Infections in Oncology

Vancomycin-Resistant Enterococci: Approach to Treatment and Control

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Introduction

Enterococci have become increasingly important nosocomial pathogens in many hospitals in the United States within the past few years. This is a result of an increased incidence of enterococci resistance to many antimicrobials. Drugs that were once the mainstay in the treatment of enterococci, including penicillins, aminoglycosides, and vancomycin, are no longer effective in many situations where resistant enterococci are encountered. The treatment of enterococci that are resistant to single or combination antibiotic regimens now presents a clinical challenge to physicians, pharmacists, and other health care professionals.

Enterococci

Enterococci are Gram-positive, facultative, anaerobic organisms that were previously considered to be of the genus streptococcus (streptococcus group D) because of similar morphology. Enterococci were found to have different nucleic acid hybridizations and were separated into their own class in 1984.[1] Enterococcus faecalis-faecium are the two most common species, comprising 80% to 90% and 5% to 10% of clinical isolates, respectively. The prevalence of E faecium is increasing, with the majority of this species being resistant to several antibiotics.[2] At least 10 other species that are rarely implicated as a source of infection have been identified.

Patterns of Enterococci Resistance

Enterococci may have two types of resistance - intrinsic and acquired. Intrinsic resistance is chromosomally mediated and nontransferable, while acquired resistance is mediated by plasmids or transposons.

Intrinsic Resistance

Intrinsic resistance includes enterococci that exhibit a low-level resistance to many of the antibiotics used for Gram-positive infections. Enterococci have a low-level intrinsic resistance to beta-lactams due to the production of penicillin-binding proteins with low affinities. Ampicillin and penicillin G are somewhat more effective against enterococci than other beta-lactams.[1] A tolerance phenomenon also can occur with beta-lactams. Streptococci show minimum inhibitory concentrations (MICs) that are 10 to 100 times lower than those for enterococci. Resistance to cephalosporins is relatively greater than for ampicillin or penicillin, making cephalosporins a poor choice for treatment.[2] The E faecium species appears to have a higher intrinsic resistance to beta-lactams than other species.

A low-level intrinsic resistance is also seen with aminoglycosides due to decreased ability of the antibiotic to penetrate the outer cell envelope of enterococci. This penetration is necessary for the antimicrobial actions of the aminoglycoside, since the drug acts intracellularly. Synergistic combinations of cell-wall active antibiotics (eg, penicillins, carbapenems, or glycopeptides with aminoglycosides) are useful when bactericidal activity is needed as in the treatment of bacteremia, endocarditis, or meningitis. E faecalis appears to have a higher level of intrinsic resistance to aminoglycosides than other species. Enterococci are marginally susceptible to fluoroquinolones and are not susceptible in vivo to sulfamethoxazole/trimethoprim due to endogenous sources of folate.[1] Clindamycin generally is considered to be inactive against enterococcal organisms at clinically achievable concentrations.[3] Antibiotics other than those used for Gram-positive infections and aminoglycosides have shown limited efficacy in the treatment of enterococci.

Acquired Resistance

While intrinsic resistance is chromosomally mediated, acquired resistance is mediated by plasmids or transposons. This allows for transfer to other enterococci species or other genuses, such as streptococci and staphylococci. Acquired resistance generally results in a higher level of resistance compared with that of intrinsic resistance. Penicillin-acquired resistance is due to further alteration of the penicillin-binding proteins, which decreases the affinity of these agents further.

Aminoglycoside-acquired resistance develops from aminoglycoside-modifying enzymes that decrease the ability of the drug to bind to ribosomes. Many species with high-level gentamicin resistance also produce beta-lactamase, and it has been suggested that these two resistances share the same plasmids.[3] Once aminoglycosides or penicillins acquire high-level resistance, the combination of these two agents is no longer synergistic. High-level resistance was first seen with streptomycin and gentamicin resistance (HGR) with an MIC of 2000 µg/mL or more was discovered as relapses occurred in endocarditis infections treated with penicillin and gentamicin.[2] HLRG has become a problem over the past decade. Certain enterococci strains possess HLRG without high-level streptomycin resistance (18 to 45%),[1]

Vancomycin Resistance and Epidemiology

Vancomycin-resistant enterococci (VRE), first described in the late 1980s in the United States, is an acquired resistance mediated by plasmids or transposons, which can produce serious infections. Phenotypically different varieties of this resistance are seen. The VanA phenotype is highly resistant to both vancomycin (MIC of 64 µg/mL or more) and to teicoplanin, the investigational glycopeptide (MIC of 16 µg/mL or more).[4] The VanB phenotype shows moderate to high-level resistance to vancomycin (MIC of 32 to 256 µg/mL) but usually remains susceptible to teicoplanin (MIC of less than 1 µg/mL).[1] These two phenotypes are the most prominent and are seen primarily in E faecium, but they also occur in E faecalis. A third phenotype, VanC, shows low-level resistance to vancomycin (MIC of 8 to 32 µg/mL) without teicoplanin resistance; this phenotype is seen primarily in E gallinarum and E casseliflavus. Vancomycin resistance occurs when proteins are synthesized by the resistant enterococci, called "VanA," "VanB," and "VanC." These proteins produce resistance by acting as ligases that alter the cell-wall precursors, which are the targets of vancomycin.[2]
The National Nosocomial Infections Surveillance System (NNISS) of the Centers for Disease Control and Prevention (CDC) provides national epidemiologic data on nosocomial infections. Information is compiled from hospitals in 33 states associated with the system. NNISS analysis on enterococcal infections from January 1989 to March 1993 found a 20-fold increase in vancomycin-resistant strains of all nosocomial enterococcal infections reported. VRE has been hypothesized to be related to the increased usage of vancomycin due to the development of methicillin-resistant Staphylococcus aureus (MRSA) in 1982, as well as other Gram-positive organisms that have developed beta-lactam resistance. In addition, many of the VRE strains reported were found to be resistant to penicillins and aminoglycosides. Intensive care units were found to have an even higher increase in VRE, ranging from 0.4% in 1989 to 13.6% in 1993 (a 34-fold increase).

Prevalence of resistance to vancomycin varied by site of infection, with 7.8% of enterococcal isolates from intra-abdominal infections being vancomycin-resistant, 4.1% for skin, and 3.8% for blood isolates. Older studies have shown mortality associated with enterococcal bacteremia to be 42% to 68%. This survey found that 17.2% of patients with enterococci in their bloodstream died, with a higher mortality in the VRE groups vs non-VRE groups (36.6% vs 18.4%). The authors stressed that this information cannot be used to predict risk of death as there were many other comorbid factors present to confound the results. The NNISS reported VRE occurring in nine of the 33 states, with the highest numbers in New York, Pennsylvania, and Maryland. Teaching hospitals significantly more cases of VRE than nonteaching hospitals. The number of cases reported also varied with the hospital size; those with fewer than 200 beds had no cases reported, while those with more than 500 beds showed vancomycin resistance in 3.6% of their enterococcal cases. Of 32 various VRE isolates that were divided into phenotypes, 20 showed high-level resistance to vancomycin and teicoplanin (VanA), while 10 showed moderate to high resistance to vancomycin but susceptibility to teicoplanin (VanB phenotype).

Another epidemiologic study that also demonstrated striking results, 105 VRE were isolated from 31 hospitals in 14 states with the following distribution of species: 82 E. faecium, 8 E. faecalis, 5 E. gallinarum, 3 E. casseliflavus, 1 E. raffinosus, and 6 E. sp.[7] Penicillin resistance was seen in 85% of these isolates, while 53% of these isolates were resistant to both gentamicin and streptomycin, 50% were resistant to all three, and none were beta-lactamase producers. The 105 resistant isolates isolated 71 VanA phenotypes, 26 VanB, 5 VanC, and 3 undetermined. The VanA phenotype was reported primarily from the Northeast, while the VanB phenotype was more dispersed. Only two cases of VRE were reported from the West (California). It should be noted that the VanB phenotype is more easily missed by automated laboratory techniques, since it has a lower level of resistance that may confound laboratory results. Microbiology laboratories should follow the most recent guidelines of the National Committee for Clinical Laboratory Standards to ensure the most accurate results.

Treatment Options For Vancomycin Resistance

A typical treatment of choice for enterococcal infections is penicillin G or ampicillin, with vancomycin being the alternative in penicillin-allergic patients or in cases of non-beta-lactamase-mediated penicillin resistance. These cell-wall agents should be combined with an aminoglycoside that does not exhibit high-level resistance in order to obtain bacteriologic cure. Based on these guidelines, problems arise once the organism is resistant to an aminoglycoside and/or penicillin. Combination resistance to gentamicin and ampicillin has been reported in 55% and 33% of E. faecalis and E. faecium, respectively.[4] Vancomycin is the only remaining alternative, but it may not be useful in a patient who has been infected with a vancomycin-resistant organism. Vancomycin resistance leads to difficulties when treating patients with concomitant high-level beta-lactam and/or aminoglycoside resistance (multidrug resistance), which is common.

Selection of treatment of VRE depends on the presence of other resistances. When HLG is present, no reliable bactericidal combination is available. Susceptibility tests should be done for streptomycin when an organism exhibits a high level of resistance to gentamicin. In some cases, single-dose therapy with cell-wall agents (ampicillin, vancomycin, or teicoplanin) has been effective in endocarditis; however, this therapy usually results in a high failure or relapse rate.[1] Ampicillin administered by continuous infusion is more effective than intermittent intramuscular injections of ampicillin in the treatment of enterococcal endocarditis that is caused by an organism with high-level aminoglycoside resistance but is susceptible to ampicillin.[8]

High-level penicillin resistance (usually seen in E. faecium) also leaves no alternative in VRE, as cell-wall agents are needed for synergy with aminoglycosides. Ciprofloxacin combined with either ampicillin or novobiocin has some in vitro activity against E. faecalis that has a high-level resistance to ampicillin, vancomycin, and aminoglycosides.[9] Ciprofloxacin alone has MIC values that are close to the achievable tissue and blood levels, giving it only moderate in vivo activity as a single agent. It also develops resistance quickly when used alone.

In vitro studies have shown that penicillin plus vancomycin has moderate activity against some organisms that are resistant to both drugs.[10,11] Penicillins may have an increased affinity for the penicillin-binding proteins in the presence of vancomycin resistance.[10] Combinations of gentamicin, vancomycin, and ampicillin also have shown moderate activity in experimental models of endocarditis caused by ampicillin- and vancomycin-resistant E. faecium.[12] However, few strains of high-level resistance to beta-lactams were included. More recent studies have not found vancomycin with ampicillin to be effective in highly ampicillin- and vancomycin-resistant strains.[13,14]

Although rifampin shows in vitro inhibitory activity in the treatment of enterococcal infections, it is not generally used and may be antagonistic when combined with beta-lactams.[1] However, a review of two cases of bacteremia caused by E. faecalis showed bacteriologic cure was achieved with the combination of rifampin, ciprofloxacin, and gentamicin.[15] These results were confirmed in time-kill studies on the isolates.

As of April 1995, eight cases of VRE had been confirmed at the Moffitt Cancer Center, with the majority being multidrug-resistant. Bacteriologic cure of VRE has been achieved with a combination of three of the four drugs including ampicillin/sublactam, imipenem, gentamicin, and/or vancomycin. These treatment regimens are based on time-kill studies at Vanderbilt University School of Medicine (C. Stratton, MD, unpublished data, 1995). The deaths of two patients could not be attributed directly to the VRE. One of the patients developed a necrotizing cellulitis with VRE sepsis, which is illustrated in Figs 1 and 2.

VRE as a cause of nosocomial infections is a serious problem in the health care system. Its incidence is rapidly increasing, and no treatment has been demonstrated to eradicate these multidrug-resistant organisms. VRE is highly adaptable and acquires resistance easily, making transmission control measures indispensable in preventing the incidence and spread of this organism.

Prevention of the Spread and Development of VRE

While the treatment for vancomycin-resistant and multidrug-resistant enterococcal infections remains controversial and undefined, measures can be taken to prevent further development and transmission of these infections. The organisms can survive on surfaces for long periods of time, thereby allowing transmission through contact. Up to 20% of organisms may remain on the hands after a five-second wash, so health care workers who are in contact with patients with infections should wash their hands for at least 30 seconds.[16] Gloves are worn and changed prior to contact with other patients. Instruments used in patient care, such as stethoscopes, blood glucose monitors, weighing scales, and rectal thermometers, also may be contaminated with these organisms.[16] A recent outbreak of E. faecium (VanA) in an intensive care unit had electronic thermometers implicated as the vehicle for transmission.[15] Electronic thermometers may become contaminated even with the use of probe sheaths. Such instruments should be allocated only to individual patients if the institution is unable to implement strict disinfection measures.[17] The organism can remain in the gastrointestinal tract for over a year, which is a concern once patients are released from the hospital.[16] It has been suggested that hospitals isolate newly admitted patients who have been previously infected with VRE until persistent VRE colonization can be excluded.[17]

Risk Factors for VRE

The oncology unit at Western Pennsylvania Hospital found that neutropenia as well as prior anaerobic antibiotic therapy increased the risk for development of VRE bacteremia. All patients with VRE had received either metronidazole, clindamycin, imipenem, or ampicillin/sublactam compared with only 54% of controls who had not received these antibiotics.[16] Other reported risk factors include prior regimens of oral vancomycin, cephalosporins, or multidrug regimens.[17] Prior antibiotic use may allow overgrowth of a resistant strain that is already part of the patient's normal flora. Results from the NNISS report show that a hospital stay in a large institution, a teaching hospital, or an intensive care unit increase the risk for development of VRE. The CDC also has cited risk factors for acquiring VRE infections (Table 1).

The theories on the risks of transmission and development of VRE will most likely change as more is learned about its resistance, epidemiology, and control strategies. In the meantime, the impact of VRE can be minimized by implementing the published guidelines for its prevention and control.[18,19] Each hospital should develop strict detection and reporting guidelines for all health care team members on the prudent use of vancomycin, completion of an education program, isolation procedures, and microbiology laboratory involvement.[18] Pharmacists should participate in all roles of prevention that emphasize the development and implementation of the prudent use of vancomycin in their institutions. Conditions for which vancomycin is not recommended are summarized in (Table 2). Antibiotic use in general (eg, cephalosporins and multidrug regimens)}
A hospital education program that involves all employees, including students, and strict isolation procedures should be developed to prevent nosocomial spread. To ensure quick isolation procedures, the microbiology laboratory must stay in close contact with the health care team and needs to immediately notify the primary physician when an isolate is identified as VRE. It is recommended that the laboratory use brain heart infusion agar with vancomycin for detecting vancomycin resistance to allow for detection of those strains with low-level resistances. No cases of vancomycin-resistant \textit{S. aureus} have been reported to the CDC, but evidence suggests they can be produced in the laboratory.[5] The microbiology laboratory should routinely test for the vancomycin susceptibility of \textit{S. aureus} and \textit{S. epidermidis} and report positive results immediately to the primary physician and to the CDC. These suggestions should be considered by institutions when developing individualized guidelines. An in-depth discussion on implementing and developing control measures is presented in the Federal Register.[19]

**New Approaches**

Teicoplanin is undergoing clinical trials in the United States, but its status for approval by the Food and Drug Administration is unclear. The usefulness of teicoplanin may be limited, since it is targeted at the VanB phenotype that has been shown to acquire teicoplanin resistance. Pristinamycin is a streptogramin antibiotic aimed at treating Gram-positive infections such as MRSA, and its approval by the Food and Drug Administration also is unclear.[20] Pristinamycin has bactericidal activity by targeting ribosomes and may prove to be of use in VRE infections. Other new approaches include fluoroquinolones such as sparfloxacin, which works against \textit{E. faecium} at lower blood levels than required with ciprofloxacin.[20]

**Conclusions**

Treatment options for VRE are limited to various combinations of antimicrobials, none of which has been found to be absolutely effective. A review of 69 cases of VRE found that 42 different combinations of antibiotics had been used,[16] which illustrates both the extent and the limitations of the treatment options now available. Since successful treatment for VRE and multidrug-resistant enterococcal infections are yet to be defined, current therapies are guided by microbiology laboratory reports. Caution is needed by pharmacists and physicians when reviewing studies of treatment of VRE. The usefulness of any regimen in a particular institution is affected by local factors such as the presence of other resistances besides vancomycin resistance, levels of resistance, phenotypes, and species being studied.

Studies documenting patient outcomes are needed as new therapies are developed. Since the organism is so adaptable, the answer to controlling these difficult and resistant infections may lie not in the development of new antibiotics, but rather in research that focuses on methods to overcome the resistance. A national group is currently addressing these problems.[21] At present, the most effective control measures are the prevention of the spread and development of infection.

**References**