those with higher MICs [54, 55]. Where available, teicoplanin has been used to treat infections with VanB enterococci, often in combination with an aminoglycoside, although the concern exists that these organisms will become resistant to teicoplanin during treatment. In the case of the typical multidrug-resistant VanA *E. faecium,* there is no current therapy that consistently provides bactericidal activity. Some studies have shown that combinations of various β-lactams with vancomycin have shown synergistic activity against VRE, possibly because of differences in the PBPs used to cross-link the vancomycin-resistant PG precursors [13, 56]. However, synergy has not uniformly been demonstrated, and even when present, resistance to these combinations may occur while the patient is on therapy [57, 58]. In fact, a wide variety of combinations of various drugs, including cell wall–active agents, quinolones, aminoglycosides, tetracyclines, and rifampin, have been advocated, but none have been accepted as having consistent bactericidal activity.

Bacteriostatic antimicrobial drug therapy is sufficient for most enterococcal infections. For uncommon infections caused by ampicillin-susceptible VRE, ampicillin is the drug of first choice. A number of agents have activity against some isolates of VRE, including chloramphenicol, quinolones, tetracyclines, rifampin, and 2 agents used specifically for cystitis, nitrofurantoin and fosfomycin. Most isolates of VRE are resistant to currently available fluoroquinolones. Chloramphenicol has retained in vitro activity against most VRE isolates in the United States and has shown modest efficacy in one study [59, 60]. A subsequent study showed no difference in the mortality rate among patients with catheter-associated VRE bacteremia who were treated with chloramphenicol, catheter removal, or both [52]. Quinupristin-dalfopristin was introduced to the US market in 1999. It is a parenteral combination of 2 streptogramins with good, typically bacteriostatic activity against *E. faecium,* including VRE, but it has poor activity against *E. faecalis.* Relatively few clinical isolates of *E. faecium* are resistant to quinupristin-dalfopristin (95% of initial patient isolates from a study of 875 geographically diverse vancomycin-resistant *E. faecium* were susceptible to $\leqslant$2 μg/mL of the drug). However, this figure declined to 86% when the survey also included subsequent patient isolates, indicating that resistance may develop in a minority of patients while on therapy [59]. The drug has been clinically effective in approximately three-quarters of patients infected with vancomycin-resistant *E. faecium* [61]. A number of studies have assessed antibiotic combinations including quinupristin-dalfopristin to improve the drug's activity or spectrum of activity. The addition of ampicillin to quinupristin-dalfopristin provides antimicrobial activity against *E. faecalis,* although the combination was not synergistic against *E. faecium* (G. M. Eliopoulos, personal communication). Doxycycline augmented the inhibitory activity of quinupristin-dalfopristin against a number of *E. faecium* isolates, but this inhibitory synergy was not uniform (G. M. Eliopoulos, personal communication). Common adverse effects of treatment with quinupristin-dalfopristin include venous phlebitis, prompting the recommendation that the drug be infused through a centrally placed venous catheter, and arthralgias or myalgias.

The most recently approved drug with good (though only bacteriostatic) activity against enterococci is linezolid, which is available in parenteral and oral formulations. This compound is an oxazolidinone, the first representative of this new and totally synthetic class of antimicrobial drugs. Linezolid has nearly uniform activity against enterococci, with MICs of 1–4 μg/mL in one study of 180 isolates of various enterococcal species, regardless of vancomycin susceptibility [62]. Initial clinical trials show that the drug has efficacy that is probably at least as good as that of quinupristin-dalfopristin, with fewer adverse reactions [63, 64]. Although enterococcal resistance to this drug was thought to be rare, published reports of this problem have begun to appear, and numerous unpublished cases are known to exist [65]. For cystitis caused by VRE, nitrofurantoin is often active, and fosfomycin has activity against some isolates [66]. Novobiocin and bacitracin are 2 "old" drugs that have been used against enterococci. Both have

been used in attempts to eliminate stool carriage of VRE with equivocal success, and the former was combined with doxycycline to successfully treat VRE bacteremia in a handful of patients [67–69]. Other drugs with activity against VRE that are currently undergoing clinical trials include LY333328, daptomycin, glycylcyclines, ketolides, and ramoplanin.

Given the difficulty of treating VRE when they are recovered from infected sites and the fact that enterococci are not highly virulent, the question sometimes arises: Do we really need to treat the patient with antibiotics active against VRE? Certainly, infective endocarditis, urinary tract infections, and any infection of a sterile space with VRE should be treated aggressively. Patients with VRE infective endocarditis may benefit from early valve removal. VRE bacteremia related to iv catheters may resolve spontaneously after removal of the infected catheter. However, treatment with the best available drug for any VRE bacteremia is probably warranted and highly recommended for patients with prosthetic or otherwise abnormal heart valves in an attempt to prevent endocarditis. Linezolid and quinupristin-dalfopristin are most likely to be active (the latter against *E. faecium* only), but tetracycline drugs and chloramphenicol may be considered as well. There are no prospective comparative clinical trials to assess the efficacy of these drugs against VRE. Treatment is clearly indicated for VRE bacteremia related to abdominal infections or complicated soft-tissue infections [70].

Although studies can be found in the surgical literature that suggest that patients with community-acquired polymicrobial intra-abdominal infections can be successfully treated with antibiotic regimens that lack activity against enterococci, VRE are typically isolated in hospitalized patients with severe underlying illnesses [43, 71]. In those patients, treatment regimens that include antibiotics with activity against enterococci should be used to treat polymicrobial infections of the abdomen (e.g., abdominal abscess or biliary tract infection) wherein enterococci are isolated [71]. The role of enterococci, including VRE, in polymicrobial skin and soft-tissue infections is debated. Infections at sites such as surgical wounds and decubitus ulcers and in the diabetic foot that involve mixed flora including VRE may resolve without specific therapy for VRE if the more virulent pathogens are effectively treated. However, the overall clinical picture should be considered, and treatment directed at VRE is indicated in some cases. VanC enterococci (*E. gallinarum* and *E. casseliflavus*) are relatively uncommon pathogens. They are typically susceptible to penicillins and other drugs and consequently are less difficult to treat.

INFECTION CONTROL OF VRE

VRE are significant multidrug-resistant opportunistic pathogens in the hospital environment that are maintained by the selective pressure of widespread use of broad-spectrum antimicrobial drugs. Enterococci are resilient organisms that survive on the hands of health care workers and on inanimate objects [72]. VRE have been demonstrated to be carried in the stool of colonized patients, sometimes for extended periods. Effective control of VRE infection should address all of these factors, including judicious use of antibiotics, particularly vancomycin (oral and parenteral administration), cephalosporins, and drugs with antianaerobic activity [73, 74]. Patients who are infected or colonized with VRE should be isolated, preferably in private rooms. Some authors have suggested cohorting patients colonized or infected with VRE [75]. This allows for dedicated nursing staff and patient-care equipment for those patients, resulting in improved compliance with infection control measures and reduced transmission of VRE. Adherence to good handwashing procedures is critical, but it is an area of infection control in which compliance is chronically deficient.

The Centers for Disease Control and Prevention guidelines support the use of gloves by health care workers when they enter the patient's room and of gowns for substantial contact with the patient, environmental surfaces in the room, or sites of likely fecal soilage, or when infected wounds are drained [73]. Surveillance cultures for VRE, typically by means of rectal swabs or stool, should be performed for patients who inadvertently are exposed to VRE (e.g., roommates of patients found to be colonized or infected) and more widely in the setting of a potential or defined outbreak. In the latter instance, culture of samples from health care workers who have contact with the patients and from the environment may be warranted [73]. Last but not least, thorough terminal cleaning of the rooms and hospital beds of VRE patients with the "bucket method" (drenching all surfaces with disinfectant) is recommended, because standard methods are less than completely effective [76]. Medical centers detecting their first cases of VRE should be particularly aggressive in implementing infection control to prevent the organisms from becoming endemic. Once VRE have become endemic, infection control becomes increasingly difficult. Because VanC organisms are intrinsically resistant to vancomycin and resistance is nontransferable, isolation of patients found to be colonized or infected with *E. gallinarum* and *E. casseliflavus* is not thought to be required [77].

THE FUTURE

In the near term, VRE will become established, endemic, nosocomial pathogens in an increasing number of medical centers, continuing the trend of movement from large, urban, tertiary-care teaching hospitals to other types of medical facilities, such as suburban hospitals and chronic care facilities. In centers in which the organism has become endemic, an equilibrium of sorts will likely be reached, as we see for methicillin-resistant *S. aureus,* with a certain percentage of enterococcal isolates

typically being vancomycin-resistant (e.g., 25%–50%) and episodic outbreaks producing upward spikes in the prevalence of resistant isolates. The mechanism for relative resistance to vancomycin that has been seen in staphylococci differs from that of acquired glycopeptide resistance in enterococci, but the potential spread of enterococcal vancomycin resistance determinants to other species will remain a concern. Continued development of new drugs by the pharmaceutical industry, aided by genomics, high-throughput screening, and rational drug design, offers the prospect of effective bactericidal monotherapy for enterococci, including VRE. Wiser use of antimicrobial drugs, possibly guided by novel techniques for rapid microbiological diagnosis, and the nascent trend toward the development of narrower-spectrum antimicrobials may diminish some of the selective pressures favoring VRE. Novel therapies, such as vaccine-based immunotherapies, phage therapy, and gene therapies to reverse drug resistance, may offer long-term solutions to the problem of VRE.

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