

Vancomycin-resistant enterococcal infections: epidemiology, clinical manifestations, and optimal management

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Abstract: Since its discovery in England and France in 1986, vancomycin-resistant *Enterococcus* has increasingly become a major nosocomial pathogen worldwide. Enterococci are prolific colonizers, with tremendous genome plasticity and a propensity for persistence in hospital environments, allowing for increased transmission and the dissemination of resistance elements. Infections typically present in immunosuppressed patients who have received multiple courses of antibiotics in the past. Virulence is variable, and typical clinical manifestations include bacteremia, endocarditis, intra-abdominal and pelvic infections, urinary tract infections, skin and skin structure infections, and, rarely, central nervous system infections. As enterococci are common colonizers, careful consideration is needed before initiating targeted therapy, and source control is first priority. Current treatment options including linezolid, daptomycin, quinupristin/dalfopristin, and tigecycline have shown favorable activity against various vancomycin-resistant *Enterococcus* infections, but there is a lack of randomized controlled trials assessing their efficacy. Clearer distinctions in preferred therapies can be made based on adverse effects, drug interactions, and pharmacokinetic profiles. Although combination therapies and newer agents such as tedizolid, telavancin, dalbavancin, and oritavancin hold promise for the future treatment of vancomycin-resistant *Enterococcus* infections, further studies are needed to assess their possible clinical impact, especially in the treatment of serious infections.

Keywords: Gram-positive, *Enterococcus faecalis*, *Enterococcus faecium*, VRE, antibiotic resistance, multidrug resistance

Introduction

Vancomycin-resistant *Enterococcus* (VRE), belonging to the species *Enterococcus faecium*, was first encountered in clinical isolates in England and France in 1986, followed the next year by isolation of VRE *faecalis* in the United States.^{1–3} In Europe, the rise of VRE was principally in the community setting, due to transmission from animal food products to humans, thought to arise from the use of a glycopeptide antibiotic avoparcin as a growth promoter in livestock,⁴ whereas in the US the predominance of VRE was in the hospital setting, believed to be due to the increasing use of the glycopeptide antibiotic vancomycin.⁵ Subsequently, the US experienced a rapid spread of VRE in hospitals in the 1990s, Europe followed suit in the 2000s, and eventually a worldwide spread ensued.^{6–8} In 2002, the threat of VRE colonization and infections increased when the first patient case of VRE transmitting *vanA* resistance genes to methicillin-resistant *Staphylococcus aureus* (MRSA) to form a vancomycin-resistant *Staphylococcus aureus* (VRSA) isolate was reported.⁹

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Currently, 54 different species and two subspecies of enterococci have been described, with *E. faecalis* and *E. faecium* being the most clinically relevant species, isolated in the US at a ratio of 1.6:1, respectively.^{8,10} *E. faecalis* is more pathogenic than *E. faecium*, but the latter exhibits more resistance, composing the majority of VRE infections.^{11,12} The emergence of VRE as an important nosocomial pathogen is due to its propensity for colonization of the gastrointestinal (GI) tract, persistence in hospital environments, genome plasticity, mobile genetic elements, and increased mortality.¹³ Due to the multiple resistance mechanisms found in VRE, treatment options are limited, but several new agents have come to market recently and recent data on combination therapies have looked promising, broadening the treatment options that are currently available. This review highlights the epidemiology, clinical manifestations, and optimal management of VRE infections.

Resistance

Enterococci are incredibly efficient at attaining antimicrobial resistance, displaying a variety of mechanisms for acquired and intrinsic resistance. They have remarkable genome plasticity and utilize plasmids, transposons, and insertion sequences to efficiently attain and transfer mobile resistance elements, facilitating dissemination of resistance genes.¹⁴

β -lactam resistance

Enterococci exert a low-level intrinsic resistance to β -lactams due to penicillin-binding proteins (PBPs) with a low-affinity for these agents.¹⁵ Compared to streptococci, *E. faecalis* is 10–100-fold less sensitive to penicillin, and compared to *E. faecalis*, *E. faecium* is 4–16-fold less susceptible.¹⁶ Therefore, most enterococci are tolerant to the bactericidal activity of β -lactams, making them bacteriostatic. However, if bactericidal activity is needed to treat severe infections such as endocarditis or meningitis, a synergistic bactericidal combination of a β -lactam with an aminoglycoside can be used.^{17,18}

High-level β -lactam resistance in enterococci is principally due to two mechanisms: the production of low-affinity PBP5, or the production of β -lactamases.¹⁸ Overproduction of PBP5 with low-affinity binding to β -lactams is characteristic of *E. faecium* but uncommon among *E. faecalis*.¹⁹ In fact, most VRE *faecium* strains in the US express high-level resistance (HLR) to ampicillin, while most VRE *faecalis* strains remain susceptible to ampicillin.^{14,20} The production of β -lactamases is infrequent in enterococci, but can lead to HLR by hydrolyzing β -lactams before they reach their target in the

cell wall. It is almost universally due to *E. faecalis* strains and is constitutive, low level, and inoculum-dependent.²¹

Aminoglycoside resistance

Enterococci are intrinsically resistant to low levels of aminoglycosides due to decreased cellular permeability of these agents, but this can be overcome with the addition of a cell-wall-active agent such as a β -lactam, which increases the entry of the aminoglycoside into the cell.¹⁷

First reported in the US in 1979, HLR to gentamicin was found in both *E. faecalis* and *E. faecium*, and was followed shortly by the isolation of HLR to both gentamicin and streptomycin in 1983.^{22,23} HLR to aminoglycosides is acquired through two mechanisms of resistance: modification of ribosomal attachment sites, and the production of aminoglycoside-modifying enzymes.¹⁷ Gentamicin or streptomycin are the recommended synergy agents for use with β -lactams to obtain bactericidal activity. The presence of HLR to aminoglycosides destroys the bactericidal activity obtained with β -lactam and aminoglycoside synergy in clinical practice.²⁴

Glycopeptide resistance

Bacterial cell walls are made of peptidoglycan that is formed when cell wall pentapeptide precursors ending in D-Ala-D-Ala translocate from the cytoplasm to the cell surface and are incorporated into nascent peptidoglycan by transglycosylation, forming cross-links by transpeptidation to strengthen the cell wall.²⁵ Glycopeptides, such as vancomycin and teicoplanin, are cell-wall-active agents, exerting their antibacterial effect by binding with high affinity to the D-Ala-D-Ala termini of pentapeptide precursors in order to inhibit the synthesis of peptidoglycan. Glycopeptide resistance arises when low-affinity pentapeptide precursors D-Ala-D-Lac or D-Ala-D-Ser are formed and high-affinity precursors D-Ala-D-Ala are eliminated.²⁶

Currently, eight phenotypic variants of acquired glycopeptide resistance in enterococci have been described (VanA, VanB, VanD, VanE, VanG, VanL, VanM, and VanN), with one type of intrinsic resistance (VanC) being unique to *E. gallinarum* and *E. casseliflavus* (Table 1).^{27–31} A change in the precursor to D-Ala-D-Lac (VanA, VanB, VanD, VanM) causes a 1,000-fold decrease in affinity for vancomycin, and a change to D-Ala-D-Ser (VanC, VanE, VanG, VanL, VanN) causes a 7-fold decrease in affinity for vancomycin.^{32,33} VanA is responsible for most of the human cases of VRE around the world, and is mostly carried by *E. faecium*.

Table 1 Characteristics of glycopeptide resistance phenotypes in *Enterococcus*

Resistance	Acquired			Moderate			Low			Intrinsic	
	High	Variable	VanB	VanD	VanE	VanG	VanL	VanN	VanC	Low	VanC
Phenotype	VanA	VanM	VanB	VanD	VanE	VanG	VanL	VanN	VanC	Low	VanC
Vancomycin MIC (mg/L)	64–1,000	>256	4–1,000	64–128	8–32	≤16	8	16	2–32		
Teicoplanin MIC (mg/L)	16–512	96	0.5–1	4–64	0.5	Sensitive	≤0.5	≤0.5	0.5–1		
Modification	D-Ala-D-Lac	D-Ala-D-Lac	D-Ala-D-Lac	D-Ala-D-Lac	D-Ala-D-Ser	D-Ala-D-Ser	D-Ala-D-Ser	D-Ala-D-Ser	D-Ala-D-Ser		
Location	Plasmid or chromosome	Plasmid or chromosome	Plasmid or chromosome	Plasmid or chromosome	Chromosome	Chromosome	Chromosome	Plasmid	Chromosome		
Transferable	Yes	Yes	Yes	No	No	Yes	No	Yes	No		
Expression	Inducible	Inducible	Inducible	Constitutive or inducible	Inducible	Inducible	Inducible	Constitutive	Constitutive or inducible		
Main Species	<i>E. faecalis</i> , <i>E. faecium</i>	<i>E. faecium</i>	<i>E. faecalis</i> , <i>E. faecium</i>	<i>E. faecalis</i> , <i>E. faecium</i>	<i>E. faecalis</i>	<i>E. faecalis</i>	<i>E. faecalis</i>	<i>E. faecium</i>	<i>E. faecium</i> , <i>E. casseliflavus</i>		

Notes: Data from Boyd et al.²⁸ Lebreton et al.²⁹ McKessar et al.³⁰ and Xu et al.³¹ Adapted from Courvalin P. Vancomycin resistance in Gram-positive cocci. *Clin Infect Dis.* 2006;42(Suppl 1):S25–S34, by permission of Oxford University Press.²⁷

Abbreviations: MIC, minimum inhibitory concentration; D-Ala-D-Lac, D-alanine-D-lactate; D-Ala-D-Ser, D-alanine-D-serine.

Epidemiology Colonization, transmission, and risk factors

The majority of VRE colonization occurs in the GI tract, but can also be found to a lesser extent on the skin, in the genitourinary (GU) tract, and in the oral cavity.^{34,35} *E. faecalis* is the major colonizer in these sites. Once GI colonization with VRE occurs, it can persist for months to years and efforts at decolonization are typically transitory, with recurrence of VRE days or weeks later.^{36,37} Health care workers' hands are the most consistent source of transmission.³⁸ VRE can persist for up to 60 minutes on hands and as long as 4 months on surfaces.^{39,40} The common pathway for nosocomial VRE starts with acquisition via person-to-person contact or exposure to contaminated objects. Gut microbiota are then suppressed through antimicrobial selective pressure, allowing for overgrowth of VRE, as it is intrinsically resistant to several antibiotics. When the patient becomes immunosuppressed, VRE can flourish, causing a clinical illness.³⁴

Risk factors for colonization include host characteristics and exposure to antimicrobials. An increased risk of VRE colonization occurs with immunosuppression, hematological malignancies, organ transplantation, increased intensive care unit (ICU) or hospital stay, residence in a long-term care facility, infection of an additional body site, proximity to another colonized or infected patient, hospitalization in a unit with a high prevalence of VRE, serious comorbid conditions such as diabetes, renal failure, and high Acute Physiology and Chronic Health Evaluation (APACHE) II scores.^{41–44} Prior exposure to antimicrobials is the largest predictor of VRE colonization, including oral and intravenous (IV) administration of vancomycin,⁴⁵ aminoglycosides,⁴⁶ cephalosporins,^{47,48} antianaerobic agents such as clindamycin and metronidazole, and carbapenems.⁴⁶

Distribution of VRE

Among enterococci, *E. faecalis* is the most common cause of infections, but *E. faecium* is intrinsically more resistant to antibiotics with more than half of nosocomial isolates in the US expressing resistance to ampicillin and vancomycin and HLR to aminoglycosides.⁴⁹

Around the world, the rates of VRE are at their highest in North America (Table 2). According to the National Healthcare Safety Network (NHSN), from 2009 to 2010, 35.5% of enterococcal hospital-associated infections were resistant to vancomycin, ranking as the second most common cause of nosocomial infections in the US.¹¹ In contrast, Canada has a

Table 2 Surveillance of vancomycin-resistant enterococci around the world

Species	Percent of <i>Enterococcus</i> isolates resistant to vancomycin by region (no of isolates)					
	Europe ⁸ 2013	US ¹¹ 2009–2010	Worldwide ¹⁵ 2007–2012	Canada ⁵⁰ 2007–2011	Asia-Pacific ¹¹⁸ 2007–2008	Latin America ¹¹⁸ 2007–2008
<i>E. faecium</i>	8.8 (729)	79.4 (2,572)	–	22.4 (60)	14.1 (270)	48.1 (54)
<i>E. faecalis</i>	1.0 (126)	8.5 (444)	10.3 (27)	0.1 (1)	0.01 (440)	3.1 (195)
All enterococci	4.0 (855)	35.5 (3,016)	–	6.0 (61)	11.9 (710)	12.9 (249)

Note: Adapted by permission of Oxford University Press from Cattoir V, Leclercq R. Twenty-five years of shared life with vancomycin-resistant enterococci: is it time to divorce? *J Antimicrob Chemother.* 2013;68(4):731–742.¹⁴

Abbreviations: VRE, vancomycin-resistant *Enterococcus*; US, United States.

much lower prevalence of VRE; according to CANWARD, 6% of enterococci in Canada were resistant to vancomycin from 2007 to 2011.⁵⁰

In Europe, VRE is much less prevalent, but on the rise. For 2013, the European Antimicrobial Resistance Surveillance System (EARSS) reported only 4% prevalence of VRE.⁸ However, this prevalence is variable depending on the country, with VRE ranging from less than 1% in France, Spain, and Sweden, to greater than 20% in Greece, Ireland, Portugal, and the United Kingdom.

Clinical manifestations

Bacteremia

Bacteremia without endocarditis is a common presentation of enterococcal disease, especially in debilitated patients who are seriously ill and receiving antibiotics.⁵¹ In the US, 18% of all central line associated bloodstream infections (CLABSIs) are due to enterococci, ranking second overall.¹¹ Common sources for community-acquired bacteremia are the GI and GU tracts.⁵² Nosocomial enterococcal bacteremias are commonly acquired from intravascular or urinary catheters, but have also been associated with intra-abdominal, burn wounds, pelvic, biliary, and bone sources. VRE bacteremia is associated with a 2.5-fold increase in mortality when compared to vancomycin-sensitive *Enterococcus* (VSE) bacteremia.^{53,54}

Infective endocarditis

Enterococci are the second most common cause of infective endocarditis (IE) at 5%–20% of cases.⁵⁵ Endocarditis caused by VRE *faecalis* is associated with central venous lines, liver transplantation, and mitral valve infections, whereas VRE *faecium* endocarditis is associated with infection of the tricuspid valve.⁵⁶ The common sources for seeding originate from the GI or GU tract.⁵⁷ Enterococcal endocarditis typically presents as a subacute course, with the most common clinical manifestations being the presence of a murmur, fever, weight loss, malaise, and generalized aches.^{52,58} Less commonly seen are peripheral signs of endocarditis such as Osler's nodes, petechiae, and Roth's spots.

Intra-abdominal and pelvic infections

As enterococci are commensals of the GI tract, it is common for them to be isolated from pelvic and intra-abdominal infections (IAIs), usually along with Gram-negative and anaerobic organisms.⁵² Most consider the treatment of IAIs in the immunocompromised and severely ill associated with abscesses, wounds, or peritonitis in patients with damaged heart valves as acceptable means of avoiding bacteremia or endocarditis.⁵⁹ In contrast, enterococci are able to cause monomicrobial peritonitis infections, most commonly in patients undergoing chronic peritoneal dialysis or suffering from liver cirrhosis, and treatment is considered more appropriate in these settings.⁵⁷

Urinary tract infections

VRE is fast becoming a major cause of health care-associated urinary tract infections (UTIs). Enterococci account for 15% of all catheter-associated urinary tract infections (CAUTIs), ranking second overall in the US, which is an increase from previous years when it was ranked third.^{11,49} They are more common in men and are usually associated with recurrent UTIs, previous antibiotic treatment, indwelling catheters, instrumentation, and abnormalities of the GU tract.⁵² Discerning between colonization and infection can be difficult with VRE, as it is a colonizer of the GU tract and often results in asymptomatic bacteriuria.⁶⁰

Central nervous system infections

Central nervous system (CNS) infections are an extremely rare presentation for VRE.⁶¹ They typically occur in older patients with serious underlying diseases, such as hematologic malignancies, solid tumors, pulmonary disease, and cardiac disease. VRE *faecium* is a more typical cause of these infections compared to VRE *faecalis*, at 82% versus 5%, respectively. Clinical manifestations include acute courses of fever, altered mental status, and rarely with coma, shock, focal CNS deficits, and petechial rash. Cerebrospinal fluid findings typically include pleocytosis, low glucose, and increased protein levels.

Skin and skin structure infections

Enterococci are colonizers of the skin and have been associated with skin and skin structure infections (SSSIs).⁵² They are usually a part of polymicrobial infections, and their pathogenic role can be questioned. Enterococci are typically isolated from decubiti and diabetic foot ulcers, and rarely have been known to cause osteomyelitis, septic arthritis, and soft tissue abscesses.⁶²

Optimal management

Treatment of VRE infections can be controversial, as it commonly presents as a nonvirulent colonizer in polymicrobial infections, although serious infections such as bacteremia and IE do warrant treatment. Treatment should start with source control, as most infections represent colonization, and cure can be obtained without antibacterial therapy directed at the enterococci.³⁴ Agents with in vitro activity against ampicillin and vancomycin-resistant enterococci with HLR to aminoglycosides are summarized in Table 3, and potential treatment options based on indication are presented in Table 4.

β -lactams and aminoglycoside synergy

Ampicillin monotherapy should be used preferentially for any ampicillin-susceptible VRE infection that does not require bactericidal activity. For UTIs, high doses of ampicillin (18–30 g/day) or amoxicillin (500 mg every 8 hours) obtain sufficient urine concentration to make treatment of ampicillin and vancomycin-resistant *Enterococcus* feasible.^{35,63} In the rare case of a VRE *faecalis* β -lactamase producer, ampicillin/sulbactam should be used.

For bacteremia caused by ampicillin-sensitive VRE, monotherapy with ampicillin is recommended, as no benefit has been found with aminoglycoside synergy.⁶⁴ If bactericidal activity is required for the treatment of an endovascular infection, a synergistic combination of a β -lactam with an aminoglycoside (gentamicin or streptomycin) should be used.^{18,65} For ampicillin and vancomycin-resistant *Enterococcus* without HLR to aminoglycosides, high-dose ampicillin with an aminoglycoside can be considered for a minimum inhibitory concentration (MIC) ≤ 64 mg/L, as sufficient serum concentrations are obtained.^{66,67} For IE due to ampicillin-susceptible *E. faecalis*, ampicillin with ceftriaxone should be considered an alternative treatment option, as it has shown efficacy similar to that of ampicillin with gentamicin, but with less nephrotoxicity.^{66,68} The mechanism for this bactericidal synergy is due to the saturation of different PBPs by each agent.⁶⁹

Quinupristin/dalfopristin

Quinupristin/Dalfopristin (Q/D) is a parenteral combination of streptogramin type A (70% dalfopristin) and type B (30% quinupristin). It has bactericidal activity against various Gram-positive bacteria, but is bacteriostatic against VRE *faecium*, and lacks activity against *E. faecalis* due to efflux pumps.⁷⁰ Q/D was approved for the treatment of VRE, but this indication was removed due to a failure to show a clinical benefit.⁷¹ Resistance to Q/D by VRE *faecium* is mediated by target modification, drug inactivation, or active efflux.⁶² Dose-limiting toxicities of myalgias and arthralgias can lead to treatment discontinuation, and administration through a central venous catheter is required to avoid phlebitis.

For the treatment of various VRE infections, Q/D has an overall success rate of 66%.⁷² Q/D is recommended as an option for the treatment of ampicillin and vancomycin-resistant *E. faecium* with HLR to aminoglycosides, but it does not have bactericidal activity and only anecdotal support as a monotherapy treatment in this setting.⁷³ Q/D has demonstrated clinical cure for IE when administered concurrently with high-dose ampicillin or doxycycline.⁷⁴ It has poor CNS penetration due to its high molecular weight, and has shown failures in the treatment of VRE CNS infections when used alone.⁷⁵ Only 15%–19% of its active metabolites are excreted in the urine, but it has been used in the treatment of VRE UTIs with a response rate of 80%.^{72,76} Due to adverse effects and treatment failures, Q/D should be considered as an alternative option for VRE infections after the use of linezolid or daptomycin.

Oxazolidinones

Linezolid

Linezolid is a parenteral and oral bacteriostatic oxazolidinone with broad-spectrum activity against Gram-positive organisms, including VRE *faecalis* and *faecium*. It is the only agent approved by the Food and Drug Administration (FDA) for the treatment of VRE infections. Resistance to linezolid is rare, but it has been described in the literature and is associated with the duration of previous linezolid therapy.⁷⁷ Resistance to linezolid in VRE is a result of decreased binding due to mutations at the 23S ribosomal RNA or acquisition of a *cfr* (chloramphenicol–florfenicol resistance) gene through horizontal transmission, causing methylation of the 23S ribosomal RNA.⁷⁸

Linezolid has displayed efficacy in the treatment of VRE *faecium* bacteremia with an open-label, nonrandomized, compassionate-use program reporting microbiological and clinical cure rates of 85.3% and 79.0%, respectively.⁷⁹ Linezolid is recommended as a first-line treatment option for

Table 3 Agents used for the treatment of serious ampicillin and vancomycin-resistant enterococcal infections with high-level resistance to aminoglycosides

Therapeutic class and agent	Mechanism of action	Dosing by FDA-approved indication(s)	Dosage adjustment
Oxazolidinone			
Linezolid ¹¹⁶	Inhibits protein synthesis by binding to the 23S ribosomal RNA of the 50S subunit	Vancomycin-resistant <i>Enterococcus faecium</i> infections, including concurrent bacteremia; nosocomial pneumonia; CAP; complicated and uncomplicated SSSI: 600 mg IV or PO every 12 hours	For HD, normal dose, but dose post-HD on HD days
Tedizolid ¹¹⁹	Inhibits protein synthesis by binding to the 50S ribosomal subunit	Acute bacterial SSSI: 200 mg IV or PO every 24 hours	None
Streptogramin			
Quinupristin/dalfopristin ⁷¹	Each agent acts differently with the 50S ribosome to inhibit early and late phase protein synthesis	Complicated SSSI: 7.5 mg/kg IV every 12 hours	None
Cyclic lipopeptide			
Daptomycin ¹¹⁷	Binding to cell membrane (concentration- and calcium-dependent); causes rapid depolarization of the membrane, inhibiting protein, DNA, and RNA synthesis, leading to cell death	Complicated SSSI: 4 mg/kg IV every 24 hours; <i>Staphylococcus aureus</i> bacteremia, including those with right-sided endocarditis: 6 mg/kg IV every 24 hours (consider higher dosing for severe VRE infections =8–12 mg/kg IV every 24 hours)	Complicated SSSI: CrCl <30 mL/min =4 mg/kg IV every 48 hours HD =4 mg/kg IV every 48 hours following HD on HD days Bacteremia: CrCl <30 mL/min =6 mg/kg IV every 48 hours HD =6 mg/kg IV every 48 hours following HD on HD days
Glycylcycline			
Tigecycline ¹¹⁸	Inhibits protein translation by binding to the 30S ribosomal subunit	Complicated SSSI; IAI; CAP: 100 mg IV loading dose, then 50 mg IV every 12 hours	Severe hepatic impairment (Child-Pugh C): 100 mg IV day 1, then 25 mg IV every 12 hours
Lipoglycopeptide			
Telavancin ¹⁰⁹	Dual mechanism: Disrupts cell wall synthesis by binding to D-Ala-D-Lac of peptidoglycan, preventing cross-linking Disrupts membrane integrity and increases cell membrane permeability, causing cell lysis	Complicated SSSI; HAP/VAP: 10 mg/kg IV every 24 hours	CrCl 30–50 mL/min =7.5 mg/kg every 24 hours CrCl 10–30 mL/min =10 mg/kg every 48 hours CrCl <10 mL/min = IE HD = IE
Dalbavancin ¹⁰⁸	Disrupts cell-wall synthesis by binding to D-Ala-D-Lac of peptidoglycan, preventing cross-linking	Acute bacterial SSSI: 1,000 mg IV on day 1, then 500 mg IV on day 8	CrCl <30 mL/min and no HD =750 mg on day 1, 375 on mg day 8
Oritavancin ¹²⁰	Triple mechanism: Inhibition of cell wall transglycosylation by binding to D-Ala-D-Lac Inhibition of cell wall transpeptidation by binding to the bridging segment Disruption of membrane integrity, increasing permeability, causing cell lysis	Acute bacterial SSSI: 1,200 mg IV once	None (not studied in CrCl <30 mL/min)

Abbreviations: CAP, community-acquired pneumonia; D-Ala-D-Lac, D-alanine-D-lactate; aPTT, activated partial thromboplastin time; SSSI, skin and skin structure infection; IV, intravenous; PO, oral; HD, hemodialysis; UTI, urinary tract infection; IAI, intra-abdominal infection; CNS, central nervous system HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; IE, insufficient evidence; GI, gastrointestinal; INR, international normalized ratio; VRE, vancomycin-resistant *Enterococcus*; ALT, alanine aminotransferase; FDA, Food and Drug Administration.

VRE indication(s)	Notable adverse events	Comments
FDA approved for vancomycin-resistant <i>Enterococcus faecium</i> infections, including concurrent bacteremia	Headache (5.7%–8.8%), nausea (5.1%–6.6%), vomiting (2%–4.3%), diarrhea (8.2%–8.3%), serotonin syndrome, lactic acidosis Duration related: optic neuritis, peripheral neuropathy, myelosuppression	<ul style="list-style-type: none"> • Bacteriostatic; • Nonselective monoamine oxidase inhibitor; Avoid use with serotonergic agents; • Myelosuppression with duration >2 weeks
Bacteremia; pneumonia	Diarrhea (4.0%), nausea (8.0%), vomiting (3.0%), headache (6.0%), thrombocytopenia (2.3%), neutropenia (0.5%)	<ul style="list-style-type: none"> • Bacteriostatic; • Weaker monoamine oxidase inhibitor than linezolid; • Extent of myelosuppression not fully elucidated due to short study durations
Serious or life-threatening infections associated with vancomycin-resistant <i>Enterococcus faecium</i> bacteremia 7.5 mg/kg IV every 8 hours Complicated SSSI, UTI, IAI	Injection site reactions: edema (17.3%), inflammation (42.0%), pain (40.0%), rash (2.5%) Asymptomatic hyperbilirubinemia (0.9% to 25%), dose and/or frequency related arthralgias and myalgias (3.3% to 47%)	<ul style="list-style-type: none"> • Bacteriostatic; • No activity against <i>E. faecalis</i>; • Inhibitor of liver enzymes
Complicated SSSI, bacteremia, IE, CNS, IAI, UTI	Myopathy (especially with higher dose and/or concurrent HMG-CoA reductase inhibitor therapy), neuropathy, acute eosinophilic pneumonia	<ul style="list-style-type: none"> • Concentration-dependent bactericidal activity; • Inactivated by pulmonary surfactant (avoid use for primary pulmonary infections)
Complicated SSSI, IAI, CNS, UTI	Nausea (24% to 35%), vomiting (16% to 20%), acute pancreatitis	<ul style="list-style-type: none"> • Bacteriostatic; • Avoid in pregnancy (Class D) and for pediatric patients; • Low blood concentrations, avoid use in bacteremia; • Increased mortality with VAP treatment
Complicated SSSI, pneumonia	Taste disturbance (33%), foamy urine (13%), renal impairment (5%), GI disturbance (5%–27%), QT prolongation (8%)	<ul style="list-style-type: none"> • Concentration-dependent bactericidal activity (static against VRE expressing VanB); • Only active against VRE expressing VanB; • Higher nephrotoxicity compared to vancomycin; • Black box warning: increased mortality in moderate or severe renal impairment; • Avoid in pregnancy (class C, animal studies demonstrate fetal harm)
Acute bacterial SSSI; bacteremia	Constipation (18.2%), diarrhea (4.4%), nausea (5.5%), headache (4.7%), anaphylactoid reactions (<2%), “Red-Man syndrome” with rapid infusion (<30 minutes)	<ul style="list-style-type: none"> • Concentration-dependent bactericidal activity; • Only active against VRE expressing VanB; • Increased risk of hypersensitivity with a history of glycopeptide sensitivity has been noted
Acute bacterial SSSI; bacteremia	Nausea (9.9%), vomiting (4.6%), headache (7.1%), arm abscesses (3.8%), asymptomatic ALT elevations (2.8%), hypersensitivity (<1.5%) infusion site reactions (slow or stop infusion to abate)	<ul style="list-style-type: none"> • Concentration-dependent bactericidal activity; • Falsely elevated aPTT and INR post-infusion; • Weak inducer and inhibitor of liver enzymes

Table 4 Suggested regimens for the treatment of serious ampicillin and vancomycin-resistant enterococcal infections with high-level resistance to aminoglycosides

Infection type	Therapeutic regimen	Comments
Bacteremia		
Preferred	Linezolid	
Alternatives	Daptomycin	• Consider 8–12 mg/kg/day
	Q/D	• Only active against <i>E. faecium</i>
	Daptomycin combination	• Combine with either HD ampicillin, ceftaroline, ceftobiprole, or tigecycline
Infective endocarditis		
Preferred	Daptomycin	• Consider 8–12 mg/kg/day
Alternatives	Q/D	• Only active against <i>E. faecium</i>
	Daptomycin combination	• Combine with either HD ampicillin, ceftaroline, ceftobiprole, or tigecycline
	Linezolid	
Central nervous system		
Preferred	Linezolid	
	Daptomycin	• ± concurrent intrathecal/intraventricular administration
Alternatives	Q/D	• Q/D + daptomycin is an option
		• ± concurrent intrathecal/intraventricular administration
	Tigecycline	• Only active against <i>E. faecium</i>
Intra-abdominal		
Preferred	Linezolid	
	Daptomycin	• Intraperitoneal administration is an option
	Tigecycline	
Alternatives	Q/D	• Only active against <i>E. faecium</i>
Skin and skin structure		
Preferred	Linezolid	• Oral option
	Daptomycin	
Alternatives	Tedizolid	• Oral option
	Oritavancin	
	Dalbavancin	• Only active against VanB
	Telavancin	• Only active against VanB
	Q/D	• Only active against <i>E. faecium</i>
Urinary tract		
Preferred	Nitrofurantoin	• Only for uncomplicated UTI
	Fosfomicin	• Only for uncomplicated UTI
	Linezolid	• ± concurrent bladder irrigation with linezolid
		• Oral option
Alternatives	Daptomycin	
	HD ampicillin or amoxicillin	
	Q/D	• Only active against <i>E. faecium</i>

Abbreviations: UTI, urinary tract infection; HD, high-dose; Q/D, Quinupristin/dalfopristin.

IE due to ampicillin and vancomycin-resistant enterococci with HLR to aminoglycosides, but it is not bactericidal.⁷³ It has successfully treated several VRE IE cases, but treatment failures have also been reported.^{39,80} Linezolid has good urine penetration at roughly 40%, but this decreases dramatically in renal dysfunction.⁸¹ In the case of renal dysfunction, it can

be administered via bladder irrigation.⁸² Linezolid has good penetration into the CNS at roughly 70% and has been used successfully as monotherapy for VRE CNS infections.^{75,83} As the only agent approved for the treatment of VRE infections, linezolid is a preferred agent in the settings of bacteremia, UTI, CNS infection, IAI, and SSSI, but should be considered an alternative option for IE where it lacks bactericidal activity.

Tedizolid

Tedizolid is a next-generation parenteral and oral oxazolidinone with a broad spectrum of bacteriostatic activity against resistant Gram-positive bacteria including both VanA and VanB VRE.⁸⁴ Against VRE, tedizolid has a fourfold lower MIC when compared to linezolid, and has activity against linezolid-resistant strains with a *cfr* mutation.⁸⁵ This increased potency is thought to be due to additional interactions with the ribosomal subunit of Gram-positive bacteria.⁸⁶ It has been approved for the treatment of acute bacterial SSSIs, and is currently undergoing clinical trials for the treatment of bacteremia and pneumonia. With more potent activity against VRE compared to linezolid, tedizolid has the potential to be a first-line agent for the treatment of serious VRE infections.

Daptomycin

Daptomycin is a cyclic lipopeptide with rapid concentration-dependent bactericidal activity against many resistant Gram-positive organisms, including VRE *faecalis* and *faecium*. Two recent meta-analyses comparing daptomycin to linezolid for the treatment of VRE bacteremia found higher mortality in patients treated with daptomycin compared to linezolid. However, these studies are limited by heterogeneity, variable daptomycin dosing, and selection bias for daptomycin use in those with hematological abnormalities.^{87,88} Both linezolid and daptomycin should still be used as first-line options for the treatment of VRE bacteremia, but high-dose daptomycin use should be considered (8–12 mg/kg).

Treatment failures and resistance development while using daptomycin monotherapy for enterococcal endocarditis have led to studies into combination therapies and the use of high-dose daptomycin at 8–12 mg/kg/day.⁸⁹ High-dose daptomycin may be of clinical benefit to reach the higher MICs required for bactericidal activity against *Enterococcus*, to increase the free fraction of drug as it is highly protein bound, and to avoid resistance.^{52,90,91} Daptomycin resistance is associated with longer durations of therapy and is a function of genetic mutations in the genes responsible for biogenesis, permeability, and cell membrane potential. Daptomycin dosed up to 12 mg/kg has proven safe and well-tolerated by patients.⁹² A recent retrospective multicenter study assessed the efficacy of high-dose

daptomycin at a median dose of 8.2 mg/kg for the treatment of VRE, with an overall clinical success rate of 89% and microbiological eradication achieved in 93% of patients.⁹³

Daptomycin achieves poor CNS penetration at 5%–6% with inflamed meninges; therefore, monotherapy for CNS infections is not advised.⁷⁵ There have been successful case reports with intravesicular administration of daptomycin and combination therapy of daptomycin plus linezolid, gentamicin, or Q/D for VRE meningitis reported in the literature.⁷⁵ Daptomycin administered intraventricularly along with systemic linezolid was successful for the treatment of a CNS infection due to VRE.⁹⁴ Daptomycin is a treatment option for IAIs and has been administered intraperitoneally for successful treatment of VRE peritonitis.⁹⁵ It achieves high renal clearance at 50%–70%, giving it a favorable profile for the treatment of VRE UTIs.⁹⁶ Daptomycin is a preferred agent for the treatment of bacteremia, IE, UTI, CNS infection, IAI, and SSSI, but higher doses should be considered for the treatment of serious VRE infections, and synergy with a β -lactam can be attempted for refractory cases.

Daptomycin and β -lactam synergy

Recent in vitro studies and a case report have shown synergy for combinations of daptomycin and various β -lactams in VRE, including the new-generation cephalosporins ceftaroline and ceftobiprole (Table 5).^{97–102} These combinations increase daptomycin's bactericidal activity and reduce resistance formation in VRE *faecalis* and *faecium*. The mechanism of synergy is due to decreased net positive bacterial surface charge, allowing for increased binding affinity of the daptomycin cationic complex to the cytoplasmic membrane, thereby increasing activity. Although promising, this combination therapy is best saved as an alternative treatment regimen for serious VRE infections until further studies are performed in vivo.

Tigecycline

Tigecycline is a glycylcycline, a derivative of minocycline with a functional group substitution, allowing activity against tetracycline-resistant Gram-positive and Gram-negative organisms including VRE *faecalis* and *faecium*.¹⁰³ Resistance to tigecycline in VRE has not been reported yet.

The CNS penetration of tigecycline is not fully elucidated; therefore, its use for the treatment of VRE CNS infections is undetermined. Tigecycline has roughly 22% renal excretion, which exceeds the MIC₉₀ of VRE, but clinical data is lacking to support the use of tigecycline for the treatment of UTIs.¹⁰⁴ No quality studies have been performed to assess the efficacy of tigecycline monotherapy for the treatment of IE, but it has been used successfully along with daptomycin

for the treatment of IE due to VRE.¹⁰⁵ Tigecycline should not be used for the treatment of VRE bacteremia due to a high volume of distribution (7–17 L/kg) causing low levels in serum.¹⁰³ Tigecycline achieves high penetration into the peritoneal space at roughly 50% and has a broad spectrum of activity, making it an ideal option for the treatment of IAI involving VRE.¹⁰⁶ Tigecycline can be considered a preferred treatment for polymicrobial IAIs associated with VRE, should not be used for VRE bacteremias due to low serum concentrations, and is lacking in clinical data to support its use for other indications.

Lipoglycopeptides

Lipoglycopeptides are parenteral semisynthetic glycopeptides that contain lipophilic side chains to increase their half-life and allow for anchoring to the cell membrane of Gram-positive bacteria, enhancing their activity.¹⁰⁷

Telavancin and dalbavancin

Telavancin and dalbavancin exhibit concentration-dependent bactericidal activity against various resistant Gram-positive bacteria including VRE expressing VanB, with little to no activity against VanA expressing VRE.^{108,109} Telavancin was approved for the treatment of complicated SSSI in 2009, and for hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) in 2013. Dalbavancin was approved for the treatment of acute bacterial SSSI in 2014 and is currently undergoing clinical trials for the treatment of bacteremia. Both represent treatment options for cABSSI caused by VanB expressing VRE, and dalbavancin could potentially be used for VRE bacteremia, although the usefulness of this is questionable given that most VRE express VanA resistance.

Oritavancin

Oritavancin has the broadest spectrum of the lipoglycopeptides having bactericidal activity against almost all resistant Gram-positive bacteria including both VanA and VanB expressing VRE.¹¹⁰ It is able to bind to the D-Ala-D-Lac that is produced by VanA. An extended half-life reduces its post-antibiotic effect and opens the possibility for mutant formation.¹⁰⁷ In a rabbit IE model, oritavancin was able to effect a significant reduction in bacterial counts but also selected for mutant formation; however, no resistance was seen when oritavancin was combined with gentamicin for synergy.¹¹¹ It has been approved for the treatment of acute bacterial SSSIs and is currently undergoing clinical trials for the treatment of bacteremia. Oritavancin represents a promising option for the treatment of VRE SSSIs and possibly

Table 5 Overview of recent evidence supporting combination therapy with daptomycin and a β -lactam for the treatment of vancomycin-resistant enterococcal infections

Regimen	Indication	Methodology	Outcomes	Comments	Reference
In vitro					
Daptomycin + ampicillin	–	Broth macrodilution	Prevention of daptomycin resistance in VRE <i>faecalis</i> and <i>faecium</i>	VRE <i>faecium</i> isolate also ampicillin-resistant due to PBP5	99
Daptomycin (6 and 12 mg/kg/day) + ceftriaxone (2 g every 24 hours)	Infective endocarditis	Simulated endocardial vegetations	Increased activity against VRE <i>faecalis</i> and <i>faecium</i> Prevented resistance in VRE <i>faecalis</i> and <i>faecium</i> (only daptomycin 12 mg/kg + ceftriaxone combination)	Combination decreased surface charge of VRE <i>faecium</i> increasing daptomycin binding	100
Daptomycin + ampicillin and Daptomycin + ceftaroline	–	Time-kill assays	Synergy against VRE <i>faecium</i> (ampicillin and ceftaroline combinations) Synergy against daptomycin-nonsusceptible VRE <i>faecium</i> (ceftaroline combination)	Ceftaroline combination increased daptomycin surface binding with increases in membrane fluidity and net negative surface charge	98
Daptomycin + ampicillin	–	Genome sequencing, mutational analysis, and time-kill assays	Synergy against VRE <i>faecium</i> with changes in LiaFSR system No synergy against VRE <i>faecium</i> with changes in the <i>yycFG</i> system	–	102
Daptomycin + ceftobiprole and Daptomycin + ampicillin	–	Broth microdilution and time-kill assays	Synergy against 4/6 isolates of ampicillin-resistant VRE <i>faecalis</i> and <i>faecium</i> (both combinations)	Ceftobiprole combination increased daptomycin binding 2.8-fold	97
Case reports					
Daptomycin 12 mg/kg/day + ampicillin 1 g every 6 hours	Infective endocarditis with bacteremia	–	Microbiological eradication of an ampicillin-resistant VRE <i>faecium</i> strain within 24 hours of initiation	Initially refractory to 7 days of therapy with daptomycin 6 mg/kg/day + linezolid 600 mg IV every 12 hours Adding ampicillin reduced the net positive bacterial surface charge	101

Abbreviations: VRE, vancomycin-resistant *Enterococcus*; PBP, penicillin-binding protein; IV, intravenous.

bacteremia or even endocarditis, when administered with gentamicin for synergy.

Other antienterococcal agents

For the treatment of uncomplicated UTIs caused by ampicillin and vancomycin-resistant *Enterococcus*, nitrofurantoin and fosfomycin should be considered as preferred therapies. Both have good activity against VRE and favorable pharmacokinetic profiles for the treatment of uncomplicated UTIs.^{112,113} Both can be considered as first-line treatments for uncomplicated UTIs caused by VRE, but are not recommended for the treatment of complicated UTIs.

Chloramphenicol is a bacteriostatic agent that was used in the past for VRE treatment, but it is not used often anymore due to lack of availability, clinical failures, development of resistance, and hematologic toxicity.¹¹⁴

Conclusion

VRE has become a major nosocomial pathogen worldwide due to its colonization strategy, persistence in the environment, and genome plasticity. Infections typically present in the immunosuppressed, where virulence is variable, and clinical manifestations include bacteremia, IE, pelvic and IAIs, UTIs, SSSIs, and rarely CNS infections. A lack of randomized controlled trials assessing the efficacy of limited treatment options have made therapy difficult, but new agents, combination therapies, and improved dosing strategies have broadened the practitioner's armamentarium and hold promise for the future treatment of VRE.

Disclosure

The authors report no conflicts of interest in this work. The views expressed in this review article are solely those of the authors and do not necessarily reflect the views of the Chicago College of Pharmacy or Rush Copley Medical Center.

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