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
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. E. faecalis is more pathogenic than *E. faecium*, but the latter exhibits more resistance, composing the majority of VRE infections. 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. 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.

**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. 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. 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 activity is used. Beta-lactam resistance of VRE to ampicillin, while most VRE *faecalis* strains remain susceptible to ampicillin. 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.

**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. 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. HLR to aminoglycosides is acquired through two mechanisms of resistance: modification of ribosomal attachments sites, and the production of aminoglycoside-modifying enzymes. 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.

**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. 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.

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). 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. 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

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Acquired</th>
<th>Variable</th>
<th>Moderate</th>
<th>Low</th>
<th>Intrinsic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype</td>
<td>VanA</td>
<td>VanM</td>
<td>VanB</td>
<td>VanD</td>
<td>VanE</td>
</tr>
<tr>
<td>Vancomycin MIC (mg/L)</td>
<td>64–1,000</td>
<td>&gt;256</td>
<td>4–1,000</td>
<td>64–128</td>
<td>8–32</td>
</tr>
<tr>
<td>Teicoplanin MIC (mg/L)</td>
<td>16–512</td>
<td>96</td>
<td>0.5–1</td>
<td>4–64</td>
<td>≤16</td>
</tr>
<tr>
<td>Modification</td>
<td>D-Ala-D-Lac</td>
<td>D-Ala-D-Lac</td>
<td>D-Ala-D-Lac</td>
<td>D-Ala-D-Lac</td>
<td>D-Ala-D-Lac</td>
</tr>
<tr>
<td>Location</td>
<td>Plasmid or chromosome</td>
<td>Plasmid or chromosome</td>
<td>Plasmid or chromosome</td>
<td>Plasmid or chromosome</td>
<td>Chromosome</td>
</tr>
<tr>
<td>Transferable</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Expression</td>
<td>Inducible</td>
<td>Inducible</td>
<td>Constitutive or inducible</td>
<td>Inducible</td>
<td>Constitutive</td>
</tr>
<tr>
<td>Main Species</td>
<td>E. faecalis, E. faecium</td>
<td>E. faecalis, E. faecium</td>
<td>E. faecalis, E. faecium</td>
<td>E. faecalis, E. faecium</td>
<td>E. faecium</td>
</tr>
</tbody>
</table>

| Notes: | Data from Boyd et al., Lebreton et al., McKessar et al., and Xu et al. 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.

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

### 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 in the second most common cause of vancomycin-resistant enterococcal hospital-associated infections in the US, and the second most common cause of vancomycin-resistant enterococcal nosocomial infections in the US. In contrast, Canada has a high rate of VRE, ranking as the second most common cause of nosocomial infections in the US. 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 the National Health and Human Resource (HHR) to antimicrobials.

### Epidemiology, Colonization, 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, VRE can persist for up to 6 months on hands and to-person contact or exposure to contaminated objects. The common pathway for colonization with VRE occurs, it can persist for months to years at decontamination, are typically transient. Risk factors for colonization include host characteristics such as diabetes, renal failure, and high Acute Physiology and Chronic Health Evaluation (APACHE) II scores. Prior exposure to antimicrobials is the largest predictor of VRE colonization, including oral and intravenous (IV) administration.

Gut microbiota are then suppressed through antimicrobial exposure to antimicrobials is the largest predictor of VRE colonization, such as clindamycin and metronidazole, and carbapenems. Antimicrobial agents such as clindamycin and metronidazole.

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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.\textsuperscript{5} 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.\textsuperscript{51} In the US, 18% of all central line associated bloodstream infections (CLABSIs) are due to enterococci, ranking second overall.\textsuperscript{11} Common sources for community-acquired bacteremia are the GI and GU tracts.\textsuperscript{52} Nosocomial enterococal 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.\textsuperscript{53,54}

#### Infective endocarditis

Enterococci are the second most common cause of infective endocarditis (IE) at 5%–20% of cases.\textsuperscript{55} Endocarditis caused by VRE \textit{faecalis} is associated with central venous lines, liver transplantation, and mitral valve infections, whereas VRE \textit{faecium} endocarditis is associated with infection of the tricuspid valve.\textsuperscript{56} The common sources for seeding origin from the GI or GU tract.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{57} 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.\textsuperscript{60}

#### Central nervous system infections

Central nervous system (CNS) infections are an extremely rare presentation for VRE.\textsuperscript{61} They typically occur in older patients with serious underlying diseases, such as hemato logic malignancies, solid tumors, pulmonary disease, and cardiac disease. VRE \textit{faecium} is a more typical cause of these infections compared to VRE \textit{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.

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**Table 2** Surveillance of vancomycin-resistant enterococci around the world

<table>
<thead>
<tr>
<th>Species</th>
<th>Percent of Enterococcus isolates resistant to vancomycin by region (no of isolates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{E. faecium}</td>
<td>8.8 (729)</td>
</tr>
<tr>
<td>\textit{E. faecalis}</td>
<td>1.0 (126)</td>
</tr>
<tr>
<td>All enterococci</td>
<td>4.0 (855)</td>
</tr>
</tbody>
</table>

**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.\textsuperscript{14}

**Abbreviations:** VRE, vancomycin-resistant Enterococcus; US, United States.
Skin and skin structure infections

Enterococci are colonizers of the skin and have been associated with skin and skin structure infections (SSSIs). 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.

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. 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. In the rare case of a VRE faecalis β-lactamase producer, ampicillin/sulbactam should be used.

For bacteraemia caused by ampicillin-sensitive VRE, monotherapy with ampicillin is recommended, as no benefit has been found with aminoglycoside synergy. 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.

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. 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. The mechanism for this bactericidal synergy is due to the saturation of different PBPs by each agent.

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. Q/D was approved for the treatment of VRE, but this indication was removed due to a failure to show a clinical benefit. Resistance to Q/D by VRE faecium is mediated by target modification, drug inactivation, or active efflux. 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%. 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 cidal activity and only anecdotal support as a monotherapy treatment in this setting. Q/D has demonstrated clinical cure for IE when administered concurrently with high-dose ampicillin or doxycycline. 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. 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%. 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. 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.

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. 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

<table>
<thead>
<tr>
<th>Therapeutic class and agent</th>
<th>Mechanism of action</th>
<th>Dosing by FDA-approved indication(s)</th>
<th>Dosage adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxazolidinone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid&lt;sup&gt;116&lt;/sup&gt;</td>
<td>Inhibits protein synthesis by binding to the 23S ribosomal RNA of the 50S subunit</td>
<td>Vancomycin-resistant <em>Enterococcus faecium</em> infections, including concurrent bacteremia; nosocomial pneumonia; CAP (complicated and uncomplicated SSSI): 600 mg IV or PO every 12 hours</td>
<td>For HD, normal dose, but dose post-HD on HD days</td>
</tr>
<tr>
<td>Tedizolid&lt;sup&gt;119&lt;/sup&gt;</td>
<td>Inhibits protein synthesis by binding to the 50S ribosomal subunit</td>
<td>Acute bacterial SSSI: 200 mg IV or PO every 24 hours</td>
<td>None</td>
</tr>
<tr>
<td><strong>Streptogramin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinupristin/ dalfopristin&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Each agent acts differently with the 50S ribosome to inhibit early and late phase protein synthesis</td>
<td>Complicated SSSI: 7.5 mg/kg IV every 12 hours</td>
<td>None</td>
</tr>
<tr>
<td><strong>Cyclic lipopeptide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin&lt;sup&gt;117&lt;/sup&gt;</td>
<td>Binding to cell membrane (concentration- and calcium-dependent); causes rapid depolarization of the membrane, inhibiting protein, DNA, and RNA synthesis, leading to cell death</td>
<td>Complicated SSSI: 4 mg/kg IV every 24 hours; <em>S. aureus</em> 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)</td>
<td>Complicated SSSI: CrCl &lt; 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 &lt; 30 mL/min = 6 mg/kg IV every 48 hours HD = 6 mg/kg IV every 48 hours following HD on HD days</td>
</tr>
<tr>
<td><strong>Glycylcycline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tigecycline&lt;sup&gt;118&lt;/sup&gt;</td>
<td>Inhibits protein translation by binding to the 30S ribosomal subunit</td>
<td>Complicated SSSI; IAI; CAP: 100 mg IV loading dose, then 50 mg IV every 12 hours</td>
<td>Severe hepatic impairment (Child-Pugh C): 100 mg IV day 1, then 25 mg IV every 12 hours</td>
</tr>
<tr>
<td><strong>Lipoglycopeptide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telavancin&lt;sup&gt;129&lt;/sup&gt;</td>
<td>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</td>
<td>Complicated SSSI; HAP/VAP: 10 mg/kg IV every 24 hours</td>
<td>Complicated SSSI; HAP/VAP: 10 mg/kg IV every 24 hours</td>
</tr>
<tr>
<td>Dalbavancin&lt;sup&gt;128&lt;/sup&gt;</td>
<td>Disrupts cell-wall synthesis by binding to D-Ala-D-Lac of peptidoglycan, preventing cross-linking</td>
<td>Acute bacterial SSSI: 1,000 mg IV on day 1, then 500 mg IV on day 8</td>
<td>CrCl &lt; 30 mL/min and no HD = 750 mg on day 1, 375 on mg day 8</td>
</tr>
<tr>
<td>Oritavancin&lt;sup&gt;126&lt;/sup&gt;</td>
<td>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</td>
<td>Acute bacterial SSSI: 1,200 mg IV once</td>
<td>None (not studied in CrCl &lt; 30 mL/min)</td>
</tr>
</tbody>
</table>

**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.
<table>
<thead>
<tr>
<th>VRE indication(s)</th>
<th>Notable adverse events</th>
<th>Comments</th>
</tr>
</thead>
</table>
| FDA approved for vancomycin-resistant *Enterococcus faecium* 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 | • 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%) | • 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 *Enterococcus faecium* 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%) | • Bacteriostatic;  
• No activity against *E. faecalis*;  
• 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 | • 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 | • 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%) | • 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) | • 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) | • 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

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

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. It has successfully treated several VRE IE cases, but treatment failures have also been reported. Linezolid has good urine penetration at roughly 40%, but this decreases dramatically in renal dysfunction. In the case of renal dysfunction, it can be administered via bladder irrigation. Linezolid has good penetration into the CNS at roughly 70% and has been used successfully as monotherapy for VRE CNS infections. 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. Against VRE, tedizolid has a fourfold lower MIC when compared to linezolid, and has activity against linezolid-resistant strains with a *cfr* mutation. This increased potency is thought to be due to additional interactions with the ribosomal subunit of Gram-positive bacteria. 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. 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. 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. 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. A recent retrospective multicenter study assessed the efficacy of high-dose
Daptomycin achieved poor CNS penetration at 5%–6% with inflamed meninges; therefore, monotherapy for CNS infections is not advised. There have been successful case reports with intravascular administration of daptomycin and combination therapy of daptomycin plus linezolid, gentamicin, or QD for VRE meningitis reported in the literature. Daptomycin administered intraventricularly along with systemic linezolid was successful for the treatment of a CNS infection due to VRE. Daptomycin is a treatment option for IAIs and has been administered intraperitoneally for successful treatment of VRE peritonitis. It achieves high renal clearance at 50%–70%, giving it a favorable profile for the treatment of VRE UTIs. 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). 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. 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. 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. 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. 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. 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.

**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. 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. 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. 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 synergysty. 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

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

Abbreviations: VRE, vancomycin-resistant Enterococcus; PBPs, penicillin-binding proteins; 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.12,13 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.14

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 IAI, 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.

References


