Vancomycin-Resistant Enterococci

Therapeutic Challenges in the 21st Century

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KEYWORDS

• Vancomycin resistant enterococcus • Antibiotic resistance • Combination therapy

KEY POINTS

- Multidrug-resistant enterococcal infections continue to be a clinical challenge despite the advent of new therapeutic agents.
- The genetic plasticity of enterococci underscores the versatile nature of the organisms and has provided new insights into the mechanisms by which bacteria can become resistant to antibiotics and how commensal organisms evolve to become prominent hospital-associated opportunistic pathogens.
- Development of resistance to almost all antienterococcal antibiotics currently available in clinical practice highlights the difficulties facing clinicians in the setting of deep-seated enterococcal infections.
- Vancomycin-resistant enterococci infections in the 21st century will require the use of new or innovative therapeutic treatments that involve both old and new antimicrobials.

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INTRODUCTION: A REPORT FROM THE FRONT LINES

The year 1899 saw the first report of the bacterium *Micrococcus zymogenes* (thought today to be *Enterococcus faecalis*) as a cause of infective endocarditis (IE).[1] The patient, a 37-year-old German man, described a 2-month history of fever with an indolent, yet relentlessly progressive course. The medical staff could only watch helplessly as he died 18 days later from complications of his illness. One hundred fifteen years later, a man in his 40s with a hematologic malignancy was found to be colonized with vancomycin-resistant enterococci (VRE) on admission to the hospital for treatment of his cancer. During the admission, he became febrile, and *Enterococcus faecium* was isolated from the blood several times.[2] The medical team administered a progressive regimen of antimicrobials, including daptomycin, ampicillin, gentamicin, quinupristin-dalfopristin, tigecycline, and linezolid; however, after 3 months on therapy, blood cultures remained positive for VRE. Despite the availability of antibiotics, the eventual outcomes of both patients (separated by medical care that had evolved for 150 years) were not that different.

As the 21st century dawns, organisms such as multi–drug-resistant (MDR) *E faecium* present new challenges to clinicians. Medical science races to keep pace with the spread of resistance determinants and provide clinicians new drugs to combat an ever-changing enemy. The number of antibiotics in the therapeutic armamentarium that are active against enterococci has expanded over the last decade; however, there are little published clinical data to guide their most effective use. Below is a profile of the pathogen and its genomic plasticity, the attributes thought to be associated with its ability to colonize and infect the human host, and its strategies for resisting antimicrobial attack. This review concludes with a synthesis of the available therapeutic data to guide physicians in selecting the best treatment for these difficult infections.

PROFILE OF AN OPPORTUNISTIC PATHOGEN

From the Iron Age to the Antibiotic Age

Enterococci are facultative gram-positive cocci that live as commensals of the gastrointestinal (GI) tract of animals and humans. Enterococci are rugged and durable, able to survive in high salt concentrations and elevated temperatures, and able to resist chemical stress from chlorine and alcohol-based disinfectants.[3] Enterococci lack the cadre of virulence determinants of *Staphylococcus aureus* or the more pathogenic streptococci; however, their durability and commensal nature position them to not only survive but thrive in the modern medical setting. Surveys of organisms responsible for health care–associated infection have found that enterococci are second only to staphylococci in being isolated from health care–associated infections across the United States.[4]

Enterococcal infections, like most human diseases, have a history shaped not only by bacterial biology but also by the social, economic, and geographic factors that affect the human host. Whole genome sequencing and analyses of *E faecium* genomes have shed some light on the evolutionary history and adaptation of enterococci with the human host.[5,6] This story appears to emerge at the dawn of the Iron Age (ca. 3000 years ago) with the divergence of 2 genetic lineages (clades) of *E faecium*. One, designated clade B, would remain as a commensal of the human gastrointestinal tract with low potential for infectivity and general lack of antibiotic resistance determinants. The other (clade A) seems to have evolved and adapted to the gastrointestinal tract of livestock and domesticated animals. This bifurcation was driven, as Lebreton and colleagues[6] hypothesized, by the increasing contact between humans and