

VANCOMYCIN RESISTANT ENTEROCOCCI (VRE)

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Enterococci are found in the intestinal tract of virtually all humans where they help form part of the normal human flora. As well, because of their ability to withstand harsh conditions, they can survive in soil, food, water and in a wide variety of animals. Of the many different species of enterococci, two account for the vast majority of human infections: *E. faecalis* (the most common) and *E. faecium*. The spectrum of illness caused by these organisms ranges from simple uncomplicated urinary tract infections to serious, life-threatening infection of the heart valves known as endocarditis. Their role in other infections such as intra-abdominal or pelvic infections is somewhat controversial given the fact that in these situations they are usually found mixed with other bacteria and patients often improve clinically when treated with antibiotics that are not active against enterococci.

The antibiotic susceptibility profile of enterococci is quite limited. Enterococci are naturally (intrinsicly) resistant to many antibiotics including all cephalosporins and anti-staphylococcal penicillins, thus limiting the choices available for treating patients with an active enterococcal infection. Even when laboratory testing suggests that an enterococcus strain is susceptible to an antibiotic, the activity of the drug is usually borderline. Therefore, treatment of serious enterococcal infections such as endocarditis

requires combination therapy with 2 active drugs (e.g. ampicillin or vancomycin plus gentamicin) in the hope of achieving a synergistic effect. Finally, enterococci have been able to acquire resistance mechanisms which render previously active antibiotics such as vancomycin ineffective [Vancomycin Resistant Enterococci (VRE)]. To date, the emergence of acquired vancomycin resistance among enterococci has been seen most commonly in *E. faecium*.

Reports of VRE began to emerge in the late 1980s in Europe. It was not until 1993 that the first VRE isolate in Canada was reported from Edmonton followed in 1995 by the first published Canadian outbreak in Toronto. Since then, the reported rates of VRE have been quite variable with some countries reporting that a significant proportion of their enterococcal isolates have become resistant to vancomycin while others, such as Canada, have been able to contain the emergence and spread of VRE apart from isolated outbreaks.

The mechanism of resistance of enterococci to vancomycin is mediated by 5 genes referred to as *vanA*, *vanB*, *vanC*, *vanD*, and *vanE*. With the exception of the *vanC* gene which is found intrinsicly in non-pathogenic enterococcal species, the other four genes are acquired, presumably by transfer from other bacteria in the intestinal tract. Regardless of which gene is present in an enterococcal isolate, the result is the production of an altered target



site such that binding of vancomycin to its target is reduced and therefore it cannot inhibit the synthesis of the bacterial cell wall. The major difference between the various resistance genes is the level of vancomycin resistance they confer and whether other antibiotics such as teicoplanin (not available in Canada but used in Europe) are also affected. For example, the presence of the *vanA* gene results in high-level vancomycin resistance and cross-resistance to teicoplanin, while the presence of the *vanC* gene results in low level vancomycin resistance without cross-resistance to teicoplanin.

Many risk factors have been identified that may contribute to the colonization and/or infection of patients with VRE in the hospital setting. Both the administration of vancomycin and cephalosporin antibiotics has been shown to increase the risk of infection with VRE. Other factors such as prolonged hospital stay and exposure to other patients who are colonized with VRE also increase the risk of infection with VRE. Enterococci can contaminate and survive for prolonged periods of time on inanimate objects such as beds, rectal thermometers, etc. even after cleaning and thus the environment remains a potential source of spread of VRE within hospitals and other institutions. The role that animals colonized with VRE play in the spread of these organisms to humans remains unclear, but likely contributes to at least some of the VRE seen in humans.

Treatment of patients infected with VRE is difficult for many of the reasons noted above. Agents that have shown

activity in the laboratory, as well as clinically against VRE include drugs such as quinupristin-dalfopristin (although its activity against *E. faecalis* is poor), linezolid, tigecycline and daptomycin. Some people have used various antibiotic combinations to treat patients infected with VRE, but many of these reports are anecdotal. Further study is required to determine the optimal therapy of VRE, particularly for more invasive infections such as enterococcal endocarditis. To date, there is no effective way of eliminating colonization of the skin or gastrointestinal tract in those patients who harbour VRE, many of whom will carry these organisms for months or years.

Selected References:

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