Vancomycin-Resistant Enterococci

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KEYWORDS

- Vancomycin • Enterococcus • Resistant pathogen • Gram-positive cocci
- Critical care • Infection

KEY POINTS

- Enterococcal infection can be caused by vancomycin-susceptible strains, mainly *E faecalis*, and vancomycin-resistant strains, mainly *E faecium*.
- In penicillin and/or ampicillin and aminoglycoside-susceptible strains, the treatment of severe infections (eg, bacteremia, endocarditis, meningitis, brain abscess) is based on the combination of a β-lactam or vancomycin with an aminoglycoside to achieve bactericidal activity.

INTRODUCTION

Enterococci, formerly called group D streptococci, have become resistant to many antibiotic agents, including vancomycin. Vancomycin-resistant enterococci (VRE) infections are increasingly common and difficult to treat, appearing usually as long-lasting hospital outbreaks that present tremendous challenges for infection control.

Enterococci are equipped with a variety of intrinsic (ie, naturally occurring) antibiotic resistances, but are also capable of acquiring new resistance genes and/or mutations. The combination of high-level resistance to ampicillin, vancomycin, and aminoglycosides is now common with hospital-acquired *Enterococcus faecium*.

The major infections caused by enterococci in general and VRE in particular include urinary tract infections (UTI), wound infections, intraabdominal infections secondary to a perforated viscous or after surgery, cholecystitis, bacteremia, endocarditis, and rarely meningitis. UTI can be cured with a single (bacteriostatic) agent whereas bacteremia, endocarditis, and meningitis require a bactericidal agent or drug combination. Some acute infections due to VRE may be treated to resolution, although in some cases colonization may persist indefinitely.

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CLINICAL SYNDROMES
Bacteremia and Endocarditis

Bacteremia due to VRE is rarely primary, common sources are the gastrointestinal tract, the urinary tract, intravascular catheters, and wounds or burns. The relative risk of endocarditis in patients with E faecalis bacteremia is higher than with E faecium, particularly if the infection is community-acquired and there is an underlying valvulopathy. Septic shock in the setting of enterococcal bacteremia is uncommon and it should raise suspicion for a polymicrobial infection.

On occasion, Enterococcus represents a contaminant on blood culture. For that reason, positive blood cultures warrant therapy only when the clinical risk of infection and/or the adverse clinical impact of infection is high. Antimicrobial therapy for enterococcal bacteremia is warranted when there are more than two positive blood cultures, a single positive blood culture accompanied by signs of sepsis, or a single positive blood culture together with a positive enterococcal culture from another usually sterile site. In the setting of a single positive blood culture for an Enterococcus, particularly E faecalis, in a patient with preexisting prosthetic heart valve, the authors favor initiating treatment while awaiting results of additional blood cultures; other clinicians favor withholding therapy pending these results. The optimal duration of therapy in this setting is not known; 1 to 2 weeks may be appropriate for uncomplicated bacteremia. For circumstances in which an intravascular catheter is the likely source of the bacteremia, catheter removal alone may be sufficient. However, if febrile, most patients should be empirically started on antibiotics and, after additional cultures are obtained, such therapy can generally be discontinued after 5 to 7 days if symptoms have resolved. Although several studies suggest that there is no advantage of combination therapy compared with monotherapy, some investigators favor combination therapy in the setting of valvulopathy and/or critical illness.[1,2] The optimal duration of antimicrobial therapy for treatment of enterococcal bacteremia is uncertain. For uncomplicated infection, 5 to 7 days of therapy is likely adequate. Therapy should be extended in the setting of sustained high-grade bacteremia and in the setting of a prosthetic valve, even in the absence of echocardiography evidence for vegetation.

Meningitis

Enterococci rarely cause meningitis in normal adults. Most cases of enterococcal meningitis occur in patients with head trauma, neurosurgery, intraventricular or intrathecal catheters, or anatomic defects of the central nervous system.[3] Enterococcal meningitis is also seen in the setting of endocarditis, AIDS, hematologic malignancies, and in neonatal sepsis, in association with Strongyloides hyperinfection, shunt infection, and so forth.[4,5]

The optimal approach for treatment of enterococcal meningitis is not certain, although most clinicians agree that combination therapy is preferable compared with monotherapy. For patients failing to respond to systemic antibiotics, intraventricular vancomycin, gentamicin, or quinupristin-dalfopristin (if E faecium) may be useful. Daptomycin and tigecycline have poor central nervous system penetration and need to be administered intrathecally.[5]

Treatment of enterococcal meningitis caused by VRE E faecium is a difficult challenge; intravenous (IV) linezolid or IV plus intraventricular quinupristin-dalfopristin are reasonable choices. Although experience is limited, daptomycin has also been administered by the intraventricular route. If the organism is susceptible, rifampin may also be a useful adjunctive agent.[5–7]

NEWER ANTI-ENTEROCOCCAL ANTIBIOTICS

Newer anti-enterococcal antibiotics include linezolid, a bacteriostatic, synthetic oxazolidinone antibiotic that binds to the peptidyl transferase center of the 50S ribosome, preventing peptide bond formation, and thus the addition of new amino acids (**Table 1**). In one study, linezolid was associated with cure of 81% of 500 subjects with VRE infections[8] and, in another report, the cure rate of VRE bacteremia and other severe infections in organ-transplant subjects was 63%.[9] Resistance development during therapy with linezolid has been reported to result in clinical failure.[10] Adverse effects of linezolid use, particularly in courses exceeding 28 days, include thrombocytopenia (particularly common in the setting of renal failure), anemia, lactic acidosis, peripheral neuropathy, and ocular toxicity. When administered with serotonergic agents, linezolid can induce serotonin syndrome due to its inhibition of monoamine oxidase.[11] Blood counts and serum chemistries should be monitored at least weekly during linezolid therapy.

Daptomycin is a cyclic lipopeptide bactericidal antibiotic that causes depolarization of the bacterial cell membrane. The daily dose for severe infections is 8 to 12 mg/kg IV once daily (for skin and soft tissue infections the dose is 4 mg/kg). Several investigators favor the use of daptomycin for treatment of *E faecium* infections that are vancomycin-resistant. The daptomycin minimal inhibitory concentrations (MICs) for *E faecium* are higher than for *E faecalis*. There are no FDA-approved daptomycin MIC breakpoints for *E faecium*, but it has been suggested that an MIC greater than 4 µg/mL is the cutoff for nonsusceptible isolates. Patients receiving daptomycin should be evaluated regularly for clinical evidence of myopathy, through serial measurements of serum creatine kinase (at least weekly). The drug should be discontinued in patients with symptomatic myopathy and creatine phosphokinase (CPK) greater than or equal to five times the upper limit of normal (ULN) or in asymptomatic patients with CPK greater than or equal to ten times ULN.[12]

Tigecycline is a glycylcycline antibiotic derived from minocycline with in vitro activity against many gram-positive pathogens (ie, methicillin-resistant *Staphylococcus aureus* [MRSA], VRE, and penicillin-resistant *Streptococcus pneumoniae*), many gram-negatives (excluding *Pseudomonas*, *Proteus*, *Providencia*, and *Morganella* species), anaerobes, and atypical species. Although tigecycline is not approved by the Food and Drug Administration (FDA) for VRE infections, it seems that VRE would also be susceptible to tigecycline, based on in vitro and animal model data.[13] The usual dose is 100 mg IV loading dose followed by 50 mg twice a day. Some concerns were raised by clinical trials with tigecycline in skin and soft tissue infections, pneumonia, and intraabdominal infections showing higher mortality in tigecycline-treated patients than in the control arms. Major adverse effects include nausea and vomiting. Tigecycline may be useful for patients with VRE infection who are intolerant of other agents or when VRE are present along with other pathogens that are susceptible to tigecycline. It may also be useful in the setting of renal insufficiency. Tigecycline has been used in combination with high-dose daptomycin for severe nonresponding VRE infections.[14]

Quinupristin-dalfopristin is a mixture of streptogramin antibiotics with FDA approval for the treatment of VRE *E faecium* infections. It has poor activity against *E faecalis*. Central venous access requirements and adverse effects limit the use of quinupristin-dalfopristin. Adverse effects include metabolic interactions, severe myalgias, arthralgias, nausea, and hyperbilirubinemia. The agent should be administered into a central vein at a dose 22.5 mg/kg every 24 hours divided into three equal doses.

Teicoplanin is not available in North America but is in use in Europe and some South American countries. It has in vitro activity against *E gallin*arum and *E casseliflavus*

Table 1
New agents active against VRE

Antibiotic	Activity	Indications	Dose in Patients Without Renal Failure	Common Adverse Effects
Linezolid	Bacteriostatic	HAP or VAP, ABSSI, gram-positive bacteremia	600 mg q 12 h	Anemia, thrombocytopenia, leukopenia, serotonin syndrome, mitochondrial toxicity, peripheral & optic neuropathy
Daptomycin	Bactericidal	ABSSI, bacteremia, endocarditis, not pneumonia	4–12 mg/kg OD	Increase in muscle enzymes, eosinophilic pneumonia
Telavancin	Bactericidal	HAP or VAP, ABSSI	10 mg/kg OD	Renal toxicity
Tedizolid[a]	Bactericidal	ABSSI	200 mg OD either IV or PO	—
Teicoplanin[b]	Bactericidal	Similar to vancomycin	6–12 mg/kg for 3 doses, then OD	Similar to vancomycin except no renal toxicity
Tigecycline	Bacteriostatic	ABSSI, intraabdominal infections, not HAP or VAP	100 mg loading dose, then 50 mg q 12 h	Nausea, vomiting, liver-function abnormalities
Quinupristin-dalfopristin	Bacteriostatic	ABSSI, bacteremia, HAP	7.5 mg/kg q 8 h IV	Thrombophlebitis, myalgia, arthralgia, nausea, hyperbilirubinemia

Abbreviations: ABSSI, acute bacterial skin and soft tissue infection; HAP, hospital-acquired pneumonia; OD, once daily; VAP, ventilator associated-pneumonia.
[a] Not marketed yet.
[b] Not used in North America.

(vanC VRE) as well as most vanB-type VRE, although it is rarely active against vanA-type VRE. Some vanB VRE mutant strains are constitutively resistant to teicoplanin. For patients with normal renal function, teicoplanin should be administered with a loading dose of 6 to 12 mg/kg every 12 hours for three doses (for serious infections), followed by 6 mg/kg to 12 mg/kg every 24 hours (for serious infections). The addition of an aminoglycoside, in the absence of high-level resistance should be considered to reduce the emergence of vanB mutants resistant to teicoplanin.

Telavancin is a lipoglycopeptide that is more potent than vancomycin against enterococci (eg, the MIC_{90} is 0.12 μg/mL), with little to no increase in MICs against vanB strains. For vanA strains, the MIC_{90} has been reported as 4 to 16 μg/mL.

ANTIBIOTIC RESISTANCE
β-Lactam and Aminoglycosides

Serious enterococcal infections, including endocarditis, cannot be treated with penicillin alone because this agent is not for enterococci. An aminoglycoside must be added to make the treatment bactericidal and, therefore, is the optimal clinical response. Recently, enterococci have acquired resistance to these agents because of mutations (eg, causing high-level resistance to streptomycin and/or to fluoroquinolones) or the acquisition of new genes carrying resistance elements. The *Enterococcus* is capable of accepting and donating resistance genes, plasmids, and transposomes by multiple mechanisms.

E faecalis, the more susceptible of the two predominant enterococcal species, is usually inhibited by 1 to 4 μg/mL of ampicillin and 2 to 8 μg/mL of penicillin; the comparable MICs for *E faecium* are 8 to 32 μg/mL. However, *E faecium* strains that are much more highly resistant to ampicillin have emerged. This high-level resistance to ampicillin is due to a nonpenicillinase mechanism. Recently, a trend toward much higher levels of resistance has been observed among nosocomial isolates, with some strains failing to be inhibited by 256 μg/mL of ampicillin or more.[15] The intrinsic resistance of *E faecium* seems to be due to the presence of a cell wall synthesis enzyme that is relatively resistant to inhibition by penicillin. This low-affinity penicillin-binding protein (PBP) is called PBP5. Higher levels of resistance to β-lactam antibiotics seem to involve increased expression of PBP5, further alterations in the PBP5 protein, and use of a β-lactam insensitive transpeptidase for cell wall synthesis.[16,17]

Enterococci are intrinsically resistant to low-to-moderate levels of aminoglycosides. However, synergism is generally seen when enterococci are exposed to a combination of an aminoglycoside with a cell wall active agent, such as penicillin or vancomycin. With the combination, there is a marked increase in killing (ie, synergy) and a bactericidal effect is achieved.

In addition to the usual increased MICs of aminoglycosides for all enterococci, a characteristic of *E faecium* is higher MICs of tobramycin (MICs 64 to 1000 μg/mL) and resistance to synergism with this aminoglycoside but not with gentamicin. Therefore, with minor exceptions, gentamicin and streptomycin, if available, are the only aminoglycosides that should be considered to achieve synergistic therapy. High-level resistance to both streptomycin and gentamicin abolishes the synergism between gentamicin or streptomycin and a cell wall active agent such as penicillin or vancomycin. Ceftriaxone has been shown to have a synergistic effect mediated by saturation of PBP2 and PBP3 when administered together with ampicillin. In high-level resistance strains causing endocarditis, the combination of ampicillin and ceftriaxone showed a clinical cure rate of 67%—better than any other antibiotic combination.[18]

Vancomycin Resistance

High-level and low-level resistance to glycopeptides can occur in enterococci. Low-level vancomycin resistance occurs with MICs 8 to 16 μg/mL. The MIC used for defining vancomycin susceptibility and resistance in enterococci greater than or equal to 32 μg/mL are vancomycin-susceptible (≤4 μg/mL, vancomycin-resistant). An MIC of 8 to 16 μg/mL is considered vancomycin-intermediate, but vancomycin therapy is not recommended for infections caused by such isolates.

High-level vancomycin resistance is the most problematic resistance of enterococci, because it often appears in strains already highly resistant to ampicillin (primarily E faecium). Vancomycin inhibits enterococci by binding to the D-alanyl-D-alanine (D-Ala-D-Ala) terminus of cell wall precursors, compromising the subsequent enzymatic steps in the synthesis of cell wall. High-level resistance to vancomycin is encoded by different clusters of genes referred to as the vancomycin-resistance gene clusters (eg, vanA, B, D, and M). The result is the replacement of D-Ala-D-Ala-terminus precursors with D-alanyl-D-lactate termini, to which vancomycin binds with significantly lower affinity, increasing the MIC of this antibiotic almost 1000-fold.[19] VanA is the most common type of vancomycin-resistance; it usually mediates higher levels of resistance than other types and causes cross-resistance to teicoplanin. The vanA gene cluster is typically found on a transposon identical or related to Tn1546, which, in turn, is often found within a plasmid.[20–23] The vanA cluster has disseminated to other bacterial species, including clinical isolates of MRSA.

Linezolid Resistance

Linezolid resistance has been reported in clinical isolates of both staphylococci and enterococci. Oxazolidinone resistance among enterococcal isolates has been increasingly documented.[24] Associated with prolonged use of the antibiotic, linezolid resistance was initially described sporadically.[25] It is evident that the emergence of linezolid resistance is associated with the heavy use of this antibiotic; however, linezolid-resistant enterococci have also been isolated from patients without previous exposure to the antibiotic.[26]

Daptomycin Resistance

Resistance to daptomycin has been reported in enterococci, including isolates from patients who have never received this antibiotic.[27] In one patient, the development of daptomycin resistance was directly linked to mutations in genes encoding several enzymes involving phospholipid metabolism as well as a membrane protein.[28]

Quinupristin-Dalfopristin Resistance

Resistance to quinupristin-dalfopristin among E faecium can occur by enzymatic modification, active transport, and target modification.[29] In the United States, some 1% to 2% of enterococci are resistant to quinupristin-dalfopristin. Full resistance in clinical isolates appears to require a combination of mechanisms. However, resistance to dalfopristin alone is sufficient to reduce efficacy of the combined antibiotic and decrease the bactericidal effect. The vatD and vatE genes, which encode acetyltransferases that inactivate dalfopristin, are frequently found in resistant E faecium isolates. These genes are found on transposable genetic elements where they are sometimes associated with the erm genes that confer parallel resistance to streptogramin B-class (quinupristin) compounds.[30] Resistance emerged during quinupristin-dalfopristin therapy in 5 out of 396 subjects with E faecium infections; four of these cases resulted in treatment failure.[31]

Tigecycline Resistance

Resistance to tigecycline has been documented in an *E faecalis* isolate recovered from the urine of a patient who received a prolonged course of tigecycline for nosocomial pneumonia.[32]

Resistant enterococcal infections remain difficult to treat. In some cases, the pathogen cannot be eradicated despite the disappearance of infectious symptoms, including in soft tissue infections, biliary disease, pancreatic abscess, and so forth. Many experts take the position that enterococci on their own can cause only a limited number of infections (eg, UTI and endocarditis) but not abdominal abscesses and soft tissue infections. The authors concur with this notion; therefore, the situation remains unresolved.

EPIDEMIOLOGY

The presence of VRE in Europe was driven by the use of glycopeptides, including avoparcin as a food additive for growth promotion in farm animals, which was subsequently banned by the European Union. In North America, VRE followed Europe but with a different relationship. Multiple epidemics of VRE infection have been described in diverse hospital settings. Currently, VRE is endemic in many large hospitals.[33,34] The rate of hospitalization with VRE in the United States doubled during 2003 to 2006 from 4.60 to 9.48 hospitalizations per 100,000 population.[35] A single VRE clone can spread within an institution. In addition, VRE strains can transfer resistance horizontally to unrelated strains. Both methods of spread can occur simultaneously in a single institution. One report using specific typing method found 45 different profiles in a single medical center where VRE had become endemic.[36] Most VRE hospital isolates are *E faecium*. Resistance was found in 60% of *E faecium* isolates compared with 2% of *E faecalis* blood isolates. Data from the United States show that resistance trends are worsening; 80% of the 987 isolates of *E faecium* and 6.9% of the 1497 isolates of *E faecalis* reported in 2006 and 2007 were vancomycin-resistant.[37] In VRE bacteremia, the prognosis is worse than that of vancomycin-susceptible enterococci. In a meta-analysis of nine studies of enterococcal bloodstream infections, 42% were due to VRE. The mortality rate was significantly higher in patients with VRE compared with vancomycin-susceptible enterococcal isolates (summary odds ratio 2.5, 95% CI 1.9–3.4).[38]

Transmission

VRE colonize the gastrointestinal tract and, owing to fecal shedding, they are found on the skin. Colonization with VRE generally precedes infection, but not all patients with colonization become infected. Persons either colonized or infected with VRE can serve as sources for secondary transmission. Transmission is determined by selective pressure due to antimicrobial use, the proportion of colonized patients, the availability of susceptible patients, and adherence to prevention efforts.[39] Transmission can occur by both direct contact (eg, the hands of health care workers) and indirectly from environmental surfaces. Modes of transmission include rectal electronic thermometers, contaminated surfaces, bedrails, telephone handpieces, EKG leads, and so forth. It has been demonstrated that VRE-contaminated hands and/or gloves of health care personnel can transmit VRE in approximately 10% of contacts with noninfected patients or surfaces.[40] Risk factors for colonization and infection include previous antimicrobial therapy. In the ICU setting, particularly, the risks include use of vancomycin and cephalosporins, as well as long-term ceftazidime,[37,41] multiple agents with a broad-spectrum of activity,[42] and administration of antibiotics active

against anaerobic organisms.[43] Risk factors from patient characteristics include hospital stay of greater than or equal to 72 hours, significant underlying comorbidities, invasive devices,[44] colonization pressure, exposure to contaminated surfaces,[37] and residence in long-term care facilities.[45]

VRE colonization is identified using rectal or perirectal swab cultures or stool cultures. The overall sensitivity varies directly with VRE density in stool, from 100% high densities ($\geq$7.5 logs per gram feces) to 0% at low densities ($\leq$4.5 logs per gram). Prior antibiotic exposure and skin colonization with VRE are more common in patients with high stool densities.[46]

Infection Control

Because the treatment of VRE infections is so complicated and rarely successful, infection control measures are of prime importance. These include strict hand hygiene, contact precautions, cohorting of colonized patients, decolonization attempts, surveillance cultures, and source control.

Active Surveillance

Active surveillance reduces transmission of VRE when performed in outbreak settings or in high-risk patient units such as ICUs and hematology-oncology wards.[47] Legislation has been introduced in several states in the United States mandating surveillance cultures to screen all patients for carriage of MRSA and/or VRE. These laws also require treating or offering treatment to carriers and, in some states, segregating the patient from those who test negative. However, there are concerns with this approach.

Colonization suppression refers to reducing the burden of bacteria on the patient's skin by regular application of antiseptic agents, particularly daily bathing of patients with chlorhexidine gluconate, which was found to be superior to soap and water baths and led to significant reduction in the rate of VRE bacteremia.[48]

VRE Management

The optimal treatment of enterococcal infection due to VRE is unsettled (**Table 2**). VRE *E faecalis* are usually susceptible to β-lactam, as are *E gallinarum and E casseliflavus* (which are intrinsically vancomycin-resistant). In contrast, VRE *E faecium* isolates often have concurrent high-level resistance to β-lactam and aminoglycosides. Linezolid and quinupristin-dalfopristin are approved in the United States for use for infections caused by VRE. However, the usefulness of these agents for serious infections like endocarditis is uncertain. Linezolid, daptomycin, and tigecycline have activity against both vancomycin-resistant *E faecalis* and *E faecium*, whereas quinupristin-dalfopristin has activity against *E faecium* only. In addition, newer agents currently in clinical trials may also prove efficacious for VRE infections, including telavancin, tedizolid, dalbavancin, and oritavancin.

The authors believe that for severe infections caused by VRE *E faecium*-resistant to β-lactam and aminoglycosides, therapy should consist of telavancin with or without linezolid as long as the patient's renal function is normal. In patients with compromised renal functions, linezolid alone is currently the only solution.

Regimens for treatment of VRE infections are: (1) for ampicillin-susceptible VRE, (MIC <32 μg/mL), ampicillin-sulbactam 6 to 12 g per 24 hours in 6 equally divided doses or (2) for ampicillin-resistant VRE, high-dose ampicillin 8 to 30 g IV daily. Another option is high-dose linezolid 600 mg twice a day, either orally or IV.

Possible combinations for treating severe VRE infections include quinupristin-dalfopristin with doxycycline (or minocycline) and rifampin[49–52] and the combination of daptomycin with tigecycline.[53]

Table 2
Current suggested treatments for VRE infections

Infection	Pathogen	Suggested First-Line Therapy	Alternative Therapy
Severe Infections (eg, endocarditis, bacteremia, meningitis)	VRE β-lactam & aminoglycoside-susceptible (*E faecalis*; *E gallinarum*; *E casseliflavus*)	Ampicillin-sulbactam 6–12 g/24 h divided into 4 doses ± aminoglycoside	High-dose ampicillin (8–30 g) day in 6 doses
	VRE β-lactam & aminoglycoside-resistant (*E faecium*)	Telavancin[a] ± linezolid	Quinupristin-dalfopristin + doxycycline 200 mg/24 h + rifampin 600 mg/24 h
Nonsevere infections: UTI, abdominal abscesses, soft tissue infections, gynecologic infections	VRE β-lactam & aminoglycoside-susceptible (*E faecalis*, *E gallinarum*, *E casseliflavus*)	Ampicillin + aminoglycoside	Linezolid Teicoplanin Tigecycline Quinupristin-dalfopristin
	VRE β-lactam & aminoglycoside-resistant (*E faecium*)	Linezolid Teicoplanin Quinupristin-dalfopristin	Tigecycline Teicoplanin

[a] In nonrenal compromised patients (creatinine clearance >30 mL/min).

SUMMARY

VRE infections have spread and have become a daily occurrence in many hospitals. Although most VRE isolates are merely colonizers, some infections, particularly in immune-suppressed individuals or postsurgery patients, do occur. The treatment of VRE severe infections is difficult, nonconventional, and demands the use of antibiotic combinations, whereas UTI and wound infections can be treated with a single, even bacteriostatic, agent.

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