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Treatment and Prevention of Hospital Infections (D Vilar-Compte, Section Editor)

Enterococci as Increasing Bacteria in Hospitals: Why Are Infection Control Measures Challenging for This Bacteria?

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Abstract

Purpose of the review Enterococci are emerging threatening multidrug-resistant bacteria. *Enterococcus faecium* is a common pathogen associated with severe hospital-acquired infections. The goal of this report is to analyze the evolution of this nosocomial pathogen and study the state of adequate infection control measures.
Recent findings Evolution over millions of years has allowed enterococci to develop into a persistent hospital pathogen, an environment where it thrives. Vancomycin-resistant enterococci (VRE) continues to obtain antibiotic resistance elements. Enterococci assemble multiple virulence factors. VRE intestinal colonization can promote nosocomial infections. New rapid PCR laboratory tests with high sensitivity and specificity allows for screening of Enterococci in asyptomatic carriers.
Summary The efficient clonal dissemination of VRE has led to a potential multidrug-resistant bacteria that is a current and future threat to hospitals worldwide. The therapeutic options are few and decreasing. Healthcare-associated infection (HAI) prevention is critical in our fight against enterococci.

Introduction

Enterococci, specifically vancomycin-resistant enterococci (VRE), are important nosocomial pathogens worldwide [1, 2, 3••, 4, 5•]. Healthcare-associated infections (HAI) caused by VRE are associated with increased morbidity and mortality [2, 6••, 7••, 8••].

The evolving antibiotic resistance in Enterococcus, such as *Enterococcus faecium* multiple drug-resistant (MDR) pathogens, continues to make these bacteria potentially resistant to all available antibiotics.

Enterococcus faecium is included in the ESKAPE group of worrisome bacteria that includes *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanni*, *Pseudomonas aeruginosa*, and *Enterobacter spp*., all of which are dangerous threats [9].

Enterococcus also possess multiple virulence factors that coupled with antibacterial resistance make this group of bacteria a worrisome menace [2, 10].

Enterococci virulence factors include secretory factors that activate cell lysis, translocation, and adherence; cell surface determinants that are in charge of neutrophil survival, biofilm formation, adhesion to collagen; and the increased ability to infect macrophages, megaplasmids, and diverse peroxidases that confer resistance against phagocytes [2].

The evolution of enterococcal nosocomial infections

In 1987, an enterococci resistant to gentamicin was reported to be found in 55% of isolates from hospitalized adult patients. The recovery of resistant strains was associated with previous exposure to antibiotics. The resistant strains were isolated from healthcare personnel and environmental surfaces [11].

The clonal spread of a beta-lactamase-producing *Enterococcus faecalis* in hospitals in five states at USA was first reported in 1991 [12]. This single strain was different from other strains recovered in other states, including Connecticut and Massachusetts and from two countries, Lebanon and Argentina [12].

Starting in 1993, the era of *Enterococcus faecium* as an important nosocomial pathogen was noted in several reports including that of an outbreak caused by *E. faecium* resistant to vancomycin, penicillin, and gentamicin [13, 14].

The endemicity of VRE in hospitals is secondary to clonal spread, transfer of genetic elements, and the introduction of new strains [15]. In one hospital, it took 6 years from the first detection of VRE in 1990 to the establishment of the endemicity in 1996 [15]. In this particular institution during that time frame, 24 strain types were found, and 69% of the patients were infected with a vanB *Enterococcus faecium*; van A strains were detected in 1993 [15].

Nosocomial VRE outbreaks tend to be polyclonal, and their increased prevalence is associated with the high use of vancomycin or third-generation cephalosporins [16, 17].

Enterococcal healthcare-related bacteremia

Enterococcal healthcare-related bacteremia (EHCRB) is one of the most common healthcare-related infections (HCIs) associated with these pathogens.

In two early reports on HCRBE, 118 cases of HCRBE and 35 cases of community-acquired bacteremia were diagnosed during a 14-year period (1970–1983). The annual incidence rose threefold, and 42% of the episodes were polymicrobial. Endocarditis was most commonly observed in community-acquired bacteremia, complications frequently occurred in the

polymicrobial group, and the mortality was 71.4% [18, 19].

Vancomycin-resistant *Enterococcus faecium* (vanA phenotype) was responsible for an outbreak in an oncology ward. A common risk factor was a prior antibacterial therapy (metronidazole, clindamycin, and imipenem), and the mortality rate was 73% [20]. One clone was responsible for 83% of the episodes, indicating that the nosocomial spread and intestinal colonization by VRE were also significant risk factors [20].

In a different hospital, among 110 infections caused by *Enterococcus* spp., 28% were catheter-related bacteremia, 18% were primary bacteremia, 6% were endocarditis, and 1% was septic thrombophlebitis [21]. Sixty-one percent of the infections were nosocomial, and 48% of them occurred in the intensive care unit. *Enterococcus faecium* was responsible for 20% of all the infections. The overall mortality was 23%. Ampicillin resistance and a high acute physiology and chronic health evaluation (APACHE) II score were highly predictive of failures [21].

In a comparison between VRE bacteremia (VREB) and vancomycin-susceptible Enterococcus bacteremia, (VSEB), VSEB had a more recent surgical procedure and was polymicrobial. VREB risk factors included venous catheterization, hyperalimentation, and prolonged hospitalization. In both groups, an elevated APACHE II score was associated with a severe outcome [22].

In the search for risk factors associated with mortality in VRE bacteremia, 260 enterococcal bacteremia episodes were analyzed. VRE caused 72 (28%) of the incidents, and independent risk factors for VRE infection included mean number of antibiotic days ($P < 0.001$); renal failure ($P < 0.001$); mean number of days of vancomycin use ($P = 0.005$); and neutropenia ($P = 0.013$). Mortality attributable to the bacteremia occurred in 96 patients (37%). Illness severity ($P < 0.001$) and age ($P = 0.020$) were independent risk factors for mortality [23].

In a nationwide, concurrent surveillance study (Surveillance and Control of Pathogens of Epidemiological Importance of nosocomial bloodstream infections, NBSI), 24,179 NBSI episodes were detected in 49 hospitals in the USA over a 7-year period from March 1995 through September 2002 (60 cases per 10,000 hospital admissions). Eighty-seven percent of BSIs were monomicrobial. Gram-positive organisms caused 65% of these NBSIs [24]. *Enterococcus* spp. produced 9% of the episodes. Enterococcal NBSIs occurred 23 days after admission, and vancomycin resistance was observed in 2% of *Enterococcus faecalis* isolates and in 60% of *Enterococcus faecium* isolates [24].

In a retrospective review of 205 patients with enterococcal bacteremia, *Enterococcus faecalis* was isolated from 86% of the cases, while *Enterococcus faecium* occurred in 14% [25]. Antibiotic resistance to amoxicillin occurred in 69% of the *E. faecium* isolates, and high-level gentamicin resistance was present in 38% (65/171) of *E. faecalis* isolates and in 25% (7/28) of *E. faecium* isolates. No vancomycin-resistant enterococci were isolated. Mortality was associated with cirrhosis, malignancy, and not receiving the appropriate therapy [25].

The epidemiology and outcomes of patients with vancomycin-resistant *Enterococcus faecalis* (VREF) were presented in a retrospective (January 2008 to October 2010) analysis of 105 cases and compared with 197 bacteremia cases caused by vancomycin-resistant *Enterococcus faecium* [26]. Mortality in the VREF group was lower (> twofold) than in the VREF group [26].

In a report from the Canadian Nosocomial Infection Surveillance Program (CNISP) between 1999 and 2009, 128 cases of VRE were reported [27]. Eighty-one of the 128 bacteremia isolates were *Enterococcus faecium*. VanA was found in

90.1% of the isolates, and vanB was also present in 9.9% of the isolates. All of the VRE isolates were found to be susceptible to daptomycin, linezolid, and tigecycline [27].

Enterococcal bacteremia can develop in intensive care units (ICUs). A study from two ICUs from 2011 to 2013 evaluated 3080 admissions. Among them, 266 ICU-acquired bacteremia events occurred, and 76 were caused by enterococci (incidence rate, 3.0 per 1000 patient-days at risk; 95% confidence interval, 2.3–3.7) [28••]. Enterococcal bacteremia was independently associated with an increased case fatality rate [28••].

A recent systematic review focused on the treatment outcomes associated with VRE bacteremia and vancomycin-sensitive *Enterococcus* (VSE) bacteremia in an era of appropriate treatment [7••]. VRE bacteremia was associated with increased mortality compared with VSE bacteremia in both, cohort studies and case-control studies. Hospital stay was prolonged in patients in the VRE group [7••].

Enterococcus outbreaks

The development of a nosocomial outbreak is one of the most fearful healthcare-associated events. Because of its nature, the sudden initiation of a new HAI is alarming. The early diagnosis and control of an outbreak requires a multidisciplinary approach, infectious disease specialists, and epidemiology and clinical microbiology laboratory personnel at the forefront.

In one of the earliest outbreak reports, an *Enterococcus faecium* resistant to glycopeptides, penicillins, and aminoglycosides was isolated from peritoneal dialysis fluid from a patient in an intensive care unit. Over the following 6 months, multi-resistant *E. faecium* organisms were isolated from blood and urine cultures or surgical wound specimens from eight additional patients. Surveillance cultures from groin and rectal swabs were positive in eight of 37 patients, and four of 62 employees at risk. Risk factors included renal failure, length of hospital stay, duration of antibiotics treatment, and prior treatment with vancomycin [14]. This outbreak was caused by a single strain of *E. faecium*; strict infection control measures include surveillance cultures from the groin, rectum, throat, and axilla; surveillance cultures also obtained from healthcare personnel; contact precautions included gloves and gown for all personnel entering room of patients; closing of the intensive care unit, initiation of an exclusive area, daily perianal washing with chlorhexidine, shower with chlorhexidine for colonized staff members, and the use of 15% quaternary ammonium compound for surface cleaning helped to control this outbreak [14].

Other outbreak reports have identified prolonged outbreaks caused by a single clone of vancomycin-resistant enterococci (VRE), one in a burn intensive care unit that lasted 13 months [29] and another one an epidemic in an Australian hospital that affected 68 patients after the index patient, all of which were infected by a single clone of vanB vancomycin-resistant *Enterococcus faecium* [30]. A similar VRE outbreak that included 27 patients in six wards was identified in a hospital in the Netherlands; 93% of the patients were colonized with the epidemic VRE strain [31]. The infection control measures were directed toward the epidemic strain and included universal use of alcohol-based hand solution, active surveillance, isolation of carriers, and cohorting [31]. VRE outbreaks can also develop in pediatric populations. In pediatrics,

VRE is frequently reported as a cause of infection and colonization in neonatal intensive care units; it is occasionally implicated from endemic strains circulating in the hospital [32].

The problem with colonization and carriers

In a point prevalence study conducted among 636 patients admitted to a hospital, 3.5% were found to be VRE fecal carriers [33]. Eighteen strains were identified as *Enterococcus faecium*, three as *Enterococcus gallinarum*, and one as *Enterococcus faecalis*. Risk factors included hospitalization, length of stay at the hematology ward, and prior vancomycin treatment [33].

The colonization/carrier state can begin during an outbreak. During a 6-month outbreak period, 187 VRE isolates were recovered from rectal swabs and 96% of the isolates were *Enterococcus faecium*. The infection isolates were obtained from VRE carriers. The isolation of VRE from surveillance cultures preceded clinical recovery in 50% of cases, and the incidence of carriage during this period was 8% [34].

Some other risk factors for the colonization and carriage of antibiotic-resistant enterococci have included previous treatment with more than three antibiotics, empirical use of antibiotics, use of third-generation cephalosporins, and the use of enteral feeding tubes [35].

The use of some antibiotics can increase high-density intestinal colonization with VRE [36]. After treatment with anti-anaerobic agents, the density of VRE colonization increased in an animal model and patients [36].

The duration of VRE colonization/carriage can be prolonged. To ascertain the disappearance of the carrier state, three consecutive negative cultures should be obtained [37]. When patients who were VRE carriers showed VRE disappearance, new use of antibiotics may produce a recurrent high-density state [38].

Endemicity

During a 6-year period after VRE were first detected, high endemicity rates were noted, with 24 different strains in 183 patients [15]. In this study, clonal spread, transfer of genetic material, and the introduction of new strains were studied. During the first 3 years (1990 and 1993), 69% of patients were infected with the same vanB *Enterococcus faecium* strain. VanA resistance was not detected until 1993, when eight vanA strains were detected, and a 35- or 40-kb conjugative vanA plasmid was found in four of the eight strains. The clonal spread was a significant factor in the establishment of endemicity [15].

Control measures should be used continuously despite being in the endemicity phase of nosocomial infections with VRA [39], and the possibility of unknown person-to-person spread should increase infection control measures [40].

Surveillance

The importance of active surveillance for the prevention of bloodstream infections with VRE is discussed in a 2003 paper [41]. During a 6-year period, two hospitals were compared; one hospital did not perform rectal colonization

screening, while the other did. The rates of VRE bacteremia were 2.1-fold higher in the hospital that did not routinely screen patients for rectal carriage of VRE. The VRE isolates were clonally related, and the authors concluded that less horizontal transmission may result from more routine rectal screening and the prompt isolation of colonized patients [41].

Active surveillance also has an essential value in preventing VRE transmission in intensive care units [42]. When active surveillance (admission cultures and subsequent isolation) was compared to passive surveillance (isolation with known previous or current VRE colonization), active monitoring can result in a 39% reduction in the annual incidence of VRE colonization [42].

During a 30-month prospective observational study, clinical active surveillance (CAS) for VRE (culture from a rectal swab specimen for the detection of VRE was performed upon admission, weekly while the patient was in the ICU, and at discharge) was compared to laboratory-based active (LAS) surveillance (culture of a stool specimen for the detection of VRE in stool samples submitted for Clostridium difficile toxin detection) for cost evaluation [43]. The CAS method initially detected 280 (91%) of the 309 patients as colonized with VRE compared with 25 patients (8%) discovered by LAS. Most patients with colonization (76%) would have gone undetected by LAS alone, whereas use of the CAS method would have exclusively missed only three patients (1%) who were colonized; CAS cost was $1913 US dollars per month or 57,395 dollars for the 30-month study period. The cost savings of CAS from preventing cases of VRE colonization and bacteremia were estimated to range from 56,258 to 303,334 dollars per month [43].

Active surveillance for VRE in hospitals with a high prevalence of the bacteria can markedly reduce associated healthcare-related infections and reduce costs of hospital care [44].

Passive surveillance in low prevalence settings can be cost-effective in the prevention of enterococcal healthcare-related bacteremia [45].

The implementation of targeted, universal, active, passive, or weekly surveillance adds to infection control programs [44, 46–49].

The clinical microbiology laboratory in the control of enterococcal infections

The clinical microbiology laboratory (CML) is crucial in the prevention of healthcare-associated infections (HAI). The CML has an essential role in HAI surveillance, as is critical in the detection of nosocomial pathogens and their antimicrobial susceptibility patterns. The CML is a significant partner of hospital infection and prevention programs, especially in the detection and control of outbreaks.

The CML is one of the leaders in every antimicrobial stewardship program, providing timely susceptibility data for nosocomial pathogens. The CML is a decisive participant in the infection control committee and in the education of medical personnel that will participate in future infection prevention activities.

One of the initial endeavors that CMLs have embarked on is prevention strategies for enterococcal infection and the implementation of surveillance cultures [50]. Surveillance cultures can start upon all admissions or as a weekly

procedure. In a 165 unit-month retrospective cohort study, the admission prevalence for VRE was 2.2–27.2% and the monthly incidence with weekly vigilance was 0.8–9.7% [50]. As observed in other studies, surveillance increases the rate of positive cultures.

After the introduction of chromogenic agar, it was found to be a reliable test for the early identification of *Enterococcus feacalis* or *Enterococcus faecium* [51, 52]. Later, with the aim of more faster microbiological identification procedures, the use of MALDI-TOF MS (matrix-assisted laser desorption/ionization time-of-flight mass spectrometry) for antimicrobial susceptibility testing and epidemiological typing was introduced and will probably replace traditional methods [53].

The use of a PCR test (Xpert(R)vanA/vanB) was used for screening during vanA-positive *Enterococcus faecium* outbreaks in four university hospitals in Copenhagen, Denmark [54••].

The test was performed directly on rectal swabs, and the vanA PCR results were used to guide infection control measures. The diagnostic accuracy of the vanA part of the assay had 87.1% sensitivity and 99.7% specificity, with positive and negative predictive values of 98.0%, and turnaround time was 3 days [54••]. The present and future use of faster, precise, and sensitive tests for problematic pathogens will help further control HAIs [55•].

The control of *Enterococcus* in hospitals

The increasing nosocomial problem of healthcare-associated infections (HAI) produced by vancomycin-resistant *Enterococcus* (VRE) and the lack of new and better antibiotic therapies prompted the discussion and a consensus recommendation for the control of the nosocomial spread of VRE [56].

The following recommendations were some of the first to appear: (1) prudent vancomycin use, (2) education of hospital staff regarding vancomycin resistance, (3) early detection and prompt reporting of vancomycin resistance in enterococci and other gram-positive microorganisms via the hospital microbiology laboratory, and (4) the immediate implementation of appropriate infection control measures to prevent person-to-person transmission of VRE [56].

An investigation on the transmission of VRE in an endemic intensive care unit found that frequent hand hygiene, antibiotic restriction, and cohorting of nursing staff are essential for preventing nosocomial transmission in this particular setting [57].

In neonatal intensive care units, the strict application of infection control measures alleviates the problems associated with VRE transmission [32, 58]. Enhanced infection control strategies function in hospital areas where VRE is endemic [39]. The maintenance of continuous infection control interventions, including the use of surveillance cultures and patient isolation, can decrease the transmission of VRE in regional healthcare facilities [59].

Other recommendations have included the formation of an expert group to develop and follow a screening, isolation of carriers, cohorting of contacts, environmental testing and cleaning, warning notices on contact medical records, the constant use of hand hygiene with alcohol-based antiseptic, the universal use of gloves and gowns, daily chlorhexidine bathing, the use of private rooms, continuous education on the possibility of hand and glove

contamination, and antimicrobial stewardship (Table 1) [30, 31, 45, 49, 60–67].

Enterococcus antimicrobial resistance

The evolution of enterococci resistance has been of high interest for its control and for identifying novel antimicrobial agents active against vancomycin-resistant enterococci. Since the late 1980s, growing enterococci resistance has captured the attention of researchers and clinicians worldwide.

Early reports included the identification of high-level vancomycin resistance [68], multiple aminoglycoside resistance in *Enterococcus faecalis* [69], and resistance to the glycopeptides vancomycin and teicoplanin [70].

In 1993, the National Nosocomial Infection Surveillance (NNIS) system from the Centers for Disease Control (CDC) reported a 20-fold increase in the percentage of vancomycin-resistant *Enterococcus* (VRE) associated with nosocomial infections from January 1, 1989, through March 31, 1993, with many of the strains resistant to all available antibiotics [71].

In 2001, VRE developed linezolid resistance during therapy [72]. The resistance occurred in four transplant patients who received prolonged courses of the antibiotics; three of these patients had treatment failures [72]. After the initial reports of linezolid resistance in VRE, new reports demonstrated that

Table 1. Infection control measures for the prevention and control of enterococcal nosocomial infections

Recommendations	Reference
Appropriate vancomycin use, education regarding vancomycin resistance, early detection, and prompt reporting by the hospital microbiology laboratory. Prevention of person-to-person transmission	[54••]
Compliance for hand washing and cohorting of nursing staff	[55•]
Neonatal intensive care unit. Weekly surveillance of colonization, education, and cohorting. Use of gowns and gloves and hand washing before and after each contact.	[20, 56]
Surveillance cultures, geographic cohorts, nurses assigned to patient's cohorts, monitoring of infection control procedures, education of patients about VRE transmission, evaluation of patients taking antimicrobial agents by infectious diseases, and environmental surveillance.	[43]
Surveillance cultures and isolation of infected patients	[57]
Monitoring antimicrobial use and resistance	[60, 61]
Society of Healthcare Epidemiology of America (SHEA) guideline active cultures	[58]
Formation of a VRE executive work, rapid laboratory identification, mass screening, isolation of carriers, cohorting of contacts, environmental screening and increased cleaning. Chart alerts for contacts' medical records and antibiotics restrictions	[35]
Genotyping, isolation of VRE carriers, enhancement of hand- hygiene compliance, and preemptive isolation	[36]
Use of alcohol-based waterless hand antiseptics	[59]
Private rooms or patient cohorting	[62]
Daily bathing with chlorhexidine	[63]
Universal glove and gown use	[64]
Better control of the environment, decontamination, hand hygiene, environmental cleaning.	[65, 66]
Resistant enterococci reduction bundle	[67]

linezolid-resistant VRE could spread in hospital environments [73, 74].

The number of vancomycin-resistant pathogens was found to be increasing in the USA from 2003 to 2006 [75]. In contrast to the 2000–2003 period, the incidence increased from 4.60 to 9.46 hospitalizations per 100,000 population. Admissions with infection due to vancomycin-resistant pathogens also increased from 3.16 to 6.51 hospitalizations with VRE infection per 10,000 total hospitalizations from 2003 to 2006 [75].

Mobile genetic elements (plasmids and transposons) are responsible for the dissemination and persistence of antimicrobial resistance in *Enterococcus faecalis* and *Enterococcus faecium* [76]. Antibiotic resistance mechanisms in multidrug-resistant enterococci (MDRE) include the presence of modified drug targets, inactivation of antibiotics and efflux pumps, and changes in their cell membrane [77, 78]. MDRE will continue to evolve, demonstrating that surveillance for new resistant mechanisms is critical [78].

The evolution of the treatment for enterococcal infections

The appropriate treatment for infections caused by vancomycin-resistant *Enterococcus* (VRE) or multiple drug-resistant *Enterococcus faecium* (MDREF) is challenging [79–81].

The increasing worldwide occurrence of MDREF in hospitals, with > 90% resistant to vancomycin and 100% resistant to ampicillin, complicates the problem more than the selection of appropriate treatment options [79–81]. The worldwide dissemination of a single MDREF lineage further complicates the treatment options [79–81].

Clinicians are confronted with few therapeutic options when a VRE turns into an MDRE with resistance to ampicillin, aminoglycosides, linezolid, daptomycin, and quinupristin/dalfopristin, and antimicrobial combinations have to be considered [2, 82, 83••].

Conclusions

During their evolution, enterococci have developed resistance to desiccation, starvation, the ability to collect antibiotic resistance elements, and the capacity to form new clones [84••] . After their introduction to hospitals, enterococci have produced clonal and polyclonal outbreaks and become endemic. Intestinal colonization with VREF can initiate during an outbreak and continues to be associated with antibiotic pressure. The use of new laboratory methods, including chromogenic media, MALDI-TOF MS, and rapid PCR, has helped to screen, isolate, and treat appropriate HAIs caused by enterococci.

The satisfactory control of *Enterococcus* in hospitals requires an appropriate bundle of interventions adjusted to the particular environment, including the formation of an expert group to develop and follow a surveillance program, rapid laboratory detection and the identification of resistance genes, adequate screening, isolation of carriers, cohorting of contacts, environmental testing and cleaning, warning notices on contact medical records, constant use of hand hygiene using alcohol-based antiseptics, the universal use of gloves and gowns, daily chlorhexidine bathing, the use of private

rooms, continuous education on the possibility of hand and glove contamination, and antimicrobial stewardship.

Compliance with ethical standards

Conflict of interest

Dr. Rayo Morfin-Otero, Hector R. Perez-Gomez, Esteban Gonzalez-Diaz, Sergio Esparza-Ahumada, and Eduardo Rodriguez-Noriega declare that they have no conflicts of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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