Vancomycin-Resistant Enterococci

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Enterococci, a part of normal gut flora, are not particularly pathogenic organisms in humans. For example, they do not cause respiratory tract infections. The most frequent enterococcal infections are urinary tract infections. Despite their lack of pathogenicity, enterococci have emerged as significant nosocomial pathogens in the United States and elsewhere. Enterococci are formidable pathogens because of their resistance to antimicrobial agents. Enterococci are intrinsically resistant to β-lactam agents and aminoglycosides and were the first bacteria to acquire vancomycin resistance. Infection control measures have been far from effective at preventing the dissemination of vancomycin-resistant enterococci in the hospital. Therapy for infections due to vancomycin-resistant enterococci presents real challenges. Most isolates remain susceptible to nitrofurantoin, but this agent is useful only for urinary tract infections. The greatest threat posed by vancomycin-resistant enterococci is the potential to transfer their resistance genes to more pathogenic gram-positive bacteria, which could produce truly frightening pathogens.

There has been a great deal of concern in recent years about the growing menace of antimicrobial-resistant organisms [1]. Bacteria and other microorganisms have shown a remarkable ability to develop resistance to virtually every antimicrobial agent developed for therapeutic use in humans and animals. Arguably, the most impressive accomplishment of bacteria to date in this arena has been the development of vancomycin resistance in enterococci.

This achievement is impressive for a number of reasons. First, many infectious disease experts thought that it would be virtually impossible for intrinsically susceptible organisms to develop vancomycin resistance. This impossibility was based in part on the fact that vancomycin had been in clinical use for >35 years without any emergence of resistance. Furthermore, the mechanism of action of vancomycin is such that it would require a major alteration in bacterial cell wall synthesis to develop resistance unless the organisms could find a way to inactivate or “detoxify” vancomycin, which seemed highly unlikely.

Thus, it was with considerable surprise and great concern that the first reports of the occurrence of vancomycin-resistant enterococci in Europe began to appear in the mid 1980s [2]. Moreover, once scientists elucidated the mechanism by which this resistance was made possible, it was realized that it took an incredibly complex set of genetic developments to enable enterococci to become resistant [3].

No one is exactly certain why enterococci were the first to develop vancomycin resistance, but two facts might have played a role: enterococci are part of normal gut flora, and the emergence of vancomycin resistance was associated with increasing use of oral vancomycin for the treatment of documented and presumed Clostridium difficile enterocolitis. Increasing use of parenteral vancomycin for the treatment of intravascular device–related infections might also have been important [4]. The agricultural use of the related glycopeptide avoparcin may have played a role in Europe, but this drug has not been used in the United States. In any case, enterococci were the first to acquire vancomycin resistance, and as a result, vancomycin resistance is now causing significant problems in Europe and especially in the United States.

Enterococcal Infections

Enterococci, as noted above, are normal inhabitants of the intestinal tract of humans and animals. More than a dozen species of enterococci are currently recognized [5]. Of these, two species, Enterococcus faecalis and Enterococcus faecium, are the most important causes of enterococcal infections in humans. About 85% to 90% of enterococcal infections in humans are caused by E. faecalis, with another 5% to 10% caused by E. faecium [5]. The relative frequency of enterococcal infections has shifted somewhat, however, and as E. faecium has become increasingly resistant to antimicrobial agents, it has emerged as a major nosocomial pathogen [5]. Occasional infections caused by other enterococcal species including Enterococcus avium, Enterococcus raffinosus, and others have been reported.

The development of vancomycin resistance in enterococci represents a classic “bad news, good news” scenario. The “bad news,” of course, is that enterococci have become resistant to vancomycin. The “good news” is that enterococci are not particularly pathogenic organisms in humans. Enterococci do not, for instance, colonize or effectively infect the respira-
tory tract in humans, and they do not cause primary cellulitis. Unlike Streptococcus pyogenes and Staphylococcus aureus, enterococci do not possess enzymes that allow tissue spread and invasion. Enterococci do not produce potent exotoxins.

The most frequent infections caused by enterococci are urinary tract infections. The second most frequent infections are intraabdominal and pelvic sepsis and surgical wound infections, in which enterococci are almost always part of a mixed flora of colonic organisms. The third most frequent infections are bacteremias, including both primary bacteremias that are presumably from a source in the gastrointestinal tract and bacteremias that are secondary to urinary tract and intraabdominal infections or the use of intravascular devices.

Although enterococcal endocarditis is relatively rare, it is difficult to treat because of the relative resistance of enterococci to antimicrobial agents. Meningitis represents an even rarer but potentially serious infection caused by enterococci [5].

Despite their relative lack of pathogenicity, enterococci have emerged as significant nosocomial pathogens in the United States and elsewhere. According to recent National Nosocomial Infections Surveillance surveys in the United States, enterococci currently rank second or third, depending on the year, as causes of infections due to various organisms [6]. This result is particularly impressive, in view of the fact that enterococci are not a significant cause of nosocomial respiratory tract infections.

**Antimicrobial Resistance in Enterococci**

The characteristic of enterococci that makes them such formidable pathogens is their resistance to antimicrobial agents. All enterococci are intrinsically resistant to a number of antimicrobial agents [7]. Thus, they exhibit low resistance to penicillins, cephalosporins, carbapenems, and carbacephems. Enterococci exhibit low levels of resistance to aminoglycosides and lincosamides [7]. They also have acquired genes to resist virtually all other known antimicrobial agents, including vancomycin [5].

Enterococci are intrinsically resistant to β-lactam agents, as evidenced by the relatively high MICs of most penicillins, including penicillin G and ampicillin. Enterococci also exhibit ‘‘tolerance’’ to all agents that inhibit cell wall synthesis, including β-lactam agents and vancomycin. Thus, these antibiotics inhibit but do not effectively kill enterococci at clinically achievable concentrations [8]. Although this property is almost universally seen in current clinical isolates of enterococci, it too is an acquired characteristic [8].

Increasing resistance to penicillin and ampicillin has been seen in recent years in strains of E. faecium [9]. Because of this circumstance, vancomycin was rapidly becoming the agent of ‘‘last resort’’ for the treatment of infections caused by multi-drug-resistant, highly penicillin-resistant E. faecium. It was with considerable consternation, therefore, that the initial reports of vancomycin resistance in enterococci were noted, first in Europe and subsequently in the United States in the mid and late 1980s [5].

**Genetics of Vancomycin-Resistant Enterococci**

The initial observations of vancomycin-resistant strains revealed the presence of several different phenotypes of glycopeptide resistance. The so-called vanA resistance phenotype, which is the most frequently encountered, consists of high-level vancomycin resistance that is also accompanied by high-level resistance to teicoplanin [3]. Vancomycin resistance in these strains is vancomycin- and/or teicoplanin-inducible. The genes encoding vancomycin resistance are often found on a transposon that is relatively easily transferred to other enterococcal species by conjugation [3, 10].

Vancomycin-resistant enterococci with the vanB resistance phenotype have variable levels of vancomycin resistance and are susceptible to teicoplanin. The vanB resistance phenotype is also inducible by vancomycin, but not by teicoplanin, and exposure to vancomycin also produces teicoplanin resistance. The genes encoding the vanB resistance phenotype are more commonly chromosomal but can also be transferred by conjugation [10, 11].

The vanC resistance phenotype, which consists of relatively low levels of vancomycin resistance without teicoplanin resistance, is caused by chromosomally encoded genes that are found in all strains of Enterococcus casseliflavus, Enterococcus gallinarum, and Enterococcus flavescens. These genes are not transferable. Recently, Perichon and co-workers [12] described a fourth phenotype, vanD, that is similar to vanB (vancomycin MIC, 64 μg/mL; teicoplanin MIC, 4 μg/mL) and has thus far been noted only in a rare strain of E. faecium.

The genetic basis for vancomycin resistance is remarkably complex. Both vanA and vanB resistance phenotypes are made possible by the products of a group of genes that encode a two-component regulatory system, which causes the resistance to be inducible. Another set of genes encodes a group of enzymes that enable the enterococci to synthesize cell wall precursors ending in d-alanine-lactate, instead of d-alanine-d-alanine, which is the usual vancomycin binding site [3, 10]. The affinity of vancomycin (and of teicoplanin) for d-alanine-lactate is 1,000-fold less than that for d-alanine-d-alanine.

**Epidemiology of Vancomycin-Resistant Enterococci**

There has been a steady increase in the prevalence of vancomycin-resistant enterococci in the United States during the previous 10 years [10, 13]. Now, almost 15% of enterococci in intensive care units of hospitals participating in National Nosocomial Infections Surveillance surveys exhibit vancomycin resistance. The prevalence of vancomycin resistance in isolates obtained within United States hospitals, but outside the intensive care units, is also rapidly increasing [10]. About 70% of the vancomycin-resistant isolates in the United States currently
exhibit the vanA resistance phenotype, and about 25% exhibit the vanB resistance phenotype [14].

The epidemiology of the spread of vancomycin resistance in the United States and elsewhere has been extensively studied. There is evidence both for clonal dissemination of resistant strains and for rapid transfer of vancomycin resistance genes among species of enterococci in the hospital [15, 16]. In the instance of transfer of resistance genes, there are multiple different enterococcal subtypes carrying the same vancomycin resistance genes, thereby suggesting a "plasmid or transposon epidemic." There is also considerable heterogeneity in the genetic sequence of vancomycin resistance genes in the United States. This occurrence suggests that these genes are being modified as they spread among various strains of enterococci [17].

**Treating Infections Caused by Vancomycin-Resistant Enterococci**

Generally, the most serious infections due to vancomycin-resistant enterococci occur in severely ill immunocompromised patients. However, enterococcal urinary tract infections may occur in any patient, regardless of the state of debility or immunocompetence. The major factors predisposing to infection with vancomycin-resistant enterococci include stool carriage of these organisms by patients or hospital personnel; proximity to patients infected with vancomycin-resistant enterococci; hospitalization in an intensive care unit; and, particularly, exposure to antimicrobial agents, including vancomycin, broad-spectrum cephalosporins, carbapenems, and antimicrobial agents with activity against anaerobes (including metronidazole and clindamycin) [18, 19]. There is also a clear-cut association between the total number of antimicrobial agents received by a patient and the likelihood of acquisition of infection due to vancomycin-resistant enterococci.

As noted above, asymptomatic carriage of vancomycin-resistant enterococci is found frequently on the hands of personnel caring for patients infected with vancomycin-resistant enterococci and may serve as a reservoir for spread of these organisms. Although a number of infection control measures have been used to try to limit the spread of vancomycin-resistant enterococci, these measures have proven somewhat disappointing and certainly have been far from effective at preventing the dissemination of vancomycin-resistant enterococci in the hospital [20]. Several small anecdotal series of colonized patients reported some success with oral bacitracin therapy for eradicating stool carriage of enterococci [21]. Unfortunately, there are not enough currently available results to know if this measure will effectively halt the spread of vancomycin-resistant enterococci in intensive care units or in other major hospital settings.

Therapy for infections due to vancomycin-resistant enterococci presents real challenges for the clinician. Most isolates of enterococci, whether vancomycin-resistant, remain susceptible to nitrofurantoin, which has been successfully used to treat urinary tract infections caused by vancomycin-resistant enterococci [5]. Because resistance to penicillin and ampicillin is currently very infrequent in strains of *E. faecalis*, these agents can be used to treat infections caused by most strains of vancomycin-resistant *E. faecalis*. Unfortunately, most of these strains in the United States exhibit high levels of aminoglycoside resistance. Therefore, the use of combination therapy for a bactericidal effect is often impossible, which is a particular problem in cases of endocarditis and meningitis caused by these organisms.

One interesting, but on first glance somewhat counterintuitive, approach to the treatment of infections with vancomycin-resistant enterococci is based on the observation that combinations of vancomycin plus ampicillin sometimes exhibit in vitro synergism against vancomycin-resistant enterococci [22]. The mechanism by which this synergy occurs is interesting. It probably relates to the fact that subinhibitory concentrations of vancomycin induce the synthesis of modified cell wall precursors ending in β-alanine-lactate. The bacteria, in response, utilize an alternative penicillin-binding protein (PBP) for cross-linking these cell wall precursors. Because it appears that this PBP is more susceptible to penicillin and ampicillin than is PBP 5, which normally performs this function in enterococci and is intrinsically resistant to penicillin [23], the combination might be synergistic. Unfortunately, this phenomenon is inconsistent at best. In animal models, colonies resistant to synergism occur with relatively high frequency during therapy [24]. I have personally also observed this phenomenon in human trials of the combination as well (R. C. Moellering, Jr., unpublished observations).

Teicoplanin has been used to treat selected infections caused by vancomycin-resistant enterococci harboring the vanB resistance phenotype. Again, emergence of resistance during therapy has occurred. If such therapy is to be optimally effective, a second antimicrobial exhibiting in vitro susceptibility, preferably an aminoglycoside if possible, should be used.

Vancomycin-resistant strains of *E. faecium* pose even greater problems, because many of these strains are also highly resistant to penicillin and ampicillin [5]. Indeed, many of these organisms are resistant to all currently available antimicrobial agents. Selected strains are susceptible to tetracyclines, chloramphenicol, rifampin, ciprofloxacin, ofloxacin, and/or novobiocin, and there have been anecdotal reports of successes when these agents have been used alone or preferably in combination [5, 25]. Unfortunately, all of these agents are only bacteriostatic and are not particularly useful in treating enterococcal endocarditis or meningitis.

Clinical trials of the investigational drug quinupristin/dalfopristin are now under way. Preliminary results suggest that it is active both in vitro and clinically for infections caused by vancomycin-resistant *E. faecium* [26]. Unfortunately, this agent is not active against *E. faecalis*. Thus, its use will likely be limited to infections due to multidrug-resistant *E. faecium*. Other investigational agents with in vitro activity against vancomycin-resistant enterococci include the oxazolidinones, new vancomycin analogues, evenminomycin, and some of the new fluoroquinolones with enhanced activity against gram-positive bacteria. A study of these agents in the treatment of enterococcal infections is now under way.
bacteria. As of now, however, there are insufficient clinical results to know if these new agents will help solve the vexing problem of infections caused by vancomycin-resistant enterococci.

A Potentially Great Threat?

Perhaps the greatest threat posed by vancomycin-resistant enterococci comes not from these organisms themselves but from the potential that they could transfer their resistance genes to other more pathogenic gram-positive bacteria. Indeed, in the laboratory, vancomycin resistance has been transferred from enterococci to streptococci, listeria, and \( S. \) \textit{aureus} [27, 28]. In this regard, the recent description of a naturally occurring vancomycin-resistant strain of \textit{Streptococcus bovis} harboring the \textit{vanB} resistance phenotype is of great concern [29]. Thus far, there is no evidence that the vancomycin resistance genes have been naturally transferred to \( S. \) \textit{aureus}. However, the fact that it has not happened to date is no assurance that it will not happen in the future. If the transfer of resistance does occur, particularly if the strain of \( S. \) \textit{aureus} receiving the genes is already methicillin-resistant, it will produce a truly frightening pathogen.

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