



## Clinical Significance of Glycopeptide Resistant Enterococci

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**T**he virulence of enterococci is relatively low. The most common monomicrobial infections caused by enterococci are urinary tract infections, including prostatitis, infective endocarditis, infections of vascular grafts or other prostheses, including prosthetic joint infections, and less commonly disc space infections and osteomyelitis. Polymicrobial infection which usually results from intra-abdominal, biliary, pelvic, or wound infections following surgery, bowel perforation, or trauma. The most common portals of entry for enterococcal bacteremia are urine, intra-abdominal or pelvic, biliary, wound, or intravascular catheter sites.

The emergence and global spread of multiresistant strains of enterococci represents a serious threat of infection in vulnerable patients, including those with immunosuppressed conditions, hematologic malignancies, transplant recipients, hemodialysis patients, or other seriously ill hospitalized patients. Enterococci resistant to glycopeptides (GRE) are usually multiply resistant to other antimicrobial agents, including aminoglycosides and penicillins. Currently, no highly effective antimicrobial therapy exists for serious infections caused by GRE.

Infections caused by GRE are usually the result of colonization of the gastrointestinal tract by these microorganisms which, via translocation through the bowel wall, gain access to either the bloodstream or lymphatics, and result in bacteremia and distal site infection. Patients with gastrointestinal tract colonization with GRE often contaminate numerous environmental nosocomial sites. Transmission to health care workers (HCW) and consequent contamination of intravenous catheters, wounds, urinary catheters, endotracheal tubes, and other prostheses result.

Numerous studies have evaluated risk factors for acquisition of gastrointestinal tract colonization and means of transmission of GRE.<sup>1-10</sup> The major factors which predispose to gastrointestinal tract colonization are antimicrobial therapy, underlying host conditions, and hospitalization.

Gastrointestinal tract colonization with GRE has been associated with the use of a number of orally and parenterally administered antimicrobial agents, including vancomycin, metronidazole, clindamycin, cephalosporins, tetracycline, some fluoroquinolones, and aminoglycosides. The most consistent association has been with the use of antimicrobial agents with anti-anaerobic activity. Donsky et al<sup>10</sup> and others have proposed that anti-anaerobic agents promote the overgrowth of GRE in the gastrointestinal tract of patients through inhibition of gut anaerobic microflora. The use of these antimicrobial agents prolongs gastrointestinal tract colonization. The administration of anti-anaerobic antimicrobial agents significantly ( $p=0.006$ ) increased the concentration of GRE in stool in colonized patients compared with the use of antimicrobial agents with minimal or no anti-anaerobic antimicrobial activity.<sup>10</sup> In this study, the use of anti-anaerobic antimicrobial agents which resulted in increased concentrations of GRE in stool of colonized patients included vancomycin, metronidazole, clindamycin, beta-lactamase inhibitor combinations, and cephalosporins with activity against anaerobes, including cefoxitin and ceftriaxone.<sup>10</sup> These authors also reported that patients with fecal incontinence and GRE concentrations of  $\geq 4$  log/gm of stool were significantly more likely ( $p=0.002$ ) to contaminate environmental nosocomial sites than were patients with GRE  $< 4$  log/gm of stool. Environmental contamination of hospital sites with GRE usually results in contamination of

HCW which increases the risk of transmission of GRE to other patients.

A number of host factors increase the risk of gastrointestinal tract colonization and subsequent infection with GRE. These include hospitalization, transfer between hospitals or within hospitals, prolonged length of stay especially in intensive care units, older age, underlying malignancies, neutropenia and other immunosuppressed conditions, elevated APACHE II scores, use of hyperalimentation, central venous catheterization, hemodialysis, abdominal or biliary tract surgery, decubiti, and other factors. Nosocomial acquisition of GRE is thought to result from hospital cross transmission and the transfer of patients within hospitals, especially to a unit housing patients known to harbor GRE has been associated with an especially high risk of gastrointestinal tract colonization.<sup>8</sup> HCW contaminated with GRE are thought to be the most important vector in the transmission of GRE among hospitalized patients. Patients are more likely to acquire GRE from contaminated HCW than they are to acquire GRE from environmental sources.<sup>6,8</sup>

Enteral feedings are reportedly a risk factor for colonization of the gastrointestinal tract by GRE.<sup>1,8</sup> This increased risk is probably attributable to comorbidity factors associated with hyperalimentation, such as bowel dysfunction, increased length of stay in hospital, and the use of anti-anaerobic antimicrobial agents.

The clinical significance of colonization with GRE has been studied by several investigators. Patients with GRE bacteremia were compared with those with bacteremia caused by glycopeptide-susceptible enterococci (GSE).<sup>1</sup> Compared with bacteremia caused by GSE, those with GRE bacteremia were significantly more likely to have longer length of stay in hospital ( $p<0.001$ ), recent surgery ( $p=0.004$ ), hyperalimentation ( $p=0.014$ ), longer length of stay in intensive care units ( $P=0.028$ ), and higher APACHE II scores ( $p=0.044$ ). GRE bacteremia was more likely than GSE bacteremia to be caused by *Enterococcus faecium* ( $p<0.001$ ), prolonged bacteremia ( $p<0.001$ ), and more than one other culture site positive ( $p=0.005$ ).<sup>1</sup> In this same study, compared with GSE bacteremia, GRE bacteremia was more likely associated with the use of metronidazole ( $p=0.006$ ) and tetracycline ( $p<0.001$ ), but no significant difference in the risk of bacteremia was noted with therapy with vancomycin, cephalosporins, penicillins, clindamycin, or fluoroquinolones.<sup>1</sup> While the univariate analysis result showed the mortality to be significantly higher (45%) with GRE than with GSE bacteremia (27%) ( $p=0.007$ ); a multivariate analysis of mortality showed no difference in mortality in patients with bacteremia caused by GRE or GSE. These results are similar to two other studies which showed significantly higher crude mortality with GSE bacteremia but no significant differences in logistic regression models.<sup>2-11</sup> However, Lindon et al<sup>12</sup> reported a significant increase in mortality associated with GRE bacteremia in a multivariate analysis.

The overall mortality from enterococcal bacteremia reportedly ranges from 19-54%.<sup>1</sup> With the exception of infective endocarditis and other endovascular infections, such as infections of vascular grafts, the mortality associated with enterococcal bacteremia is probably related to the serious underlying conditions which predispose to enterococcal bacteremia and to the fact that enterococcal bacteremia is often associated with underlying polymicrobial infections rather than to the high intrinsic virulence of enterococci. While the role of GRE as a cause of mortality is at present not clear, infection or colonization by GRE is associated with higher cost of hospitalization as a result of increased infection control measures and probably increased length of stay in hospital.

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