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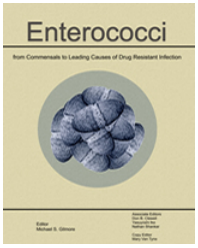

Enterococcal Disease, Epidemiology, and Implications for Treatment

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Introduction

During the past few decades, enterococci have emerged as important healthcare-associated pathogens (Arias & Murray, 2012; Austin, Bonten, Weinstein, Slaughter, & Anderson, 1999; Boyce, et al., 1994; Benenson, et al., 2009; Goossens, 1998; Handwerger, et al., 1993). The continuing progress of modern medical care toward more intensive and invasive medical therapies for human disease has undoubtedly contributed to the increased prevalence of these remarkable opportunistic pathogens. This trend has also been attributed to the increasing antibiotic resistance among clinical isolates of enterococci. The rapid spread of enterococci with resistance to vancomycin (VRE) has been of particular concern. Many healthcare-associated strains that are resistant to vancomycin also show resistance to penicillin, as well as high-level resistance (HLR) to aminoglycosides. Finally, as has historically been the case with enterococci, resistance is emerging to newer agents used to treat VRE infections, such as linezolid, quinupristin/dalfopristin, and daptomycin (Chow, Donahedian, & Zervos, 1997; Herrero, Issa, & Patel, 2002; Sabol, Patterson, Lewis II, Aaron, Cadena, & Jorgensen, 2005).

Over the past two decades, *Enterococcus faecium* has emerged as a leading cause of multidrug-resistant enterococcal infection in the United States (Hidron, et al., 2008). *E. faecium* is intrinsically more antibiotic-resistant than *E. faecalis,* with more than half of its pathogenic isolates expressing resistance to vancomycin, ampicillin, and high-levels of aminoglycosides. Treating infections caused by this species can be difficult, and the magnitude of the problem is vast. Approximately 40% of medical intensive care units in a recent National Healthcare Safety Network report found that the majority of device-associated infections (namely, infections due to central lines, urinary drainage catheters, and ventilators) were due to vancomycin- and ampicillin-resistant *E. faecium* (80% and 90.4%, respectively) (Hidron, et al., 2008). Although they were often resistant to high-level aminoglycosides and some macrolides, healthcare-associated infections in these units due to *E. faecalis* remained largely susceptible to vancomycin and ampicillin (93.1% and 96.2%, respectively) for reasons that are not entirely known. Other enterococcal species are rarer causes of human infection, including *E. durans, E. avium, E. casseliflavus, E. hirae, E. gallinarum, E. raffinosus*, and *E. muntdii* (Gordon, et al., 1992).

In the following sections, the common human infections caused by enterococci are briefly described. The epidemiology of antibiotic-resistant enterococci in healthcare settings is summarized, including the role of colonization pressure and host factors on the emergence of VRE in clinical settings. Finally, the current challenges facing clinicians who treat antibiotic-resistant enterococcal infections are reviewed.

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Enterococcal Disease

Enterococci can cause a variety of infections. For some of these, other microorganisms are also frequently isolated from the same site. In those situations, it is often not clear whether the manifestations of infection are the result of enterococci, or whether these relatively avirulent and opportunistic organisms are merely bystanders or are playing a minor role in the infection. However, for other types of infections, most notably endocarditis and bacteremia, enterococci can clearly cause serious and often life-threatening disease, and specific therapies are associated with improved outcomes (Hoge, Adams, Buchanan, & Sears, 1991).

Urinary Tract Infections

The most common type of enterococcal infection occurs in the urinary tract. Lower urinary tract infections (such as cystitis, prostatitis, and epididymitis) are frequently seen in older men. However, enterococci are exceedingly uncommon as a cause of uncomplicated cystitis in young women. Upper urinary tract infections that can lead to bacteremia occur, not unexpectedly, most often in older men (Graninger & Ragette, 1992). Enterococcal urinary tract infections are more likely to be acquired in hospital or long-term care settings, and thus, are more likely to be resistant to many antibiotics. In the ICU setting, enterococci cause almost 15% of healthcare-associated urinary tract infections. Not unexpectedly, VRE have become major healthcare-associated urinary tract pathogens among ICU patients (Hidron, et al., 2008).

Intra-Abdominal, Pelvic, and Soft Tissue Infections

Enterococci are often recovered from cultures of intra-abdominal, pelvic, and soft tissue infections. They are almost always isolated as only one component of mixed microbial flora and rarely cause monomicrobial infection at these sites. The importance of enterococci in wounds and abscesses has been debated at length. However, with enterococcal bacteremia commonly associated with intra-abdominal and pelvic abscesses and wounds (Graninger & Ragette, 1992; Maki & Agger, 1988; Noskin, Peterson, & Warren, 1995; Patterson, et al., 1995), most clinicians routinely use antibiotic regimens that treat enterococci when confronted with infections at these sites. Drainage of abscesses and debridement of wounds are often essential adjuncts to antibiotic therapy for these infections.

Peritonitis, an infection of the abdominal lining, should be considered separately from intra-abdominal or pelvic mixed aerobic-anaerobic infections. This infection occurs most often in conjunction with liver cirrhosis or in patients who receive chronic peritoneal dialysis. Enterococci can cause monomicrobial infection in these situations—although they occur far less commonly than *Escherichia coli* for spontaneous bacterial peritonitis or coagulase-negative staphylococci, and *Staphylococcus aureus* for dialysis-associated peritonitis. Finally, enterococci are frequently found in cultures from decubiti and foot ulcers, as well as in association with osteomyelitis in diabetics, but their role in infections at these sites is not clearly defined.

Bacteremia

Bacteremia and endocarditis are the more common manifestations of infections due to enterococci. Enterococci are currently the second leading cause of healthcare-associated bacteremia (Hidron, et al., 2008), an increase from the sixth most common cause in the 1980s. In the last few years, the source of a bacteremia is usually the genitourinary tract, although a bacteremia also often arises from intra-abdominal or biliary sources, indwelling central lines, or soft tissue infections. Enterococci are found as a component of polymicrobial bacteremia more often than other organisms (Maki & Agger, 1988; Patterson, et al., 1995).

Enterococcal bacteremias, in contrast to bacteremias with *S. aureus,* rarely seed distant organs or cause metastatic abscesses. The major issue when dealing with enterococcal bacteremia is the presence of endocarditis. The treatment of endocarditis can be more problematic than the treatment of bacteremia due to a noncardiac

source. However, even when a specific source is found, the overall mortality rate from enterococcal bacteremia is between 26% and 46% (Maki & Agger, 1988; Malone, Wagner, Myers, & Watanakunakorn, 1986; Patterson, et al., 1995; Shlaes, Bouvet, Devine, Shlaes, al-Obeid, & Williamson, 1989). A large retrospective review of bloodstream infections reported enterococci as the only Gram-positive pathogen associated with a high risk of death (Weinstein, Murphy, Reller, & Lichtenstein, 1983). In some studies, *E. faecium* bacteremia is associated with a higher mortality rate than *E. faecalis* (Noskin, Peterson, & Warren, 1995), and patients with rapidly fatal underlying diseases can have mortality rates as high as 75%. These high rates likely reflect patients who are at risk for developing enterococcal bacteremia—older adults with multiple underlying diseases, which may include diabetes mellitus, malignancy, heart disease, transplantation, and prior surgery.

Endocarditis

Endocarditis is one of the most serious enterococcal infections. Because of the enterococci's intrinsic resistance to the bactericidal activity of most antibiotics, treatment is difficult, even when relatively susceptible enterococci are involved. Two drugs that exhibit synergistic killing are required for effective therapy. In the situations of VRE or high-level aminoglycoside-resistant enterococcal endocarditis, antibiotic treatment often fails, and surgery to remove the infected valve is essential.

Overall, enterococci cause between 5 to 15% of cases of infectious endocarditis, and this rate has not changed substantially over several decades (Murdoch, et al., 2009). *E. faecalis* remains the more common cause of enterococcal endocarditis than E. *faecium*. These heart valve infections typically occur in older persons (Anderson, Murdoch, Sexton, & Reller, 2004; McDonald, et al., 2005; Wilson, Wikowske, Wright, Sande, & Geraci, 1984). The initial source of bacteremia leading to endocarditis is usually the genitourinary or gastrointestinal (GI) tract. Left-sided involvement is much more common than right-sided involvement. Prosthetic valve enterococcal endocarditis has been increasingly noted, which is perhaps related to the increasing use of these prostheses in older adults who are at an inherently higher risk for enterococcal bacteremia (Anderson, Murdoch, Sexton, & Reller, 2004; Rice, Calderwood, Eliopoulos, Farber, & Karchmer, 1991). In one retrospective analysis of a large endocarditis database (Anderson, Murdoch, Sexton, & Reller, 2004), an equal number of women and men had enterococcal endocarditis, although enterococcal endocarditis is typically reported more often in men than women (McDonald, et al., 2005). Unlike a previous small study (Murdoch, et al., 2009), recent large-case series of enterococcal endocarditis report that between 15% and 39% are healthcare-associated (Anderson, Murdoch, Sexton, & Reller, 2004; McDonald, et al., 2005). The clinical picture of enterococcal endocarditis is usually one of subacute infection characterized by heart failure, rather than embolic events (McDonald, et al., 2005); however, rapidly progressive disease can also occur. Enterococcal endocarditis has a lower mortality rate than other forms of infective endocarditis (odds ratio = 0.49 with 95% confidence interval of 0.24–0.97) (McDonald, et al., 2005), although death rates are still significant at 9% to 15% (McDonald, et al., 2005; Rice, Calderwood, Eliopoulos, Farber, & Karchmer, 1991; Wilson, Wikowske, Wright, Sande, & Geraci, 1984). The most problematic current issue in the management of enterococcal endocarditis is the selection of effective therapy for multidrug-resistant isolates (Stevens & Edmond, 2005).

Uncommon Infections

Other infections less commonly or rarely seen due to enterococci include meningitis, hematogenous osteomyelitis, septic arthritis, and pneumonia. The latter is quite rare, even in association with ventilators, and has only been documented in severely debilitated or immunocompromised patients who receive broad-spectrum antibiotics. There is no evidence that antibiotic-resistant isolates of enterococci, such as VRE, are more or less likely to cause these infections than antibiotic-susceptible isolates of enterococci.

Epidemiology

A large number of studies on enterococcal ecology and epidemiology have been conducted over the past two decades, especially in clinical settings (Arias & Murray, 2012). Non-healthcare–associated investigations show that enterococci are commonplace colonizers over wide swaths of the planet (Byappanahalli, Nevers, Korajkic, Staley, & Harwood, 2012). In addition to being well-recognized colonizers of the GI tract of most animals and insects, these hardy bacteria are routinely recovered from beach sands, freshwater and marine water sediments, soil, and aquatic and terrestrial vegetation. (For more information, see Enterococcus Diversity, Origins in Nature, and Gut Colonization.) Many studies correlate increasing concentrations of environmental enterococci with GI and dermatological illnesses. As a result, the Environmental Protection Agency recommends enterococci as indicator bacteria for fecal contamination for brackish and marine waters. (For more information, see Enterococci as indicators of environmental fecal contamination.) It must be remembered, however, that enterococci also naturally fill ecological niches, independent of contamination from outside sources. The development of molecular identification and typing methods allows for the facile detection and tracking of enterococci at the strain level. Despite this progress, it remains urgent to more thoroughly define ecological reservoirs, understand host and bacterial traits that promote colonization, and clarify mechanisms for transmission that enhance the spread of multi-drug resistant enterococci.

Enterococcal Reservoirs and Colonization Resistance

Enterococci are normal flora in the GI tract of humans, along with most other animals and insects. *E. faecalis* and *E. faecium* each commonly colonize humans with quantitative stool cultures indicating *E. faecalis* with a higher colonization density than *E. faecium* (Chenoweth & Schaberg, 1990; Noble, 1978; Winters, Schlinke, Joyce, Glore, & Huycke, 1998). The density of enterococci in the colon average 10^7 colony-forming units μg^{-1} (Chenoweth & Schaberg, 1990), although enterococci are found throughout the GI tract and in the oral cavity at lower concentrations. Enterococci are also normal inhabitants of the genital tract, with *E. faecalis* as the predominant species.

The emergence of VRE as leading causes of hospital infection has led to studies that better define characteristics of colonization with this organism. GI colonization, once established, may persist for months to years (Bonten, Hayden, Nathan, Rice, & Weinstein, 1998; Lai, Fontecchio, Kelley, Melvin, & Baker, 1997; Montecalvo, et al., 1995; Noskin, Cooper, & Peterson, 1995; Roghmann, Qaiyumi, Johnson, & Morris, Jr., 1997). Patients with VRE in the GI tract often have the same organism colonizing their skin (Beezhold, et al., 1997). The quantity of VRE increases in healthy volunteers who were given oral glycopeptides (Van Der Auwera, Pensart, Korten, Murray, & Leclerq, 1996). Subsequent studies in both experimental animals and colonized patients have shown that the quantity of VRE found in stool increases several logs when antibiotics with activity against GI anaerobes are administered (Donskey, et al., 2000; Donskey, Hanrahan, Hutton, & Rice, 1999; Ubeda, et al., 2010).

Colonization resistance describes the active exclusion of exogenous pathogens like multi-drug resistant enterococci from the intestine (Vollaard & Clasener, 1994). This trait is primarily provided by "limiting actions" of the normal microbiota, although these mechanisms remain ill-defined. This phenomenon is believed to be predominantly conferred by the anaerobic intestinal microbiota (for humans, this includes *Clostridium* cluster *XIVa*, *Clostridium* cluster *IV*, and *Bacteroides* spp.) (Eckburg, et al., 2005). In the small intestine, one mechanism for colonization resistance arises, in part, by the induction of defensins, cryptdins, and lectins by Paneth cells. In turn, these antimicrobial peptides serve to restrict potentially pathogenic exogenous microorganisms (Cash, Whitham, Behrendt, & Hooper, 2006). An example in mice involves RegIIIγ, a lectin with activity against Gram-positive bacteria that is produced by Paneth cells via the stimulation of toll-like receptors and confers resistance to VRE colonization (Brandl, et al., 2008). Finally, an intact epithelial barrier, coupled with physiological functions that include salivation, immunoglobulin A, peristalsis, and gastric acidity, also contribute to colonization resistance. Breakdown in these ordinary activities, especially when coupled with the administration

of broad-spectrum antibiotics, increases the risk for colonization and transmission of antibiotic-resistant enterococci, and thereby promotes infection by these opportunists (Donskey C. J., 2004).

Sources of Infection

In previous years, the source of enterococcal infection for most patients was thought to be their own endogenous flora. However, the marked rise in healthcare-associated enterococcal infections in the 1980s and 1990s led to studies that clearly demonstrated the transmission of pathogenic enterococci among patients in hospital settings (Boyce, et al., 1994; Huycke, Spiegel, & Gilmore, 1991). The primary mode of spread from patient-to-patient occurs through the hands of healthcare workers (Hayden, 2000). Transient carriage of enterococci on the hands of healthcare workers has been documented in several studies (Antony, Ladner, Stratton, Raudales, & Dummer, 1997; Noble, 1978; Patterson, et al., 1995), although not in all studies (Climo, et al., 2009; Moreno, et al., 1995). Enterococci can persist for as long as 60 minutes after inoculation onto hands (Noskin, Stosor, Cooper, & Peterson, 1995), and as long as 4 months on inanimate surfaces, where they can serve as a reservoir for ongoing transmission in the absence of regular decontamination (Kramer, Schwebke, & Kampf, 2006).

Transmission of enterococci from a healthcare worker's hands to a patient may involve direct inoculation onto intravenous or urinary catheters. A more likely mechanism, however, is that healthcare-associated strains colonize the GI tract of patients with reduced colonization resistance (Donskey C. J., 2004; Vollaard & Clasener, 1994), and then increase in numbers. In this fashion, new strains become part of the patient's endogenous flora, which then serves as a springboard for infection. Acquired enterococcal strains carrying genes that encode antibiotic resistance can persist in the GI tract via selective pressure from broad-spectrum antibiotics frequently used in hospitalized patients (Donskey, et al., 2000; Ubeda, et al., 2010).

Transmission of enterococcal strains has been documented within medical units (D'Agata, Green, Schulman, Li, Tang, & Schaffner, 2001; Handwerger, et al., 1993; Karanfil, et al., 1992), between hospitals (Donskey, et al., 1999; Moreno, et al., 1995), and even from state to state (Chow, Kuritza, Shlaes, Green, Sahm, & Zervos, 1993). The spread of VRE has been noted between acute and long-term care settings and, although uncommon, into the community (Moreno, et al., 1995; Trick, et al., 1999). Frequent contact with healthcare providers and movement of colonized patients among different healthcare settings is undoubtedly responsible for these patterns of transmission.

Role of the Hospital Environment

The hospital environment appears to play an important role in the transmission of multidrug-resistant enterococci (Hota, 2004). The dramatic rise of VRE in the 1990s led to investigations that highlighted the role of the environment in healthcare-associated infections. However, environmental reservoirs for antibiotic-susceptible enterococci are not likely to be different from those for VRE.

Thermometers and thermometer handles appear to be common surfaces involved in the transmission of VRE (Livornese, Jr., et al., 1992; Porwancher, Sheth, Remphrey, Taylor, Hinkle, & Zervos, 1997). A high concordance between strains occurring in the hospital environment and those colonizing patients has been reported (Bonilla, et al., 1997). The healthcare environment is readily contaminated with VRE, with the highest densities found on medical devices (such as blood pressure cuffs, intravenous fluid pumps, or stethoscopes), gowns, bed rails, bedside tables, bed linens, urinals, and bedpans (Bonilla, et al., 1997; Bonten, Hayden, Nathan, Rice, & Weinstein, 1998; Hota, 2004). Not surprisingly, increased environmental contamination has been noted when colonized patients have diarrhea, and there is an increased density of VRE in stool following anti-anaerobic antibiotic use (Donskey, et al., 2000; Roghmann, Qaiyumi, Johnson, & Morris, Jr., 1997; Ubeda, et al., 2010). Several studies have emphasized the tenacity with which enterococci remain viable on environmental surfaces (Hota, 2004), and its subsequent transmission to the hands of healthcare workers. Finally, in one controlled

prospective study, environmental contamination with VRE was shown to be highly predictive of VRE acquisition (Drees, et al., 2008).

Host Factors for Antibiotic-Resistant Enterococcal Colonization

Many investigators have defined specific risk factors for GI colonization with antibiotic-resistant enterococci. In the acute care setting, colonization with aminoglycoside-resistant enterococci was shown to be associated with intravenous catheters, bladder catheters, prior surgical procedures, and prior antibiotic therapy (Zervos, Terpenning, Schaberg, Therasse, Medendorp, & Kaufmman, 1987). Additional studies have defined risk factors for colonization with VRE, and have consistently shown that prior antibiotic therapy with vancomycin, third-generation cephalosporins, and/or agents with anti-anaerobic activity are important to this process (Donskey, et al., 2000).

Other risk factors for VRE colonization include the patient's length of stay in an ICU or hospital (Tornieporth, Roberts, John, Hafner, & Riley, 1996), exposure to other patients with VRE either by close proximity to a VRE-colonized patient, or by care from a nurse providing who is care to another VRE-colonized patient (Austin, Bonten, Weinstein, Slaughter, & Anderson, 1999; Boyce, et al., 1994). Drees et al. (Drees, et al., 2008) showed that "colonization pressure," defined as the percentage of patients in a unit who are colonized with VRE, increased the hazard ratio for acquisition by 1.4 per 10% increase in colonization. When VRE colonization rates exceed 50%, this becomes the dominant risk factor for spread of VRE within a unit (Bonten, et al., 1998).

Certain patient populations, notably those on chronic hemodialysis (D'Agata, Green, Schulman, Li, Tang, & Schaffner, 2001), with hematological malignancies (Ubeda, et al., 2010), or undergoing liver transplantation (Orloff, et al., 1999), are at increased risk for the acquisition of VRE. Many of these patients are cared for in specialized units, and acquisition of GI colonization can be traced back to care within these units and other factors, as noted above. Finally, increasing exposure to patients with VRE has been associated with healthcare workers also being colonized by VRE (Baran, Jr., Ramanathan, Riederer, & Khatib, 2002).

Host Factors Related to Antibiotic-Resistant Enterococcal Infection

The vast majority of VRE-colonized patients do not develop symptomatic infections. The ratio of colonization to infection with VRE is estimated to be approximately 10:1 (Hayden, 2000; Slaughter, et al., 1996). Although unproven, a similar ratio likely exists for enterococcal infections caused by healthcare-associated strains that have a high-level resistance to ampicillin or aminoglycosides (Huycke, Spiegel, & Gilmore, 1991; Willems, et al., 2005). The risk for VRE infection, however, increases among certain patient groups. Patients with neutropenia and those undergoing transplantation are at a particularly increased risk for VRE bacteremia (Lautenbach, Bilker, & Brennan, 1999; Orloff, et al., 1999). In neutropenic patients, the severity of mucositis (Kuehnert, Jermigan, Pullen, Rimland, & Jarvis, 1999) and concomitant infection with *Clostridium difficile* (Roghmann, McCarter, Jr., Brewrink, Cross, & Morris, Jr., 1997) have both been independently associated with an increased risk for VRE bacteremia.

In ICU populations and for those who are immunosuppressed, infection with VRE has been associated with vancomycin, third-generation cephalosporins, and/or antibiotics with activity against anaerobes (Donskey, et al., 2000; Handwerger, et al., 1993; Hayden, 2000; Lautenbach, Bilker, & Brennan, 1999; Montecalvo, et al., 1994; Roghmann, McCarter, Jr., Brewrink, Cross, & Morris, Jr., 1997), increased length of hospital stay (Handwerger, et al., 1993), and the severity of underlying illness (Shay, et al., 1995). A number of risk factors for infection with VRE have also been reported as risk factors for bacteremia with high-level aminoglycoside-resistant enterococci, including chronic renal failure, ICU stay, prior antibiotic use (including cephalosporins), bladder catheterization, expression of cytolysin as an enterococcal virulence determinant, and prolonged hospitalization (Caballero-Granado, et al., 1998; Huycke, Spiegel, & Gilmore, 1991; Noskin, Till, Patterson, Clarke, & Warren, 1991).

Infection Control

The majority of healthcare-acquired infections are caused by microorganisms that are resistant to at least one of the antibiotics most commonly used to treat these infections. This is especially true for infections due to VRE, where treatment options are particularly limited (see below and Enterococcal infection). Therefore, measures that minimize the spread of these resistant organisms are essential. Each healthcare facility needs a comprehensive infection control program that can decrease the transmission of VRE among patients. Specific policies should be based on the rates of resistance within the facility, and should be appropriate for the specific healthcare setting. For example, specific control measures within an acute care hospital setting may differ somewhat from those applicable to a long-term care setting.

The consensus opinion of experts highlight four interventions as being most important for controlling the spread of VRE in healthcare settings: i) active periodic surveillance cultures (or molecular testing) of patients at highest risk for carriage; ii) decontaminating the hands of healthcare workers using an antiseptic-containing preparation before and after all patient contact; iii) adherence to barrier precautions (*i.e.*, gloves and gowns) and cohorting colonized and/or infected patients; and iv) thorough terminal cleaning for rooms occupied by patient with VRE (Cookson, et al., 2006; Muto, et al., 2003). Although evidence for other control strategies for VRE—antibiotic stewardship to limit inappropriate or excessive antibiotic use, decolonizing patients and/or healthcare workers, and educational initiatives—are potentially useful in selected circumstances, these methods currently find less compelling support in the present literature.

Infection Control Measures

Specific infection control considerations should be based on the type of healthcare facility, the prevalence of VRE in that facility, and the patients' risk for infection. Not unexpectedly, acute care settings warrant strict adherence to isolation precautions, more so than outpatient or long-term care settings. The presence of serious infections in many patients may require additional investigation, including molecular typing of VRE strains, in order to fully understand and break the modes of transmission.

In acute care settings, barrier precautions are the cornerstone of infection control for VRE (Cookson, et al., 2006; Muto, et al., 2003). Assiduous hand antisepsis and use of gloves are the most important features of these precautions. This point is emphasized in studies where VRE has been shown to be transferred from contaminated hands to clean sites on patients or environmental surfaces at an average rate of 10% (Duckro, Blom, Lyle, Weinstein, & Hayden, 2005). Gloves decrease the contamination of hands of healthcare workers by VRE, although contamination is still possible as gloves are removed (Tenorio, et al., 2001). Therefore, hand antisepsis after glove removal is mandatory. When hands are not visibly contaminated with blood, body fluids, or body substances, an alcohol hand rub containing an emollient should be encouraged. Hand washing with soap and water is required when hands are visibly dirty or contaminated with blood, body fluids, or body substances. Monitoring hand hygiene compliance, with appropriate feedback given to healthcare workers, is essential, and is required by several accreditation agencies. Clean single-use gowns should be worn by healthcare workers when entering the rooms of patients with VRE. Medical devices that are required for routine patient care (such as blood pressure cuffs, thermometers, stethoscopes, etc.) should remain in isolation rooms and not be shared among patients. Non-dedicated equipment should be disinfected between uses.

Environmental contamination by VRE is common, can vary in different units, and plays a substantial role in transmission (Hayden, 2000; Muto, et al., 2003). The common occurrence of environmental contamination with VRE has led to recommendations that environmental cleaning be performed with standard disinfecting agents on a daily basis, as well as ensuring that high-touch items such as bedside rails, tables, toilets, and handles are cleaned. Although the efficacy of environmental hygiene on colonization or infection with VRE is unclear, one investigation of a medical intensive care unit with a high prevalence of VRE observed a significant decrease in

VRE transmission after the implementation of enhanced environmental cleaning (Hayden, Bonten, Blom, Lyle, van de Vijver, & Weinstein, 2006). Should the skin of patients be considered part of the healthcare environment, interventions that involve daily chlorhexidine bathing have been shown to reduce VRE acquisition by 50%, and decrease the relative risk for VRE bacteremia by three-fold (Climo, et al., 2009). Cohorting colonized or infected patients is an additional targeted intervention of value when single rooms are not available, during outbreaks, or when colonization is hyperendemic within medical units. The efficacy of these control measures has been demonstrated in numerous VRE outbreaks, where the implementation of multifaceted programs has led to successful control (Cookson, et al., 2006; Henard, Lozniewski, Aissa, Jouzeau, & Rabaud, 2011; Lin & Hayden, 2010; Muto, et al., 2003).

Surveillance for VRE

Active surveillance of asymptomatic patients for VRE colonization is a mainstay of targeted control efforts (Muto, et al., 2003). Targeted interventions can help decrease VRE transmission in settings where colonization or infection with VRE is unstable, epidemic, or hyperendemic (Lin & Hayden, 2010). The goal is to identify every colonized patient, so that all colonized patients remain in contact isolation to minimize the spread of VRE to other patients. Surveillance cultures are indicated at the time of hospital admission for patients at high risk for the carriage of VRE. Periodic (*e.g.*, weekly) surveillance cultures are indicated for patients at high risk for VRE because of ward location, antibiotic therapy, underlying disease, and/or the duration of their stay. In facilities with a high prevalence of VRE on initial sampling, a facility-wide culture survey can identify all colonized patients and allow for the implementation of contact precautions.

Colonization with VRE is typically prolonged (Byers, Anglim, Anneski, & Farr, 2002). In hospital settings, removing a patient from contact precautions involves showing that patients are no longer colonized with VRE. The Hospital Infection Control Practices Advisory Committee defines clearance of colonization with VRE as three consecutive negative rectal swabs at least one week apart (Hospital Infection Control Practices Advisory Committee (HICPAC), 1995). However, colonization with VRE can persist despite three consecutive negative weekly surveillance stool cultures (Huckabee, Huskins, & Murray, 2009). Others have proposed defining VRE clearance as a negative rectal swab obtained two to seven days after cessation of a treatment regimen with drugs known to be selective for VRE (such as third-generation cephalosporins, fluoroquinolones, carbapenems, imidazoles, or glycopeptides) implemented for at least five days (Henard, Lozniewski, Aissa, Jouzeau, & Rabaud, 2011). The issue remains unsettled.

Antimicrobial Stewardship

Appropriate use of antibiotics is not only good practice, but is important for controlling the spread of healthcare-associated VRE. The increase in vancomycin resistance among healthcare-associated *E. faecium* isolates in the United States is partially linked to a tremendous increase in vancomycin use during the 1980s and 1990s (Hayden, 2000). The 2003 Society for Healthcare Epidemiology of America published guidelines that stress the avoidance of inappropriate or excessive antibiotic prophylaxis and therapy as a means to control VRE (Muto, et al., 2003). In addition, it was recommended that the correct antibiotic dose and appropriate duration of therapy be used. Vancomycin use should be limited, when possible, to decrease selective pressures that favor vancomycin resistance. An obvious circumstance in which vancomycin restriction should be aggressively pursued is in the isolation of vancomycin-dependent enterococci (Kirkpatrick, et al., 1999). To prevent the establishment of VRE intestinal colonization, considerations should be made to decrease the use of antibiotics with little or no activity against enterococci, such as third-generation and fourth-generation cephalosporins. Finally, when clinically feasible, agents with anti-anaerobic activity should be limited in patients who are colonized with VRE, to prevent persistent high-density colonization.

Education of Healthcare Workers

It is imperative to implement institutional efforts to educate healthcare workers who have direct patient-care responsibilities on infection control policies for the containment of VRE and other multi-drug resistant microorganisms. These efforts must be frequently repeated and reinforced because new workers are constantly being hired, and adherence to the daily tasks required for isolation practices tends to fade over time. This requirement is most important on units or in facilities with high rates of VRE colonization and infection (Bonten, et al., 1998).

Role of the Clinical Microbiology Laboratory

The prompt and accurate identification of antibiotic-susceptible and antibiotic-resistant enterococci is essential to establishing diagnoses, selecting effective therapy, and instituting infection control measures. The clinical microbiology laboratory must employ techniques to identify enterococci to the species level and perform accurate susceptibility testing. In addition to routine testing, laboratories should evaluate all isolates from blood and sterile body sites for high-level streptomycin and gentamicin resistance, and isolates from all sites for vancomycin resistance (Cetinkaya, Falk, & Mayhall, 2000). Routine susceptibility testing for linezolid, daptomycin, and quinupristin/dalfopristin may be necessary at some facilities.

For VRE, the Clinical and Laboratory Standards Institute guidelines recommend standard broth macrodilution or disk diffusion methods for vancomycin-susceptibility testing (Clinical and Laboratory Standards Institute, 2013; Jenkins & Schuetz, 2012). Disk diffusion and E tests should be held for 24 h to obtain accurate readings. Isolates with intermediate zones on disk testing should be tested by an MIC method and further evaluated to the species level, so that non-*E. faecalis* and non-*E. faecium* isolates are identified, and this information should be used to guide infection control measures. Finally, the laboratory must notify the physician and nursing staff and/or infection control personnel when VRE isolates are found, so that appropriate isolation precautions can be promptly instituted.

Culture-based and/or molecular methods are used to perform active surveillance for VRE (Malhotra-Kumar, et al., 2008). Although culture-based methods are slower than molecular-based screening techniques, isolates from cultures have the advantage of being available for further study. However, the time to complete conventional cultures is two to three days, which allows for the potential spread of VRE prior to instituting barrier precautions. Several rapid diagnostic tests for VRE that decrease the time to detection have been approved and may help reduce the risk for transmission (Malhotra-Kumar, et al., 2008). Culture still remains the most commonly used method for screening stool for VRE, although new molecular screening methods are increasing in popularity.

Selective agars that identify VRE in stool samples include *Campylobacter* medium with vancomycin at 10 μg ml^{-1} and *Campylobacter* medium prepared in bile esculin azide agar with vancomycin at 6 μg ml^{-1} (Shigei, Tan, Shiao, de la Maza, & Peterson, 2002). Most VRE screening agars require 24 to 48h of incubation prior to the preliminary identification of colonies, and confirmatory identification and susceptibility testing can take up to five additional days. Chromogenic media for the direct detection of VRE (such as CHROM-agar, chromID, and Spectra VRE media) can reduce turnaround times through early visual identification of colonies (Jenkins, Raskoshina, & Schuetz, 2011; Peltroche-Llacsahuanga, Top, Weber-Heynemann, Lütticken, & Haase, 2009). However, properly assigning differential colony color can be difficult at times, and may require additional biochemical testing. These media all have adequate sensitivity and specificity for VRE screening, although performance generally improves when overnight broth enrichment in liquid media is used prior to plating.

PCR is a sensitive and rapid molecular approach for identifying VRE isolates. Although collecting stool as specimens for these assays is convenient, stool can contain PCR inhibitors that interfere with test results. Therefore, perirectal or perianal swabs are often recommended. Recently, the BD GeneOhm VanR (BD

Diagnostics, Spark, MD) and Xpert *vanA/vanB* (Cepheid, Sunnydale, CA) assays were approved for the detection of isolates containing *vanA* and *vanB* genes. These tests can provide results in two to four hours. Any increase in diagnostic speed, however, comes at a greater financial cost than that of culture methods.

Eradication of Colonization

The overall elimination of GI tract colonization with VRE is an attractive prospect for decreasing the spread of these pathogens and lessening the incidence of infection among at-risk patients. Attempts to eliminate VRE from the GI tract, however, have proven to be ineffective with a variety of oral antimicrobials, including bacitracin, gentamicin, tetracycline, novobiocin, rifampicin, and ramoplanin (Kauffman, 2003). In addition, decolonization regimens have not always been well tolerated. Although some patients have been successfully decolonized, the duration of decolonization has typically been transitory, with VRE often reappearing within several days or weeks. Recolonization most often occurs in patients who are also receiving anti-anaerobic antibiotics (Baden, et al., 2002). Clearly, novel approaches will be needed to achieve the goal of long-term VRE decolonization.

Hemodialysis Centers

Dialysis patients have high rates of VRE colonization (D'Agata, Green, Schulman, Li, Tang, & Schaffner, 2001; Roghmann, et al., 1998), and patients who have been hospitalized and those who have been treated with vancomycin are more likely to be colonized. Restricting the use of vancomycin is an important measure in a specific setting that could help decrease the selective pressure for growth of VRE. Earlier removal of vascular access lines, when feasible, helps decrease the incidence of infection of these catheters and lessen the need for prolonged courses of vancomycin. For dialysis patients who are VRE-colonized but continent, there is no need for additional infection control measures beyond the standard precautions.

Long-Term Care Facilities

The epidemiology of VRE in long-term care facilities differs from that in the acute care settings. Bonilla et al. (Bonilla, et al., 1997) observed VRE rectal colonization rates that varied from 9–22% during a 21-month period. However, transmission of VRE to roommates appeared to be uncommon, as did VRE infections, in this setting. Indeed, VRE infections were not noted until colonized patients were transferred back to an acute care facility for an underlying medical condition (Bonilla, et al., 1997).

Recommendations for infection control for VRE in the long-term care setting have been provided by the Long-Term Care Committee of the Society for Healthcare Epidemiology of America (Benenson, et al., 2009). These recommendations carefully consider the unique mission of long-term care facilities, which become homes for many residents. Because long-term care residents who are colonized with one resistant organism are often colonized with other resistant organisms (Terpenning, Bradley, Wan, Chenoweth, Jorgensen, & Kauffman, 1994), and because strict contact precautions are often impractical in these settings, recommendations for colonized residents with any antibiotic-resistant organism simply consist of standard precautions. Specific recommendations include:

i. A private room for colonized patients, when possible, although it is acceptable to allow a patient colonized with VRE and continent of stool to share a room with another patient, as long as that patient is not severely immunocompromised or has open wounds.
ii. As long as VRE-colonized patients are continent of stool, they may leave their room and participate in group events within and outside the facility.
iii. The appropriate use of gloves and careful hand washing play a primary role in the prevention of VRE transmission to other residents.
iv. Surveillance cultures are not useful unless an outbreak occurs.

v. Knowledge of VRE status should be given when a resident is transferred, but VRE colonization should not preclude transfer to or from a long-term care facility or an acute care hospital.
vi. Suggestions regarding healthcare worker education about VRE and prudent use of vancomycin are the same as in an acute-care facility.

Outpatient Settings

Healthcare continues to shift toward the greater use of outpatient settings, which include surgical centers, infusion centers, dialysis units, and ambulatory care clinics. Patients colonized by VRE in acute care facilities can become a reservoir for VRE in outpatient settings. However, isolation precautions similar to those carried out in hospitals are neither possible nor practical in most of these settings, and no current data show that they would have an impact on the spread of VRE. This is not to understate risks for VRE infection that undoubtedly exist in outpatient clinics, as posed by the devices, protocols, and therapies used in these settings (Maki & Crnich, 2005). At a minimum, some experts (Herwaldt, Smith, & Carter, 1998) recommend an alert to healthcare workers when VRE-positive patients are scheduled for clinic visits, so that VRE precautions can be instituted where appropriate. Such a strategy is perhaps best justified in outpatient clinics for high-risk patients, such as stem cell transplant recipients, but would be impractical in many outpatient settings.

Home Care

Transmission of VRE to caregivers within a home setting has rarely been reported (McDonald, Kuehnert, Tenover, & Jarvis, 1997). Although VRE colonization of the GI tract has been reported for healthcare workers and healthy adults in the United States and Europe (D'Agata, Jirjis, Gouldin, & Tang, 2001; Goossens, 1998), transmission to healthy caregivers with normal colonization resistance should be low, with colonization posing virtually no risk for VRE infection. Standard precautions (namely, consistent hand hygiene and use of gloves for potential exposure to bodily fluids) should be sufficient.

Treatment

The treatment of enterococcal infections can be difficult. *Enterococcus* species are intrinsically resistant to many antimicrobial agents, including cephalosporins, clindamycin, semisynthetic penicillinase-stable penicillins, and aminoglycosides among others, and have the capacity to acquire resistance genes and mutations (see Enterococcal infection) (Arias & Murray, 2012). In addition, compounds that inhibit the cell wall synthesis—and are considered bactericidal against other Gram-positive cocci—are usually only bacteriostatic against enterococci (Krogstad & Pargwette, 1980). This issue is important when treating life-threatening infections, such as endocarditis, that require bactericidal agents to effect a cure. For enterococci, this involves a combination of agents that can synergistically confer bactericidal activity. *In vitro* synergism is defined as a 100-fold or greater increase in killing at 24h by a combination of agents compared to either agent used alone (Arias & Murray, 2008).

Treatments of enterococcal infections vary, depending on several factors:

i. Is the causative organism susceptible to β-lactams, aminoglycosides, and glycopeptides, or is it resistant to various combinations of these antimicrobial classes?
ii. Is the infection monomicrobial or polymicrobial?
iii. Does the infection involve heart valves or other endovascular structures?

Antibiotic-Susceptible Nonendocarditis Enterococcal Infections

For susceptible isolates, ampicillin and penicillin remain the drugs of choice for enterococcal infections, other than endocarditis, in nonallergic patients. Monomicrobial enterococcal infections, such as urinary tract infections or non-endocarditis bacteremia, can be treated with penicillin or ampicillin alone. Skin and

subcutaneous infections and intra-abdominal or pelvic infections rarely yield only enterococci upon culture. Treatment of these polymicrobial infections can be accomplished with a combination of ampicillin and other antibiotics that are effective against a wide range of anaerobic and aerobic Gram-negative bacilli and staphylococci. A simpler alternative in those situations is to use a single agent, such as ampicillin-clavulanic acid or piperacillin-tazobactam, that combines a β-lactamase inhibitor with a β-lactam agent. A glycopeptide, either vancomycin or teicoplanin, can be used as a single agent to treat simple enterococcal infections when the patient has a serious allergy to penicillins. Nitrofurantoin has activity against enterococci, but should only be used to treat lower-tract urinary infections. Although *in vitro* susceptibility studies often show susceptibility to trimethoprim-sulfamethoxazole, this drug is not effective *in vivo* because enterococci circumvent the mechanism of drug inhibition by utilizing host folates (Zervos & Schaberg, 1985). Finally, quinolones are not particularly effective against enterococci and should not be used for serious infections (Zervos, Bacon 3rd, Patterson, Schaberg, & Kauffman, 1988).

Endocarditis Caused by *Enterococcus faecalis*

Most *E. faecalis* isolates remain susceptible to penicillin and aminopenicillins (Murray B. E., 1992). The combination of a cell wall-active agent and an aminoglycoside remains the standard of care (Baddour, et al., 2005; Habib, et al., 2009). Aminopenicillins are considered the β-lactams of choice as the concentrations required to inhibit enterococci are about half of those of penicillin (Murray B. E., 2000). It is important to note that in cases of serious infection, tests for β-lactamase production should be performed using a higher bacterial inoculum or a penicillinase-detection method (Clinical and Laboratory Standards Institute, 2013). An aminopenicillin combined with a β-lactamase inhibitor (*e.g.*, sulbactam) should be used if a β-lactamase–producing *E. faecalis* is encountered.

Of the available aminoglycosides, gentamicin is generally preferred over streptomycin, as the synergistic agent used with either an aminopenicillin or a glycopeptide. Gentamicin had been recommended because of its greater synergistic effect with cell-wall active agents (Harwick, Kalmanson, & Guze, 1973; Watanakunakorn & Bakie, 1973), although some have reported streptomycin as being more effective than gentamicin (Wilson, Wikowske, Wright, Sande, & Geraci, 1984). Compared to gentamicin, streptomycin is more difficult to obtain and serum concentrations for pharmacokinetic monitoring are not readily available. In penicillin-allergic patients, vancomycin or teicoplanin can be combined with an aminoglycoside. This combination should be reserved only for patients with serious allergies, and the duration of therapy should be 6 weeks (Baddour, et al., 2005).

The dosing of aminoglycosides is somewhat controversial (Falagas, Matthaiou, & Bliziotis, 2006; Graham & Gould, 2002), and until controlled clinical trials are conducted to address this issue, once-daily dosing should not be used in the treatment of enterococcal endocarditis (Baddour, et al., 2005). Gentamicin should be administered every 8 hours, with dosing adjusted to reach a peak serum level of approximately 3 μg ml^{-1} and a trough of <1 μg ml^{-1}. Streptomycin should be administered every 12 hours, with a target peak of 20 to 35 μg ml^{-1} and a trough <10 μg ml^{-1} (Baddour, et al., 2005). The duration of therapy for native valve endocarditis is at least 4 weeks, with 6 weeks favored for those with symptoms for greater than 3 months, or for those with relapse or mitral valve involvement (Wilson, Wikowske, Wright, Sande, & Geraci, 1984). Prosthetic valve endocarditis should be treated for 6 weeks (Rice, Calderwood, Eliopoulos, Farber, & Karchmer, 1991). The prolonged duration of therapy with aminoglycosides for enterococcal endocarditis comes with a significant drawback of increased toxicity in the older populations at risk for this infection. One study suggested a shorter course of aminoglycoside for patients who might be limited by toxicity (Olaison & Schadewitz, 2002).

High-Level Aminoglycoside-Resistant (HLR) Enterococcal Infections

For most simple enterococcal infections, the presence of HLR to aminoglycosides does not influence a treatment regimen, since β-lactam monotherapy is adequate and aminoglycosides are not indicated. For bacteremia, there is no benefit to adding an aminoglycoside. Outcomes are not significantly different for patients who are

bacteremic, with enterococci exhibiting HLR to aminoglycosides compared to those with bacteremia with fully susceptible strains (Caballero-Granado, et al., 1998; Patterson, et al., 1995; Watanakunakorn & Patel, 1993).

The development in E. faecalis isolates of HLR to gentamicin (MIC ≥500 μg ml-1 on brain-heart agar) and to streptomycin (MIC ≥2000 μg ml-1 on brain-heart agar or ≥1000 μg ml-1 in brain-heart infusion), eliminates synergism of aminoglycosides with β-lactams, and hence a bactericidal regimen. It is noteworthy that HLR resistance to gentamicin precludes the use of all clinically useful aminoglycosides, except streptomycin (Chow, 2000). E. faecium strains express an aminoglycoside-modifying enzyme that eliminates synergism between cell-wall inhibitors and aminoglycosides, including kanamycin, netilmycin, and tobramycin. Gentamicin, however, is not affected by this enzyme (Costa, Galimand, Leclercq, Duval, & Courvalin, 1993).

A bactericidal regimen for endocarditis caused by enterococci with HLR to both streptomycin and gentamicin has not yet been established, and as a result, treatment in this situation can be difficult (Chow, 2000). Continuous infusion, high-dose ampicillin monotherapy has been attempted based on animal experiments, but failures of this regimen have been reported (Landman & Quale, 1997). Although the optimal duration of therapy is unknown, given the risk of relapse, therapy beyond 6 weeks and early surgical intervention should both be considered (Eliopoulos, 1993).

In vitro and *in vivo* data shows synergism between amoxicillin or ampicillin and ceftriaxone against *E. faecalis* (Gavaldà, et al., 2007; Gavaldà, et al., 1999; Mainardi, Gutmann, Acar, & Goldstein, 1995). *In vivo* data indicate that for endocarditis due to *E. faecalis* without high-level aminoglycoside resistance, the combination of ampicillin and ceftriaxone is comparable in efficacy to that of ampicillin and gentamicin. The triple combination of ampicillin, ceftriaxone, and gentamicin is not superior to these regimens (Gavaldà, et al., 2003). A recent open-label trial showed that patients with endocarditis due to *E. faecalis* with HLR to aminoglycosides, treated with ampicillin and ceftriaxone, had similar mortality compared to historical controls (Gavaldà, et al., 2007). Of note, the observed synergism between β-lactams against *E. faecalis* does not apply to *E. faecium* (Mainardi, Gutmann, Acar, & Goldstein, 1995). Other therapeutic options for treating *E. faecalis* endocarditis due to strains with HLR to aminoglycosides remain anecdotal, and include combinations of imipenem, vancomycin, and ampicillin (Antony, Ladner, Stratton, Raudales, & Dummer, 1997); a fluoroquinolone and ampicillin (Tripodi, Locatelli, Adinolfi, Andreana, & Utili, 1998); and ciprofloxacin, ampicillin, and gentamicin (Sacher, Miller, Landau, Sacher, Dixon, & Dietrich, 1991).

Vancomycin-Resistant Enterococcal Infections

Infections due to enterococcal strains that express glycopeptide resistance pose a significant challenge, as therapeutic options are limited and somewhat empirical. Given the limitations of antimicrobial therapy, removal of infected foci, such as intravenous catheters, and drainage of abscesses remain important adjunctive measures.

For infections due to penicillin-susceptible VRE, ampicillin remains the drug of choice. Nitrofurantoin, fosfomycin, and doxycycline have intrinsic activity against enterococci, including VRE, and are potential oral options for treating simple VRE infections, such as cystitis (Heintz, Halilovic, & Christensen, 2010). Linezolid and daptomycin are reserved for serious VRE infections that are resistant to penicillins. Other antimicrobials, such as quinupristin/dalfopristin and tigecycline, should be evaluated on a case-by-case basis, due to toxicity concerns . Infections of the urinary tract, skin, or soft tissues due to VRE may respond to drugs such as doxycycline or fluoroquinolones, although susceptibility patterns vary (Landman & Quale, 1997). The use of fluoroquinolones as monotherapy for serious infections, although a possible option for uncomplicated urinary tract infection, is usually not recommended (Arias & Murray, 2008; Zervos, Bacon 3rd, Patterson, Schaberg, & Kauffman, 1988). Finally, trimethoprim-sulfamethoxazole should not be used to treat enterococcal infections, regardless of their susceptibility testing.

Endocarditis caused by VRE poses a great challenge, since there are no reliable bactericidal combinations of antibiotics available. Combinations of agents have been studied in animal models of VRE endocarditis, but results typically depend on the susceptibilities of the strains that are studied, and may not necessarily translate into effective therapy for human infections. In general, clinical experience in treating VRE endocarditis remains limited (Forrest, Arnold, Gammie, & Gilliam, 2011; Stevens & Edmond, 2005). A consultation with a cardiac surgeon for early valve replacement is highly recommended. Some of the varied antimicrobial approaches to the management of these infections are described below.

While most *E. faecalis* isolates expressing vancomycin resistance remain susceptible to ampicillin, the majority of *E. faecium* isolates are resistant to both. For enterococci, the Clinical and Laboratory Standards Institute defines ampicillin resistance as growth at <16 μg ml^{-1} (Clinical and Laboratory Standards Institute, 2013). Endocarditis due to VRE isolates with ampicillin MICs ≤64 μg ml^{-1}, however, have been successfully treated using higher-than-approved doses of ampicillin (*e.g.*, 18-30 gm day^{-1}), usually in combination with an aminoglycoside (Forrest, Arnold, Gammie, & Gilliam, 2011; Murray B. E., 2000). The toxicity of these doses remains unclear, and treatment failures do occur.

Daptomycin

Daptomycin is a bactericidal lipopeptide used to treat skin and soft tissue infections caused by susceptible Gram-positive bacteria, including vancomycin-susceptible *E. faecalis*. An additional indication is for the treatment of *S. aureus* bacteremia and right-sided endocarditis (Enoch, Bygott, Daly, & Karas, 2007). Although daptomycin is not FDA approved for infections caused by *E. faecium* or vancomycin-resistant *E. faecalis*, the bactericidal activity of this agent at doses of 8-10 mg kg^{-1} suggests it could be useful in multi-drug resistant enterococcal endocarditis (Arias, Torres, Singh, Panesso, Moore, & Murray, 2007; Dandekar, Tessier, Williams, Nightingale, & Nicolau, 2003). To date, available data are limited to case reports, which suggest that daptomycin can be effective at higher-than-approved doses of 6 mg kg^{-1} day^{-1} and in combination with other agents (Arias, Torres, Singh, Panesso, Moore, & Murray, 2007; Jenkins I. , 2007; Stevens & Edmond, 2005).

Non-susceptibility of enterococci to daptomycin (MIC >4 μg ml^{-1} by broth dilution, E-test, or zones of inhibition <11 mm by disk diffusion) remains infrequent (Sabol, Patterson, Lewis II, Aaron, Cadena, & Jorgensen, 2005), with an overall prevalence of 0.6% among clinical isolates in a recent series (Kelesidis, Humphries, Uslan, & Peques, 2011). Of these isolates, most were VRE (93.3%) and *E. faecium* (88%). All were from bloodstream infections, with 15% causing endocarditis. Daptomycin resistance can be selected for both *in vitro* and *in vivo* and arises from mutations in diverse genes with putative roles in the biogenesis, permeability, and potential of cell membranes (Arias, et al., 2011; Palmer, Daniel, Hardy, Silverman, & Gilmore, 2011). Limiting the development of resistance to daptomycin may be attempted by using higher than approved doses or combining this lipopeptide with other agents, as described above.

Linezolid

Linezolid is an oxazolidinone used to treat Gram-positive infections, including VRE bacteremia and urinary tract infection. The mechanism of action involves inhibiting the 30S ribosome initiation complex, which renders the drug bacteriostatic against enterococci. Because of this unique mechanism, no cross-resistance with other available agents has been described. Linezolid is active against both E. faecium and E. faecalis (Arias & Murray, 2008). A clinical advantage of linezolid involves an oral and formulation with oral bioavailability approaching 100%. However, myelosuppression, especially thrombocytopenia, is a serious complication that occurs on occasion after prolonged use (Green, Maddox, & Huttenbach, 2001).

Based on anecdotal case reports, and despite its bacteriostatic nature, linezolid has been recommended as a treatment option for VRE endocarditis (Baddour, et al., 2005). Experience using linezolid for VRE bacteremia shows microbiological cure rates of 85.3%, with clinical successes at 78% (Birmingham, Rayner, Meagher, Flavin,

Batts, & Schentag, 2003). The efficacy of linezolid in treating endocarditis due to vancomycin-susceptible and vancomycin-resistant *E. faecalis* and *E. faecium,* showed 7 of 8 cases either responded to or were cured by this agent (Falagas, Manta, Ntizora, & Vardakas, 2006). However, treatment failures have also been reported (Tsigrelis, Singh, Coutinho, Murray, & Baddour, 2006). Enterococcal resistance to linezolid remains uncommon (Biedenbach, Farrell, Mendes, Ross, & Jones, 2010). The majority of these bacteria have four to six copies of the 23S rRNA gene—nearly all of which must be mutated in order for resistance to develop (Ntokou, et al., 2012). The development of linezolid resistance has been linked to prolonged and/or inappropriate use of this antibiotic, with the subsequent spread of resistant clones. Of note, linezolid-resistant enterococci have been isolated from patients without previous exposure to the antibiotic (Ntokou, et al., 2012). To minimize the emergence of resistance, linezolid should be restricted to appropriate indications only and used in courses of therapy as short as feasible, and resistance testing should be performed based on local epidemiology, host risk factors, and/or when treatment failures occur.

Streptogramins

Quinupristin/dalfopristin is a combination agent that consists of streptogramin A (70% dalfopristin) and B (30% quinupristin), with proven efficacy for VRE infection due to *E. faecium* (Linden, et al., 2001). The efficacy of quinupristin/dalfopristin in treating VRE infections in several prospective multicenter studies showed overall showed success rates of 66% (Linden, et al., 2001; Moellering, Linden, Reinhardt, Blumberg, Bompart, & Talbot, 1999). All strains of *E. faecalis* are intrinsically resistant to quinupristin/dalfopristin. These agents work to synergistically inhibit protein synthesis through the 50S ribosomal subunit, and are bacteriostatic as a result. Quinupristin/dalfopristin is poorly tolerated in a minority of patients, due to arthralgias and myalgias. Phlebitis is another common problem that can be avoided by administering the drug through a central venous catheter. Resistance to quinupristin/dalfopristin can occur by target modification, drug inactivation, or active efflux. Clinical isolates of *E. faecium* with resistance to quinupristin/dalfopristin are rare (MIC ≥4 μg ml-1), perhaps because multiple mechanisms are needed to achieve this level of resistance (Thal & Zervos, 1999). Despite this, a high percentage (28.9%) of unrelated E. faecium isolates from Greece was recently noted to have a reduced susceptibility to quinupristin/dalfopristin. These isolates were from patients without exposure to the antibiotic, and were not associated with the veterinary use of virginiamycin, a feed additive used in food animals that promotes streptogramin resistance (Karanika, et al., 2008). Both the acquisition of resistance by E. faecium and superinfection with E. faecalis have been described during treatment with quinupristin/dalfopristin (Chow, Davidson, Sanford 3rd, & Zervos, 1997; Chow, Donahedian, & Zervos, 1997).

The data for using quinupristin/dalfopristin in the treatment of endocarditis due to VRE is limited to anecdotal reports (Bethea, Walko, & Targos, 2004; Furlong & Rakowski, 1997; Mastumura & Simor, 1998). The combination of quinupristin/dalfopristin, doxycycline, and rifampin appears synergistic in vitro and was successfully used to treat a patient with aortic valve endocarditis (Mastumura & Simor, 1998). In another case, a neutropenic patient with persistent bacteremia due to ampicillin-resistant VRE was successfully treated with high-dose ampicillin (24 gm day-1) and quinupristin/dalfopristin (Bethea, Walko, & Targos, 2004). Recently, the package insert for quinupristin/dalfopristin was revised to exclude VRE, with interpretive breakpoints for *E. faecium* deleted.

Lipoglycopeptides

Lipoglycopeptides are a new class of antibiotics that inhibit the bacterial cell wall synthesis like glycopeptides and also disrupt the cell membrane integrity (Zhanel, et al., 2010). Oritavancin, telavancin, and dalvabancin are currently available lipoglycopeptides. They exhibit activity against vancomycin-susceptible enterococci species, and VanB-containing enterococci, although telavancin has marginal activity against VanB isolates. Only oritavancin is active against VanA-containing enterococci, as it can bind to the D-Ala-D-Lac peptidoglycan

precursor. These agents are not inferior to comparator agents in clinical trials (Zhanel, et al., 2010). Pending further data, lipoglycopeptides are not routinely recommended for enterococcal infections.

Other antibiotics

Tigecycline is a bacteriostatic agent that binds the 30S ribosomal subunit, and inhibits protein synthesis. It is a broad-spectrum antibiotic that is approved for the treatment of skin and soft tissue infections caused by susceptible organisms, including *E. faecalis.* It is not approved for infections caused by *E. faecium* regardless of susceptibilities (Rubinstein & Vaughan, 2005). Although tigecycline has been successfully used in combination with daptomycin to treat endocarditis due to VRE (Jenkins I. , 2007), its use for serious infections is considered contraindicated because of excess deaths and noncures in multiple noninferiority studies (Prasad, Sun, Danner, & Natanson, 2012). Teicoplanin, a glycopeptide with a mechanism of action similar to vancomycin, is effective against some VanB-resistant VRE. However, resistance to teicoplanin has developed in some VanB isolates during therapy (Hayden, Trenholme, Schultz, & Sahm, 1993). This agent, which is not commercially available in the United States but widely used in Europe, is not often prescribed for the treatment of enterococcal endocarditis.

Enterococci as probiotics

Probiotics are naturally occurring microorganisms that confer health benefits by supplementing host commensal microbiota, modulating immunity, enhancing intestinal barrier function, or altering pain perception (Forchielli & Walker, 2005). *E. faecalis* and *E. faecium* are human intestinal commensals that also have been used as probiotics, as well as in food production (see Enterococcus Diversity, Origins in Nature, and Gut Colonization). However, no large, randomized, placebo-controlled clinical trials have been conducted to assess their safety or efficacy. As a result, no enterococcal probiotic has been approved by the FDA for the treatment, cure, or amelioration of any human disease. In 2007, the European Food Safety Authority determined that enterococci do not meet the standard for the "Qualified Presumption of Safety" (EFSA Scientific Committee, 2007). Many virulence traits that generally suggest enterococci as poor choices for probiotic therapy support these concerns. In addition, many enterococci have acquired resistance to clinically important antibiotics encoded on a wide variety of conjugative plasmids, transposons, and bacteriophages (see Enterococcal infection). Strains of *E. faecalis* or *E. faecium* should only be considered as potential probiotics when they are shown to lack virulence traits (such as cytolysin, gelatinase, serine protease, aggregation substance, capsular polysaccharide, biofilm production, extracellular superoxide production, and enterococcal surface protein, among others), are unable to translocate the intestinal mucosa, and remain susceptible to phagocytic killing. In addition, any such putative probiotic strain should have limited ability to exchange DNA *in vivo*. No such strain has yet been identified and, until then, alternatives should be explored as probiotics.

Summary and Conclusions

Enterococci are associated with a variety of different clinical syndromes, including bacteremias, endocarditis, and skin or soft tissue and urinary tract infections. The emergence of resistance has made clinicians keenly aware of these opportunistic pathogens. Molecular methods have delineated the epidemiology of VRE and have conclusively demonstrated healthcare-associated acquisition and transmission.

Colonization with VRE occurs approximately 10 times more frequently than actual infection, and occurs in patients with severe underlying illness or who are receiving antibiotics with broad-spectrum anti-anaerobic activity. Infection control efforts have been established to limit the spread of this pathogen. Treatment of serious enterococcal disease requires a synergistic combination of a cell-wall active agent and an aminoglycoside. The relatively few antimicrobial agents available to treat serious VRE infections make therapeutic decision-making for these cases quite challenging. Although enterococci are generally considered safe for use in food production,

their role as probiotics is not established, and alternatives should be sought, due to their involvement in therapeutically challenging diseases.

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