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REVIEW

Therapeutics for Vancomycin-Resistant Enterococcal Bloodstream Infections

Kelly A. Cairns,[a,b] Andrew A. Udy,[c,d] Trisha N. Peel,[a] Iain J. Abbott,[a,e] Michael J. Dooley,[b,f] Anton Y. Peleg[a,g,h]

[a]Department of Infectious Diseases, The Alfred Hospital and Central Clinical School, Monash University, Melbourne, Victoria, Australia
[b]Pharmacy Department, Alfred Health, Melbourne, Victoria, Australia
[c]Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
[d]Department of Intensive Care and Hyperbaric Medicine, The Alfred, Melbourne, Victoria, Australia
[e]Microbiology Unit, Alfred Health, Melbourne, Victoria, Australia
[f]Centre for Medicines Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia
[g]Infection Program, Monash Biomedicine Discovery Institute, Department of Microbiology, Monash University, Clayton, Victoria, Australia
[h]Centre to Impact AMR, Monash University, Clayton, Victoria, Australia

(continued)

Address correspondence to Anton Y. Peleg, anton.peleg@monash.edu.

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SUMMARY Vancomycin-resistant enterococci (VRE) are common causes of bloodstream infections (BSIs) with high morbidity and mortality rates. They are pathogens of global concern with a limited treatment pipeline. Significant challenges exist in the management of VRE BSI, including drug dosing, the emergence of resistance, and the optimal treatment for persistent bacteremia and infective endocarditis. Therapeutic drug monitoring (TDM) for antimicrobial therapy is evolving for VRE-active agents; however, there are significant gaps in the literature for predicting antimicrobial efficacy for VRE BSIs. To date, TDM has the greatest evidence for predicting drug toxicity for the three main VRE-active antimicrobial agents daptomycin, linezolid, and teicoplanin. This article presents an overview of the treatment options for VRE BSIs, the role of antimicrobial dose optimization through TDM in supporting clinical infection management, and challenges and perspectives for the future.

KEYWORDS bacteremia, daptomycin, linezolid, teicoplanin, therapeutic drug monitoring, VRE

INTRODUCTION

Enterococci are a leading cause of health care-associated infections and pose a significant challenge for infection prevention and control within the health care environment (1). Increasing rates of vancomycin resistance in *Enterococcus* spp. are being reported, and a limited number of treatment options are currently available. Vancomycin-resistant *Enterococcus* (VRE) bloodstream infections (BSIs) disproportionally affect sicker patients, are associated with greater mortality, and are a priority organism for research and drug development (2–4). Of the two most clinically relevant species, *Enterococcus faecium* has a greater propensity for antimicrobial resistance, including acquired vancomycin resistance, whereas *Enterococcus faecalis* commonly retains susceptibility to ampicillin.

Compounding the increasing rates of antimicrobial resistance in VRE is a dwindling pipeline of antimicrobial agents. Just seven new antimicrobials were approved by the U.S. Food and Drug Administration (FDA) between 2013 and 2017 (5, 6). The World Health Organization identified that most antimicrobial agents in the development pipeline are derivatives of existing antimicrobial classes with multiple resistance mechanisms in existence (7). While multiple antimicrobial agents are being developed for the treatment of Gram-negative bacteria, *Mycobacterium tuberculosis*, *Staphylococcus aureus*, and *Clostridioides difficile*, only one species-specific antimicrobial agent in this development pipeline will target *E. faecium* (7).

In this review, we present an overview of the treatment options for VRE BSIs, the role of antimicrobial dose optimization through therapeutic drug monitoring (TDM) in supporting clinical infection management, and challenges and perspectives for the future.

VANCOMYCIN-RESISTANT *ENTEROCOCCUS*

Microbiology

Enterococci are Gram-positive aerobes that are commensal pathogens of both the gastrointestinal tract and the genitourinary tract. Enterococci were considered part of the genus *Streptococcus* and classified as group D streptococci until the mid-1980s, with the *Enterococcus* genus being officially recognized in 1986 (8). There are more than 10 known species of *Enterococcus*, with *E. faecalis* and *E. faecium* being the most medically important species (9). Although *Enterococcus* spp. have traditionally been considered to lack the degree of virulence of other pathogenic bacteria, their role in

life-threatening infections is increasingly being recognized (8). *Enterococcus* spp. are well adapted to survive in the hospital environment through their ability to tolerate heat, chlorine, and some alcohol preparations (10, 11), which provides a challenge for hospital infection prevention and control practices (12). They have multiple mechanisms to increase their pathogenic potential, including the ability to evade the host immune system, attach to host cells and foreign bodies, and form biofilms that impair antibiotic killing and phagocytic attack (8).

All enterococci have an expected phenotype of resistance to virtually all cephalosporins (ceftaroline and ceftobiprole have activity against *E. faecalis*), antistaphylococcal penicillins, aztreonam, temocillin, polymyxin B/colistin, nalidixic acid, fusidic acid, aminoglycosides, macrolides, clindamycin, and trimethoprim-sulfamethoxazole (13, 14). *E. faecalis* strains have an additional expected phenotype of resistance to quinupristin-dalfopristin (QD), whereas *E. faecium* strains are commonly susceptible. For a detailed review of antimicrobial resistance mechanisms in enterococci, see a recent review by García-Solache and Rice (8).

β-Lactam resistance in enterococci is attributable to the expression of low-affinity penicillin-binding proteins (PBPs). These are PBP4 and PBP5 for *E. faecalis* and *E. faecium*, respectively. If an *Enterococcus* species isolate tests resistant to ampicillin, the isolate would also be considered resistant to ureidopenicillins and imipenem (resistance due to alterations in PBP5). The vast majority of *E. faecium* isolates are ampicillin resistant, whereas high-level penicillin resistance in *E. faecalis* is a much rarer event and should prompt the laboratory to confirm the species identification. As for other antimicrobial classes, acquired resistance to tetracyclines (except tigecycline) is widely encountered, mediated by the ribosomal protection mechanism *tet*(M), which is carried by conjugative transposons. Fluoroquinolones tend to have limited activity, with moxifloxacin having greater activity than ciprofloxacin or levofloxacin. Aminoglycoside-modifying enzymes lead to high-level aminoglycoside resistance, which negates any synergistic benefit when used in combination with cell wall-active agents. The oxazolidinones and daptomycin remain broadly active against both *E. faecalis* and *E. faecium*, although acquired resistance can occur via ribosomal mutations and bacterial membrane modification, respectively. Linezolid resistance, as described by García-Solache and Rice (8) and Miller et al. (15), demonstrates a dynamic nature with the emergence of resistance depending on the number of ribosomal genes that contain the relevant mutations.

Glycopeptide resistance remains one of the most important acquired resistance phenotypes in enterococci. This occurs through the acquisition of transferrable plasmids carrying a *van* gene, which encodes a modification of the primary D-alanine-D-alanine-binding site of glycopeptides (16). At least nine mechanisms of glycopeptide resistance in *Enterococcus* spp. have been identified (*vanA* to *vanE*, *vanG*, and *vanL* to *vanN*) (8, 17, 18); *vanA* and *vanB* are the most common worldwide, with the *vanA* genotype being associated with high-level resistance to vancomycin and teicoplanin, while *vanB* retains susceptibility to teicoplanin (16, 17). The transfer of the *vanB* operon from anaerobic flora to glycopeptide-susceptible enterococcal strains in the human bowel is thought to be a driver of the emergence of *vanB* VRE (19). It is not yet known where the natural reservoir of the *vanA* operon is (18). More recently, vancomycin-variable *Enterococcus* (VVE) strains have been reported, which are *E. faecium* strains that test phenotypically susceptible to vancomycin but harbor a *vanA* or *vanB* gene (9). Such strains can be a diagnostic challenge for the laboratory and are not identified on commonly used chromogenic screening media. As such, many diagnostic laboratories will now routinely perform molecular methods for the detection of *vanA* and *vanB* genes on all invasive *E. faecalis* or *E. faecium* isolates cultured from a sterile site (20).

Epidemiology of VRE

Vancomycin resistance in *Enterococcus* spp. is a global concern. The acquisition of glycopeptide resistance was first reported in England and France in the late 1980s (21, 22). While glycopeptide resistance occurs in both *E. faecalis* and *E. faecium*, it is predominantly associated with *E. faecium*. Vancomycin resistance rates of >40% in *E.*

faecium isolates have been reported in many countries, including Australia, the United Sates, and parts of Europe (23). Comparatively, the rates of vancomycin resistance in *E. faecalis* isolates are reported to be <5% across the same countries (24–26). The increasing rate of vancomycin resistance in *E. faecium* has been linked to a number of factors, including patient colonization, a contaminated hospital environment, colonization pressure, antibiotic selection pressure, and inadequate hospital infection prevention and control strategies (17).

International rates of VRE bloodstream infection. (i) The United States and Canada. Vancomycin resistance in *E. faecium* (VRE*fm*) was first identified in the United States in the 1980s, with rates of 60.0% reported in 2001, which increased to 80.7% in 2010 (25). The United States remains one of the countries with the highest rates of VRE*fm* BSIs in the world. Reductions in vancomycin resistance among *E. faecium* isolates over time have been observed, with a reduction from 79.6% in 2010 to 2011 to 62.8% in 2018 to 2019 (27). *vanA* is the most common phenotype in VRE*fm* BSIs (93.9%), with the *vanB* phenotype being identified in 6.1% of infections in 2018 to 2019 (27). Daptomycin nonsusceptibility (MIC of >32 μg/mL) was first reported in the United States in 2005, and linezolid nonsusceptibility was first reported in 2000 (28, 29). A 10-year review of all VRE*fm* BSIs demonstrated that linezolid and oritavancin were the only two antimicrobial agents with VRE activity to have >90% susceptibility against all *E. faecium* and vancomycin-resistant subsets from 2010 to 2019 (27, 30). The rate of vancomycin resistance among *E. faecalis* BSIs (MIC of >4 μg/mL) is low in the United States, reducing from 4.5% (2010 to 2011) to 2.2% (2018 to 2019) (27).

The Canadian Nosocomial Infection Surveillance Program (CNISP) collects data from 87 hospitals across the country, with an observed increase in VRE BSIs from 0.18 to 0.31 infections per 10,000 patient days between 2016 and 2020 (31). No major fluctuations were observed for VRE BSI rates during the 2020 coronavirus disease 2019 (COVID-19) pandemic. Canadian VRE BSIs are driven largely by *vanA* VRE*fm*, with only very small numbers of vancomycin-resistant *E. faecalis* (VRE*fs*) infections being reported (31). Both daptomycin and linezolid nonsusceptibilities in *E. faecium* were first reported in 2016 (31).

(ii) Europe. VRE*fm* was first identified in Europe in the 1980s (21, 22). The European Antimicrobial Resistance Surveillance Network (EARS-Net) demonstrated a steady increase in the rate of VRE*fm* BSIs between 2012 and 2018, from 8.1% to 19.0% (24). These data include the 27 countries of the European Union, in addition to Norway, Iceland, and the United Kingdom. While the pooled rates of resistance appear relatively low, data from individual nations highlight that rates of invasive VRE*fm* isolates are disproportionately higher in Lithuania (56.6%), Cyprus (44.2%), and Greece (41.8%) (32, 33). Similarly, the SENTRY Antimicrobial Surveillance Program, which collects isolates and reports rates of resistance from blood culture isolates from 21 European countries, demonstrated rates of vancomycin resistance in *E. faecium* of 23.2% in 2010 and 19.4% in 2016 (25). The rate of vancomycin resistance among *E. faecalis* BSIs (MIC of >4 μg/mL) is low in Europe, with proportions of 0.0 to 2.1% in 2010 to 2018 (25) and a European-weighted mean of 1.1% in 2012 to 2019 (24).

(iii) The United Kingdom and Ireland. The British Society for Antimicrobial Chemotherapy (BSAC) Resistance Surveillance Programme has identified a consistent increase in the proportion of *E. faecium* bloodstream infections over time, from 31% in 2001 to 2003 to 51% in 2017 to 2019 (34). The rate of vancomycin resistance in these *E. faecium* infections was approximately 30%, with annual rates ranging from 19% to 40% and *vanA* being the predominant phenotype (approximately 95%) (34). Linezolid-resistant enterococci were first reported in 2002 (35). The rate of vancomycin resistance in *E. faecalis* isolates included in the BSAC data set was low (<3%) (34).

(iv) Australia and New Zealand. The first isolate of VRE*fm* in Australia was identified in Melbourne in 1994 (36). The Australian Enterococcal Sepsis Outcome Program (AESOP) arm of the Australian Group on Antimicrobial Resistance (AGAR) demonstrated relatively consistent rates of VRE*fm* BSIs since 2011, with the exception of 2020. In *E. faecium* BSIs,

the rates of vancomycin resistance were 41.7% in 2013 and 41.6% in 2019 (37). In 2020, there was a decrease in the proportion of VRE*fm* BSIs, with vancomycin resistance being identified in 32.6% and 32% of reported isolates using the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical and Laboratory Standards Institute (CLSI) guidelines, respectively (26). The postulated reason for this observed reduction is hospital restrictions on elective surgery due to the COVID-19 pandemic (26). *vanB* is the predominant genotype (21.3% of isolates harboring *van* genes) of VRE*fm* in Australia (26, 37). As a consequence, the proportion of *E. faecium* bloodstream infections with teicoplanin resistance has been lower, at 13.0% and 11.1% in 2020 according to EUCAST and CLSI guidelines, respectively (26). Both daptomycin- and linezolid-nonsusceptible VRE BSIs were identified in Australia in 2014 (37–39). The rate of vancomycin resistance among *E. faecalis* BSIs is low in Australia, with a proportion of 0.2% according to both CLSI and EUCAST guidelines reported in 2020 (26).

Rates of VRE in New Zealand are significantly lower than those observed in Australia, with national surveillance of all New Zealand VRE isolates provided by the Institute of Environmental Science and Research, funded by the Ministry of Health, with the cooperation of the diagnostic laboratories. A total of 38 isolates, from all body sites, were confirmed to be VRE in 2020, a single isolate of which was from a blood specimen (40). Of all 2020 VRE isolates, *vanA* VRE*fm* was the predominant species and genotype (40). As observed in Australia, the numbers of VRE isolates reported in New Zealand in 2020 ($n = 38$) were markedly reduced compared to those in 2019 ($n = 95$) (41). Teicoplanin resistance in *vanB* VRE*fm* was first publicly reported in 2008 (42), linezolid resistance in *vanA* VRE*fm* was first reported in 2017 (43), and no data are publicly available for daptomycin nonsusceptibility.

(v) Central and Southeast Asia. In contrast to many other countries around the world, the prevalence of VRE is relatively low in China, with the China Antimicrobial Surveillance Network (CHINET) reporting a prevalence of VRE*fm* of $<5\%$ during the 2005–2017 surveillance period (44). Specific data on BSIs are not readily available; however, the authors of that study explained that this low rate of VRE may be related to the infrequent use of vancomycin oral preparations (44). Southern India reported 19.2% vancomycin resistance in enterococcal BSIs in 2020, with a predominance of *E. faecium* with the *vanA* phenotype (45). Thailand reported a prevalence of vancomycin resistance in *E. faecium* BSIs of 8.1% in 2018 and 2020 (46, 47).

(vi) Other countries for which data are lacking. While this is not a comprehensive review of international VRE BSI rates, data have been variably reported in other countries and regions. Improved global reporting and governance for the reporting of VRE BSIs, in addition to increased investment in AMR surveillance, are essential to combat the ongoing threat posed by VRE.

VRE Colonization

Enterococci are commensal pathogens of the human body, with the main reservoir being the gastrointestinal tract (48) (see Fig. 1). The most significant risk factor for VRE colonization is previous exposure to antimicrobial therapy. Multiple antimicrobial agents have been implicated, including both oral and intravenous (i.v.) vancomycin, broad-spectrum cephalosporins, agents with anaerobic activity, and antimicrobial agents that are active against Gram-negative pathogens (17, 49).

Additional risk factors for the acquisition of VRE colonization include frequent contact with health care facilities, prolonged hospitalization, immunosuppression, admission to the intensive care unit (ICU) or a surgical unit, and the presence of an indwelling catheter (e.g., urinary and vascular catheters) (49, 50). Given the risk factors for acquisition, certain patient cohorts have been shown to have higher rates of VRE colonization, including patients with hematological malignancy and hematopoietic stem cell transplant (HSCT) and solid-organ transplant (SOT) recipients. A 2016 systematic review and meta-analysis of 8,391 patients with hematological malignancy demonstrated that the pooled prevalence of VRE colonization was 20%, and those who were colonized were 24 times more likely to develop a BSI than patients without VRE colonization (50). All SOT recipients are

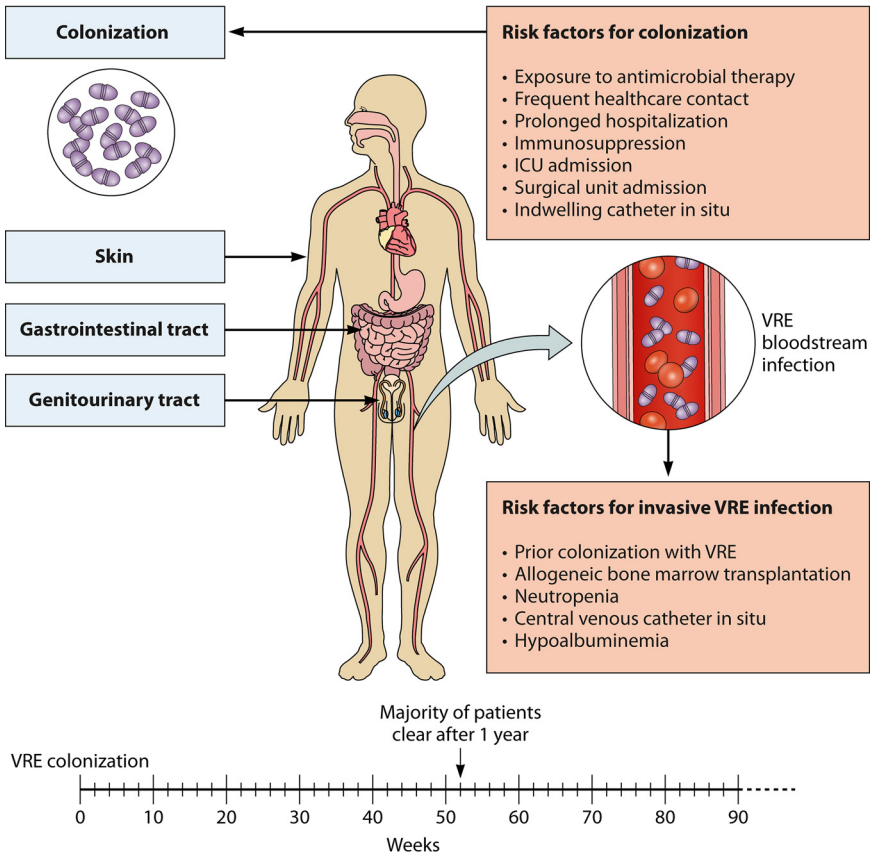

FIG 1 Role of VRE in colonization and infection.

considered to be at a high risk for VRE colonization; however, liver transplantation has been associated with the highest rates. A 2014 meta-analysis of colonization in SOT recipients reported an 11.9% prevalence of pretransplant colonization with VRE, which was predominantly driven by liver patients (51). The rate of posttransplant colonization for liver transplant recipients was 16% (51). The authors of that study estimated that pretransplant VRE carriage in liver transplant recipients was associated with a 6.7-times-higher risk of VRE infection posttransplant than for those who were not VRE colonized (51). In contrast, a recent 10-year retrospective review of nonliver SOT recipients at a Canadian hospital with routine rectal VRE screening in place showed that 4.6% of recipients were colonized with VRE during the peritransplant period (that is, 90 days before until 30 days after transplant) (52). When reviewed according to organ, lung, heart-lung, and kidney-pancreas transplant recipients had the highest colonization prevalences, at 10.6%, 5.6%, and 4.8%, respectively; however, only a small proportion of patients went on to develop a clinical VRE infection (3.7%) (52).

Studies have attempted to determine the duration of VRE colonization to assist with infection prevention strategies and the clinical management of patients. A retrospective review of 103 patients discharged from an Australian hospital demonstrated that the majority of patients clear VRE (or stop shedding) after 1 year; however, ongoing colonization was detected in a small proportion for up to 4 years (53). A second study of 127 patients in South Korea demonstrated that the median time to VRE clearance was 8.9 weeks following discharge from the hospital (range, 2 to 90 weeks) (54). The roles of routine VRE colonization screening and control interventions vary widely between institutions, with no international guidelines being available. A recent systematic review evaluated the economic value associated with VRE control practices and identified varied results (55). Most of the included studies showed that some form of VRE screening and the use of contact precautions were cost-effective, with values as

high as US$419,346 in savings per year when taking into account intervention costs and improved health outcomes (55, 56). A 2020 retrospective multicenter interrupted time series study demonstrated that the discontinuation of routine contact precautions for VRE (while continuing other routine horizontal infection prevention strategies such as hand hygiene and device- and procedure-related infection prevention bundles) did not increase the number of hospital-acquired VRE central-line-associated BSIs or catheter-associated urinary tract infections (UTIs) (57). At this stage, approaches to VRE screening and infection control practices remain mixed, with conflicting cost-effectiveness data. The direct costs and logistics of active screening are often a hurdle within health care institutions, and further data showing an impact on patient outcomes may provide a greater impetus for health care institutions to implement such approaches.

VRE Bloodstream Infections

Risk factors for developing VRE bloodstream infections. One of the key risk factors for the development of a VRE BSI is previous VRE colonization (50). As described above, patients with hematological malignancy and HSCT and SOT recipients in particular are at an increased risk of VRE colonization. A number of studies have quantified the occurrence of VRE BSIs in these patient cohorts, including 10.6% of patients undergoing cytarabine-based induction chemotherapy (58), 7.8% of patients undergoing liver transplant (also including vancomycin-susceptible enterococci [VSE]) (59), and 3.6% of patients undergoing a first allogeneic HSCT (60). In patients with hematological malignancy undergoing HSCT, 13% to 34% develop VRE BSI after VRE colonization (58, 61–63). Of note, patients receiving umbilical cord blood allografts have been shown to have the highest rate of VRE BSI compared to other recipients (bone marrow and peripheral blood stem cells) (60).

A 2011 retrospective Australian case-case-control study identified risk factors for developing both vancomycin-susceptible and -resistant enterococcal BSIs (64). Of the included cases, 95% of VRE isolates were *E. faecium*. Multivariate analysis identified that allogeneic bone marrow transplantation, neutropenia, the presence of a central venous catheter, and hypoalbuminemia were independently associated with VRE BSI (64). Notably, other described risk factors that were significant upon univariate analysis, including VRE colonization, receipt of chemotherapy agents associated with mucositis development, recent (<30 days) exposure to antibiotics, ICU admission, receipt of total parenteral nutrition, and having a urinary catheter *in situ*, were no longer significant after adjustment for other covariates (64). A number of studies have previously identified that antibiotic exposure (namely, vancomycin and agents with anaerobic activity) is associated with VRE BSI (65–68); however, these studies did not utilize a case-case-control study design that was specifically developed to assess risk factors for antimicrobial-resistant pathogens (69).

Persistent enterococcal BSI (p-EB), defined as the further isolation of the same species of *Enterococcus* from blood cultures after at least 72 h of appropriate antibiotic therapy, has been shown to occur in approximately 15 to 20% of patients (70–72). A 2022 retrospective European study in two tertiary teaching hospitals found that hematological malignancy, infective endocarditis (IE), and the initial use of daptomycin as antimicrobial therapy were independently associated with p-EB (72). The isolation of *E. faecium* was also identified as an independent risk factor for p-EB; however, this finding was driven by vancomycin-susceptible isolates (72).

Outcomes of VRE bloodstream infections. (i) Clinical outcomes. Despite significant advances in infection prevention and control and the development of antimicrobial treatment options (e.g., linezolid and daptomycin), the morbidity and mortality rates associated with VRE BSI remain high. Compared to VSE BSIs, VRE BSIs are associated with prolonged hospital stays, high health care costs, and high mortality rates (50, 73). A 2021 European systematic review demonstrated a pooled all-cause mortality rate of 33.5% (95% confidence interval [CI] 13.0 to 57.3%; range, 19.1 to 41.3%) for patients with health care-associated VRE BSI (74), with one included study reporting a 19.1% attributable mortality rate (75). A recent Australian cohort study showed that VRE*fm* BSIs

were associated with an odds ratio (OR) for all-cause in-hospital mortality of 5.01 (95% CI, 2.26 to 10.39) compared to an uninfected patient (76). HSCT recipients who develop VRE BSI have a 2.9-fold-increased risk of death compared to HSCT recipients without BSI at 1 year posttransplant (60). Importantly, the reported mortality rate from VRE BSI has reduced since the early reports, which included a 1995 cohort of patients with cancer who had an all-cause in-hospital mortality rate of 73% (65). At a national level, an all-cause mortality rate of 32.7% over the 2016–2020 period was reported in Canada (31). Australia has observed a marked reduction in mortality rates, falling from 30.9% and 30.1% in 2019 and 2018, respectively, to 19.6% in 2020 (11, 12, 26). The reason for this reduction in mortality is not yet known; however, this time period aligns with the onset of the COVID-19 pandemic, and a reduction of *vanA* isolates was observed by AESOP. The challenge with reporting mortality rates from VRE BSIs is that these patients are often unwell with other comorbidities, including patients with cancer receiving chemotherapy, those admitted to the ICU, and those with mucositis, and therefore, determining mortality attributable to the infection is difficult.

Patients with p-EB have been shown to have a higher 30-day mortality rate than patients without p-EB (32% versus 18%) (72). These data were supported by the VENOUS I study, a prospective observational study of enterococcal BSIs in the United States, which demonstrated that microbiological failure, defined as a lack of clearance $\geq$4 days after the index blood culture, was the strongest predictor of all-cause in-hospital mortality for *E. faecium* (hazard ratio [HR], 5.03 [95% CI, 3.25 to 7.77]) (77). Similarly, Chuang et al. showed a higher rate of microbiological failure in patients who did not survive VRE*fm* BSI than in survivors (50.7% versus 16.8% [$P < 0.001$]) (78). These data highlight the importance of early interventions to clear enterococcal BSI, including aggressive source control and appropriate antimicrobial choice and dose (77).

Disparity remains between mortality rates associated with VRE and VSE BSIs. A single-center retrospective study in Germany showed overall survival rates of 74.5% and 90.7% for VRE and VSE BSIs, respectively (79), while a prospective multisite study across 10 U.S. hospitals (VENOUS I) identified in-hospital mortality rates of 35.7% and 12.5% for VRE and VSE, respectively (77). Australian national data from 2020 showed similar 30-day all-cause mortality rates between VRE*fm* and VSE*fm* BSIs (19.8% versus 19.4% [$P = 0.9$]) (26). Changes in hospitalized patient case mix related to the COVID-19 pandemic may explain these contrasting findings as the 2019 mortality rates were 30.9% and 24.0% ($P = 0.17$) for VRE*fm* and VSE*fm*, respectively (12).

Studies on the impact of delays in the administration of appropriate antimicrobial therapy for the treatment of VRE BSIs have identified conflicting results. Increased 30-day and 1-year mortality rates were observed by Aslam et al., while Cheah et al. demonstrated no association between the number of days to appropriate antimicrobial therapy and mortality for patients with *vanB* VRE BSIs (80, 81). Despite these findings, antimicrobial stewardship interventions, including the early review of positive blood cultures with the goal of optimizing the antimicrobial spectrum of activity and dosing, are recommended for patients with VRE BSIs. Further research is required to determine the impact of delayed appropriate antimicrobial therapy on VRE BSIs.

Culture-based methods for determining the presence of viable bacteria in the blood remain the reference standard for the microbiological diagnosis of enterococcal BSIs. However, the main limitations include false-negative cultures (due to either low numbers of circulating bacteria or concurrent antimicrobial therapy), time delays for culture positivity (anywhere from 12 to 72 h from the time of blood draw), bacterial identification, and the finalized phenotypic susceptibility results (potentially after an additional 24 h). To expedite the time to targeted therapy, several rapid diagnostic tests (RDTs) have been developed for BSI diagnosis, including the direct detection of *vanA* and *vanB* genes (82). The principles behind these RDTs include matrix-assisted laser desorption ionization–time of flight (MALDI-TOF), multiplex real-time PCR, fluorescent *in situ* hybridization (FISH), and microarray-based assays (82). These assays can largely be split into two main categories: assays performed on blood culture bottles that have flagged

positive after a period of incubation and assays performed on blood samples drawn directly from patients. The application of these assays in routine clinical practice, however, is limited by the cost and requirement for specialized equipment, limiting their application in low-resource settings. The implementation of RDTs has been shown to identify enterococcal species, including the direct detection of *vanA* and *vanB* genes, more rapidly than traditional culture-based methods (83), resulting in a reduced time to effective and appropriate antimicrobial therapy (83–85) and reduced hospital costs (84). Clinical outcome studies of RDTs for patients with enterococcal BSIs have reported variable results, including reduced mortality (83); however, no statistically significant differences have been observed for attributed mortality rates (84), rates of infection-related readmission within 90 days (84), or hospital length of stay (LOS) (83, 84). Further studies are required to determine the clinical outcome benefits of RDTs and their role in VRE BSI management.

Nonpharmacological interventions to reduce enterococcal BSI mortality have been investigated, including the implementation of an infection management bundle and infectious diseases (ID) consultation. Bartoletti et al. found significantly reduced all-cause 30-day (20% versus 32% [$P = 0.0042$]) and 1-year (50% versus 68% [$P < 0.001$]) mortality rates in a quasiexperimental study following the nonmandatory implementation of a bundle comprising ID consultation, echocardiography, follow-up blood cultures, and early targeted treatment (70). Only a small proportion of isolates were VRE ($<$5%). A recent 2022 systematic review and meta-analysis found no association between ID consultation and overall enterococcal BSI mortality rates when the results of all studies were pooled. Notably, those authors found a significant protective association when studies were limited to those reporting results from multivariate analyses (pooled OR [pOR, pooled odds ratio], 0.40 [95% CI, 0.24 to 0.68]; $I^2 = 0\%$). No association between ID consultation and VRE BSI mortality was found when analyzing five studies that exclusively evaluated VRE BSIs (pOR, 1.07 [95% CI, 0.58 to 1.98]; $I^2 = 60\%$) (86). However, the studies included in this meta-analysis did not specifically aim to compare patients who received ID consultation against those who did not, representing a key limitation of this finding. Despite these findings, ID consultation should be considered the standard of care for all VRE BSIs to drive appropriate antimicrobial use in an often-complex patient cohort.

(ii) Nonmortality outcomes. Hospital LOS and economic impacts are the two most commonly assessed nonmortality outcomes reported in the literature. Irrespective of the pathogen involved, prolonged hospital admissions ($\geq$14 days) are associated with an increased risk of hospital-acquired infections, an increased risk of in-hospital death, and a reduced likelihood of being discharged home (87). A 2016 systematic review and meta-analysis identified that VRE BSI is associated with a longer hospital LOS than VSE BSI, with a mean difference of 5.01 days (95% CI, 0.58 to 9.44 days) (73). The recent prospective VENOUS I study demonstrated an increased hospital LOS of 12 days in patients with VRE BSIs compared to those with VSE BSIs, while two retrospective studies showed an additional 9 to 10 days of hospital admission for patients with VRE BSIs (77, 80, 88). A 2018 European retrospective matched case-control study aimed to investigate the economic burden directly attributable to vancomycin resistance in *Enterococcus* spp. The isolation of VRE from a surgical site, the bloodstream, an intra-abdominal infection, and organs within the visceral cavity was associated with a significantly higher total hospital cost than for patients with a VSE infection (€57,675 versus €38,344 [$P = 0.03$]) (88). This increase in cost was related to the period after the onset of infection, with pharmacy, nursing staff, medical products, and assistant medical technicians making up the cost differential (88). Cheah et al. reported similar findings in Australia in relation to *vanB* VRE BSIs. Patients with VRE BSI had almost twice the total cost compared to that of VSE BSI (AU$86,540 versus AU $43,178 [$P = 0.002$]) (80). These increased costs were driven by pharmacy, nursing, and pathology costs. The predominant antimicrobial agent used by Cheah et al. was teicoplanin, and it is anticipated that this cost difference would be higher when using alternative VRE treatment options such as linezolid or daptomycin.

ANTIMICROBIAL THERAPY FOR VRE BLOODSTREAM INFECTIONS

There are limited therapeutic options available for the management of VRE BSIs. High-level resistance of *Enterococcus* spp. to antibiotics, unfavorable pharmacokinetics (PK), drug interactions, adverse effects, and/or limited routes of administration all add to the challenge of treating VRE BSIs (89, 90). There is also a paucity of new antimicrobial agents in the pipeline, and those that have been developed have been iterations of existing antimicrobial classes. Given the challenges of antimicrobial therapy for VRE BSI, nonpharmacological approaches are essential, including source control and the removal of indwelling lines and devices (where possible). Here, we describe the available antimicrobial treatment options for VRE BSI and the evidence supporting their use. We also review more complex syndromes, including persistent VRE BSIs, IE, and osteoarticular infections.

Until the introduction of quinupristin-dalfopristin in 1993 and teicoplanin in the early 1990s, enterococcal BSIs with ampicillin and vancomycin resistance relied on combinations of two to three cell wall-active agents, including combinations of penicillin, vancomycin, and gentamicin (91, 92) or gentamicin plus at least two of imipenem-cilastatin, ampicillin-sulbactam, or vancomycin (93). Doxycycline (94), novobiocin (in combination with doxycycline or rifampicin) (95), chloramphenicol (94, 96, 97), and line removal alone (98) were all used historically with varying outcomes, and there have been various combinations studied in animal and *in vitro* models (91, 99–101).

Daptomycin

Daptomycin is a cyclic lipopeptide approved for clinical use in the United States (approved in 2003), the European Union (approved in 2006), and Australia (approved in 2008) (102). It is approved for complicated skin and skin structure infections (cSSTIs) (4 mg/kg of body weight) and *S. aureus* right-sided IE and/or *S. aureus* BSI (6 mg/kg). The use of daptomycin for VRE infections is considered to be "off-label" (103). Daptomycin has a unique mode of action whereby its lipophilic tail binds and inserts into the bacterial membrane, generating an ion-conducting channel that causes the release of intracellular potassium, membrane depolarization, and subsequent cell death (102). Daptomycin has relatively good penetration into most body sites; however, it is inhibited by pulmonary surfactants and therefore should not be used for primary infections of the lung (104). There is evolving literature demonstrating efficacy in models of hematogenous pneumonia (e.g., *S. aureus* septic pulmonary emboli [105]); however, the advice remains to avoid the empirical use of daptomycin in the setting of suspected primary pulmonary infection.

Despite not being approved for use in VRE infections, daptomycin is considered one of the key antimicrobial agents for the management of this pathogen. Recent literature has focused on the dose-dependent effect of daptomycin in the treatment of VRE BSIs (90). Standard dosing (6 mg/kg/day), as approved for *S. aureus* infections, has been shown in a number of studies to be associated with increased mortality rates compared to higher doses ($\geq$9 mg/kg/day) in VRE BSI (106–111). A 2017 retrospective review of 911 patients with VRE BSIs in U.S. Veterans Affairs hospitals showed that high-dose daptomycin ($>$10 mg/kg/day) was associated with improved survival compared with the standard dose (6 [$\pm$0.5] mg/kg/day) (adjusted HR [aHR], 2.58 [95% CI, 1.27 to 4.88] [$P = 0.004$]) and a medium dose (8 [$\pm$0.5] mg/kg/day) (aHR, 2.52 [95% CI, 1.27 to 5.00] [$P = 0.008$]) (107). No survival difference was observed between standard- and medium-dose daptomycin-treated patients. These data were supported by a prospective study in Taiwan that showed that higher doses ($\geq$9 mg/kg/day) were associated with lower mortality rates compared to lower doses (6 mg/kg/day), irrespective of the daptomycin MIC (108). Multivariate logistic regression identified that the mortality odds for patients with VRE BSIs were reduced by almost one-third for each milligram-per-kilogram increase in the daptomycin dose (adjusted OR [aOR], 0.62 [95% CI, 0.41 to 0.93] [$P = 0.02$]) (108). A more recent analysis from the same group showed that patients who received $\geq$11 mg/kg/day had lower rates of in-hospital mortality and microbiological failure (78). The ongoing data supporting higher dosing of daptomycin have led to guidelines recommending a dose of $\geq$10 mg/kg/day for the treatment of VRE*fm* BSI (112).

The pharmacodynamic (PD) target for predicting the efficacy of daptomycin for *Enterococcus* spp. is the AUC_{0-24}/MIC ratio (area under the concentration-time curve over

TABLE 1 Daptomycin and linezolid susceptibility breakpoints for *Enterococcus* spp. according to CLSI guidelines[d]

		Breakpoint (μg/mL)			
Drug	**Pathogen(s)**	**Susceptible**	**Susceptible dose dependent**	**Intermediate**	**Resistant**
Daptomycin	*Enterococcus* spp. except for *E. faecium*	≤2[a]		4	≥8
	E. faecium		≤4[b]		≥8
Linezolid	*Enterococcus* spp.	≤2		4	≥8
Tedizolid	*E. faecalis* only	≤0.5[c]			

[a]Based on a dose of 6 mg/kg daily.
[b]Based on an increased dose of 8 to 12 mg/kg daily.
[c]Based on a dose of 200 mg daily.
[d]See reference 14.

24 h in the steady state divided by the MIC). Complexities exist when determining daptomycin MICs in the microbiology laboratory, with reproducibility issues being observed between broth microdilution (BMD) and Etest (113). Of note, the CLSI and EUCAST recommend BMD determination of daptomycin MICs (14, 114). The increased tolerance of enterococci to daptomycin compared to *S. aureus* may explain the need for higher dosing. Notably, the MIC values of the upper end of the wild-type population distribution (also known as the epidemiological cutoff values [ECVs or ECOFFs]) for *E. faecalis* (2 to 4 μg/mL) and *E. faecium* (4 to 8 μg/mL) are much higher than that of *S. aureus* (1 μg/mL) (14, 115). The relationship between the MIC of daptomycin and outcomes of VRE BSI has been assessed by various studies, including a large multicenter registry (Cubicin Outcomes Registry and Experience [CORE]) where clinical failure was more common with higher daptomycin MICs (MICs of 3 to 4 μg/mL) than with MICs of ≤2 μg/mL (116). Two further studies demonstrated that a higher initial daptomycin MIC was associated with higher rates of microbiological failure (MIC of 3 to 4 μg/mL versus ≤2 μg/mL) (110) and mortality (MIC of ≥2 μg/mL versus ≤1 μg/mL) (78). Using Monte Carlo simulation to determine the probability of target attainment (PTA), Chuang et al. showed that for infecting isolates with an MIC of 1 μg/mL, daptomycin dosing at 12 mg/kg/day achieved PTAs of 73.8% for men and 89.7% for women (117). Isolates with an MIC of ≥2 μg/mL were unable to achieve a PTA of ≥50%, supporting concerns that daptomycin at 12 mg/kg/day may be insufficient for treating VRE BSIs with higher MICs (117). A further aspect that may impact outcomes but has not been evaluated rigorously in human studies is the effect of the inoculum. A recent simulated endocardial vegetation PK/PD model showed that the efficacy of daptomycin monotherapy at 6, 8, and 10 mg/kg/day may be subject to the inoculum effect (118). Increased daptomycin efficacy and no emergence of resistance were observed at lower inoculum levels of VRE*fm* compared to higher inoculum levels (118). This observation warrants further investigation in human studies to determine the impact of the inoculum size on serious VRE infections, including IE and BSIs.

The provision of daptomycin susceptibility breakpoints for *Enterococcus* spp. differ between the CLSI and EUCAST guidelines. As shown in Table 1, the CLSI provides breakpoints for "susceptible dose dependent" and "resistant." Conversely, EUCAST does not provide breakpoints due to uncertainty around the ability to achieve adequate exposure against wild-type isolates of *E. faecium* with even the highest reported daptomycin doses (114). A key influence on the lack of a EUCAST breakpoint is the fact that daptomycin is not licensed by the European Medicines Agency (EMA) for the treatment of enterococcal infections. Furthermore, the dose of daptomycin required to treat a bloodstream infection is 10 to 12 mg/kg, which greatly exceeds the maximum EMA-licensed dose of 6 mg/kg (114).

Daptomycin is a generally well-tolerated drug, with two notable adverse effects: muscle toxicity (e.g., myopathy/rhabdomyolysis) and eosinophilic pneumonia. A number of risk factors for muscle toxicity have been identified (119, 120); however, most pertinent to VRE BSI is the association between higher daptomycin doses and elevated creatinine phosphokinase (CPK) levels, including reports with doses of >8 mg/kg (121) and >11 mg/kg (78). Despite conflicting data, at least weekly testing of CPK levels is recommended while

TABLE 2 Daptomycin and linezolid susceptibility breakpoints for *Enterococcus* spp. according to EUCAST guidelines[a]

Drug	Pathogen	Breakpoint (μg/mL)	
		Susceptible	Resistant
Daptomycin	*Enterococcus* species	IE	IE
Linezolid	*Enterococcus* species	≤4	>4
Tedizolid	*Enterococcus* species	IE	IE

[a]See reference 274. IE, insufficient evidence.

receiving daptomycin, increasing to twice weekly in the setting of other risk factors (e.g., renal impairment). TDM may have a role, which is discussed further below. Postmarketing follow-up of daptomycin has uncovered an association with eosinophilic syndromes, including pneumonia (122). A number of risk factors have been identified (123); however, there are conflicting data about the association with daptomycin dosing (123–125).

Oxazolidinones (Linezolid and Tedizolid)

The oxazolidinone antimicrobial class comprises linezolid and tedizolid, with linezolid being approved for the treatment of VRE infections in the United States (approved in 2000), the European Union (approved in 2001), and Australia (approved in 2001). Tedizolid, a newer oxazolidinone, is approved in the United States (approved in 2014) and the European Union (approved in 2015) for acute bacterial skin and skin structure infections (ABSSSIs) caused by susceptible bacteria; however, it is not approved in Australia. The oxazolidinones bind to the 50S ribosomal subunit and disrupt the formation of the 70S ribosomal complex, preventing the formation and elongation of peptide chains (126, 127). Both agents have broad Gram-positive activity *in vitro*, including activity against VRE*fm* and VRE*fs*.

The pharmacodynamic target for predicting linezolid efficacy is the AUC_{0-24}/MIC ratio (128, 129). As shown in Tables 1 and 2, the clinical breakpoints for linezolid susceptibility for *Enterococcus* spp. differ slightly between the CLSI and EUCAST recommendations. The CLSI reports isolates as being susceptible with an MIC of ≤2 μg/mL and intermediate with an MIC of 4 μg/mL, whereas EUCAST reports isolates as being susceptible with an MIC of ≤4 μg/mL. The resistance breakpoints (MIC of ≥8 μg/mL) are concordant. Tedizolid clinical breakpoints are less well established. The CLSI recommends testing only for *E. faecalis* and that linezolid-susceptible strains can be considered susceptible to tedizolid, although linezolid-resistant strains may also be susceptible to tedizolid (tedizolid MIC of ≤0.5 μg/mL for susceptibility). EUCAST currently reports insufficient evidence to set tedizolid breakpoints but reports ECOFFs for both *E. faecalis* and *E. faecium* at 1 μg/mL.

Linezolid has long been considered a bacteriostatic, concentration-independent agent; however, *in vitro* data have demonstrated concentration-dependent killing at higher exposures against VRE*fs* isolates with intermediate and resistant MICs (4 μg/mL and ≥8 μg/mL, respectively) (130). Tedizolid also appears to have enhanced potency compared to linezolid, resulting in lower enterococcal MICs, and has *in vitro* activity against linezolid-resistant isolates carrying the chloramphenicol-florfenicol resistance gene (*cfr*) (131).

Linezolid is one of the key antimicrobial agents for the treatment of VRE BSIs and remains the only approved antimicrobial for this indication. A number of studies have compared the clinical outcomes of linezolid to those of daptomycin, with five subsequent meta-analyses showing conflicting results. Linezolid has been shown to be superior to daptomycin in terms of mortality in earlier meta-analyses (132–134); however, later meta-analyses have shown comparable mortality rates (89), including Shi et al., who performed a subgroup analysis comparing studies using high-dose daptomycin (>6 mg/kg) to studies using daptomycin at ≤6 mg/kg or where dosing data were not provided (90). The findings of the five meta-analyses are summarized in Table 3. The evidence for the use of tedizolid for the management of VRE BSI is currently limited to case reports only, including a report on the successful treatment of a daptomycin-nonsusceptible VRE*fm* BSI (135). The comparative efficacies of linezolid and tedizolid have been investigated in a murine acute VRE BSI model using two well-characterized VRE

TABLE 3 Comparison of meta-analyses of daptomycin versus linezolid for VRE BSIs[b]

Authors (reference)	No. of studies	Daily dose(s)		Primary outcome	Findings
		Daptomycin (mg/kg/day)	Linezolid (mg/day)		
Shi et al. (90)	22	All patients, 3.4–11.5 Subgroup analysis, >6 (HD) (n = 3); irrespective of dose[a] (n = 18)	1,200 (n = 10), NR (n = 12)	Mortality as described in individual studies	All patients, ↑ mortality for daptomycin (OR = 1.27 [95% CI, 0.99–1.63]; I^2 = 42.9%) Subgroup analysis, comparable mortality when HD daptomycin was used (OR = 0.92 [95% CI, 0.46–1.84]; I^2 = 49.4%)
Zhao et al. (89)	11	Median, 6 (n = 9); median, 6.1 (n = 1); mean, 7.4 (n = 1); range, 6–11.5	1,200 (n = 8), NR (n = 3)	Crude overall mortality	Similar mortality rates (RR = 1.07 [95% CI, 0.83–1.37] [P = 0.61]; I^2 = 48%)
Chuang et al. (133)	13	Median, 6 (n = 4); median, 5.5 (n = 1); mean, 6.4 (n = 1); 6 (n = 2); NR (n = 5)	1,200 (n = 7), NR (n = 6)	Mortality	↑ mortality for daptomycin (OR = 1.43 [95% CI, 1.09–1.86] [P = 0.009]; I^2 = 0%)
Balli et al. (134)	10	Median, 6 (n = 6); median, 5.5 (n = 1); NR (n = 3)	1,200 (n = 6), NR (n = 4)	Mortality (30-day all-cause)	↑ mortality for daptomycin (OR = 1.61 [95% CI, 1.08–2.40]; fixed-effects model [heterogeneity P = 0.42])
Whang et al. (132)	9	Usual dose, 6; range, 3.4–10.4	1,200 (n = 4), NR (n = 5)	Mortality as defined by the study investigators	↑ survival with linezolid (OR = 1.3 [95% CI, 1.0–1.8]; I^2 = 0 [P = 0.053])

[a]Studies that did not provide dose data or did not meet the criteria for high-dose daptomycin dosing.
[b]HD, high dose; NR, not reported; RR, risk ratio; OR, odds ratio; CI, confidence interval.

strains (*E. faecalis* 613 and *E. faecium* 447) (136). Neither drug had bactericidal activity *in vitro* against either VRE strain, and overall, linezolid yielded better treatment outcomes than tedizolid. The approved doses of linezolid and tedizolid are 600 mg every 12 h (q12h) and 200 mg daily, respectively (137, 138). Given the scarcity of evidence supporting tedizolid for VRE BSI, the remainder of this section focuses on linezolid.

Wide variations in linezolid plasma concentrations have been reported for different patient groups, including those with normal, impaired, and augmented renal function (139–143); elderly patients (140); and those with critical illnesses (144, 145). Concern exists that standard linezolid dosing (600 mg q12h) may result in insufficient exposure to effectively treat VRE isolates with elevated MICs ($\geq$1 μg/mL). A recent study using Monte Carlo simulations of patient data found that a linezolid dose of 600 mg q12h was unable to achieve a PTA of $\geq$90% for isolates with an MIC of $\geq$1.5 μg/mL, with higher doses (e.g., 600 mg q8h) or a continuous infusion (1,200 mg/day) being required (46). The hematological toxicity of the various dosing regimens was assessed using a minimum concentration of the drug in serum (C_{min}) of $\geq$9 mg/L as a surrogate marker, and that study showed that dosing of 1,200 mg once daily or divided dosing every 12 h (given as a 0.5- to 4-h infusion) produced a hematological toxicity rate of $<$20%, whereas significantly higher rates were observed with doses of 600 mg q8h (40.7%) and 1,200 mg as a continuous infusion (99.6%) (46). These data were also supported by a recent retrospective PK analysis with Monte Carlo simulations of linezolid levels from 338 acutely hospitalized patients that showed that linezolid doses of up to 2,400 mg q12h were required to achieve a PTA of $\geq$90% for isolates with an MIC of up to 4 μg/mL (146). Standard doses of linezolid of 600 mg q12h failed to achieve an optimal PTA by day 3 for those isolates with an MIC of $>$0.5 μg/mL (146). Taken together, the results of PK/PD studies suggest challenges in achieving appropriate levels with standard linezolid dosing when treating bacteria with an MIC of $\geq$1 μg/mL, and there are concerns plus a lack of clinical data to support the safety of higher doses.

Drug interactions and toxicity significantly limit the use of oxazolidinones. In particular, myelosuppression, lactic acidosis, and peripheral and optic neuropathies due to mitochondrial toxicity have been associated with linezolid use, with manufacturers recommending a maximum treatment duration of 28 days (138). Low body weight ($<$55 kg) has also been shown to be a risk factor for thrombocytopenia, with evidence suggesting that a dose reduction to 10 mg/kg q12h can delay the onset (147). As a consequence of toxicity issues, there is increasing evidence for the use of linezolid TDM (discussed below).

Teicoplanin

Teicoplanin is a bactericidal glycopeptide antibiotic with activity against VRE*fm* isolates harboring the *vanB* operon; however, it is inactive against those with a *vanA* genotype. Teicoplanin is used in both the European Union (approved in 1988) and Australia (approved in 1994); however, it is not available for use in the United States. The approved dose of teicoplanin for cSSTIs, pneumonia, and complicated UTIs is 6 mg/kg/day, while 12-mg/kg/day dosing is indicated for bone and joint infections and IE (148, 149). Loading doses are recommended to enable faster attainment of therapeutic concentrations, and these should be independent of renal function (150). Three to five loading doses are recommended in the product information (148, 149); however, more recently, the use of 5 loading doses has been shown to increase the probability of achieving therapeutic concentrations at steady state (151, 152).

There is limited published evidence supporting clinical outcomes with teicoplanin for the treatment of *vanB* VRE BSIs despite being routinely used in parts of the world for this indication (80, 153, 154). A retrospective Australian study found that definitive linezolid therapy for *vanB* VRE BSI was associated with lower odds of in-hospital mortality than with teicoplanin (80). Patients in this study were dosed with teicoplanin at 6 to 12 mg/kg (400 to 800 mg) q12h for 3 doses and then with maintenance doses of 400 to 800 mg daily, with adjustments for renal impairment. Xie et al. demonstrated that teicoplanin monotherapy for *vanB* VRE*fm* BSIs in an Australian cohort of cancer

patients was not associated with 30-day all-cause mortality and was associated with lower rates of ICU admission within 48 h of VRE BSI than for patients who received multiple sequential VRE-active antibiotics (teicoplanin, daptomycin, or linezolid) (153). The doses used in this cohort were a 6- to 12-mg/kg load for 3 doses and then 400- to 1,200-mg daily maintenance doses, with adjustment for renal function (153). Those authors acknowledged that there may be a tendency for clinicians to use alternative VRE treatment options (e.g., daptomycin or linezolid) for patients who are more unwell (153). Higher doses of teicoplanin (≥9 mg/kg/day) have been associated with greater treatment success in a small cohort of 20 patients from South Korea with Gram-positive BSIs. Of note, this cohort comprised 55.5% methicillin-resistant *S. aureus* (MRSA), with only 30% isolating VRE (154). Despite this, higher doses of 12 mg/kg/day are often used in clinical practice for invasive VRE infections, and TDM is recommended at the conclusion of the loading doses and 1 week thereafter (discussed below). Treatment failure and the emergence of resistance are ongoing concerns (155, 156).

Teicoplanin is relatively well tolerated, with associated adverse effects including hypersensitivity, fever, rash, neutropenia, and, less commonly, thrombocytopenia and nephrotoxicity. A relationship between high-dose regimens (≥12 mg/kg/day) and higher trough levels with adverse effects has been reported (154).

Quinupristin-Dalfopristin

Quinupristin-dalfopristin (QD) is a streptogramin antimicrobial agent that is bacteriostatic against *E. faecium*, including vancomycin-resistant strains (157). *E. faecalis* is a notable gap in its spectrum of activity. QD was used predominantly for the treatment of VRE BSIs before the introduction of linezolid and daptomycin; however, it is no longer available for use in Australia, the United States, or the European Union. The dose of QD for VRE BSI is 7.5 mg/kg every 8 h (158–160), with infusion site reactions and drug interactions due to cytochrome 3A4 inhibition limiting its utility for the management of VRE*fm* infections (159). Dalfopristin is hydrolyzed to pristinamycin IIA (159), which is available as an oral formulation. The most extensive use of pristinamycin is in France (157), with it generally being reserved as an oral tail to complete a treatment course or for long-term antimicrobial suppression (161, 162).

Most commonly, QD has been compared to linezolid for the treatment of VRE*fm* BSIs, with similar 30-day mortality and microbiological response rates (158, 163). Erlandson et al. found significantly more deaths in patients with VRE BSIs treated with QD than in those treated with linezolid upon univariate analysis; however, after adjustment for the severity of illness and other comorbidities, treatment group was not a significant independent factor (164). Prolonged BSI and the development of resistance while on treatment have also been described with QD (158) and, taken together, explain why this combination antibiotic is now reserved only for salvage treatment when other options are not available.

Lipoglycopeptide Antibiotics (Dalbavancin, Telavancin, and Oritavancin)

Lipoglycopeptide antibiotics are bactericidal agents with a broad spectrum of activity against Gram-positive organisms, including *in vitro* activity against *E. faecium* (165). Of note, oritavancin has *in vitro* activity against *vanA* and *vanB* VRE, whereas dalbavancin and telavancin have *in vitro* activity only against *vanB* VRE (165, 166). Over a 10-year period (2010 to 2019), oritavancin susceptibility has remained stable (>96%) for both *E. faecium* and *E. faecalis* in the United States, including BSI isolates (27). The lipoglycopeptides contain lipophilic side chains that prolong their half-life and increase their activity against Gram-positive cocci (165). Dalbavancin and oritavancin have long half-lives (~346 and ~393 h, respectively), which enables a weekly or a single dosing regimen (166), while telavancin has a half-life of 8.1 h and requires daily dosing (165). Presently, all three agents are approved in the United States for the treatment of ABSSSI, while dalbavancin and oritavancin are authorized for use in the European Union. The lipoglycopeptides are not yet registered in Australia. A paucity of clinical data exists for their use in treating VRE*fm* infections. A small number of case reports

have described the use of oritavancin for the treatment of BSIs caused by nonenterococcal Gram-positive bacteria (167, 168) and those caused by VRE (169, 170), but further clinical data are still required.

Tetracycline Derivatives

The tetracycline derivatives provide broad bacteriostatic coverage of Gram-positive and Gram-negative organisms, including activity against vancomycin-resistant strains of *E. faecium* and *E. faecalis* (171–174). The agents bind to the 30S subunit of bacterial ribosomes and inhibit bacterial protein translation (175). The newer derivatives eravacycline and omadacycline have modifications at C-7 and C-9 enabling them to overcome efflux pumps (*tet*K and *tet*L) and ribosomal protection proteins (*tet*M, *tet*O, and *tet*S) that are commonly associated with tetracycline resistance (174, 176, 177).

Tigecycline. Tigecycline is a lipophilic glycylcycline antibiotic that is approved for use in cSSTIs and complicated intra-abdominal infections (cIAIs) in the United States (approved in 2005), the European Union (approved in 2006), and Australia (approved in 2008). Its large volume of distribution enables good tissue penetration but results in low serum concentrations, limiting its clinical utility as a single agent for the management of VRE BSIs (171, 178). A 2017 systematic review and meta-analysis showed that tigecycline monotherapy was associated with an odds ratio of 2.73 (95% CI, 1.53 to 4.87) for mortality compared with tigecycline combination therapy for BSIs caused by a number of Gram-positive and Gram-negative pathogens (171). Its use for BSIs should be limited to combination therapy with an agent with favorable PK/PD characteristics (171).

Eravacycline. Eravacycline is a synthetic fluorocycline antimicrobial agent that is approved for use in the United States and the European Union for the treatment of cIAIs. It is not available for use in Australia. The evidence supporting the use of eravacycline for BSIs is relatively limited, with a *post hoc* analysis of patients with Gram-negative BSIs in cIAI phase 3 trials (IGNITE1 and IGNITE4) demonstrating efficacy for BSIs (179). Its use for the management of VRE BSI is limited to case reports at this time (180–182).

Omadacycline. Omadacycline is a semisynthetic aminomethylcycline antibiotic, approved in the United States for community-acquired bacterial pneumonia (CABP) and ABSSSI (183). It is not approved for use in the European Union or Australia. Omadacycline has been shown to be effective in the management of secondary BSI associated with ABSSSI or CABP in a *post hoc* analysis of three phase 3 trials (184). To our knowledge, there are no reports in the literature on the use of omadacycline for the specific management of VRE BSI.

Doxycycline and minocycline. The use of doxycycline and minocycline for the management of severe VRE bloodstream infections, including IE, is generally limited to older case reports in combination with other VRE-active agents (94, 185, 186). Doxycycline has been shown in an *in vitro* dynamic model to protect against the development of resistance when combined with linezolid (187). More recently, the role of doxycycline has been explored for the management of VRE UTIs (188).

Other Treatment Options

Fosfomycin. Fosfomycin is an old antimicrobial agent that has seen a resurgence in recent years due to increasing rates of Gram-negative antimicrobial resistance. Fosfomycin has broad activity against Gram-negative and Gram-positive pathogens, including bacteriostatic activity against VRE*fm* (189). Despite activity against VRE*fm*, there is a paucity of literature supporting its role as a single agent for the treatment of BSIs. Despite this, a role for fosfomycin may lie in its combination with other antimicrobial agents as salvage therapy (see below).

Chloramphenicol. Chloramphenicol is a broad-spectrum bacteriostatic antibiotic with activity against vancomycin-resistant isolates of *E. faecium* and *E. faecalis* (190). The use of chloramphenicol for VRE BSI treatment was more common in the late 1990s/early 2000s due to a lack of alternative treatment options. Chloramphenicol use for VRE BSIs has been shown in case series to be associated with favorable microbiological and clinical responses (96, 97, 191); however, its use has been associated with

TABLE 4 VRE-active agents in the development pipeline[a]

Drug (reference)	Class	Mechanism	Progress in pipeline (reference[s])
PS-757 (194)	Ring-fused 2-pyridone antibiotics (GmPcides)	Bacteriostatic against dividing cells, bactericidal against nondividing cells via autolysin	Preclinical
VRELysin	Bacteriophage cocktail	Cell lysis	Phase 1/2a study for VRE colonization (275)
Contezolid (7)	Oxazolidinone	Protein synthesis inhibitor	Phase 2 study for ABSSSI completed (276); approved in China in 2021 for cSSTI (277)
Delpazolid (7)	Oxazolidinone	Protein synthesis inhibitor	Phase 2a study for MRSA BSI (278)
Iclaprim (279)	Diaminopyrimidine	Dihydrofolate reductase inhibitor	Completed 2 phase 3 trials for ABSSSI (280) and 2 phase 3 trials for cSSTI (281, 282); a phase 2 trial for HAP/VAP was terminated (283)

[a]VRE, vancomycin-resistant enterococci; ABSSSI, acute bacterial skin and skin structure infection; cSSTI, complicated skin and skin structure infection; MRSA, methicillin-resistant *S. aureus*; BSI, bloodstream infection; HAP/VAP, hospital-associated pneumonia/ventilator-associated pneumonia.

the emergence of chloramphenicol resistance (192, 193). Doses of 750 to 1,000 mg i.v. q6h have been used (191), but serious adverse effects such as bone marrow suppression have limited its use (97). Chloramphenicol remains an important antibiotic in resource-limited settings and/or where no alternative treatment options are available.

Future VRE Drugs on the Horizon

A small number of new antimicrobial agents are in the development pipeline, such as contezolid and delpazolid; however, they do not offer a novel mechanism of action (Table 4). The development of bacteriophages and novel compounds such as VRELysin and GmPcides for the management of VRE infections is being explored with agents; however, human safety and outcome data are still lacking (194, 195). The repurposing of nonantimicrobial agents (e.g., acetazolamide) is also under investigation (196). New agents are still in early development and are predominantly in the early stages of clinical trials.

Duration of Treatment for Uncomplicated VRE Bloodstream Infections

The optimal duration of therapy for uncomplicated VRE BSIs is not yet known. A 2020 systematic review and meta-analysis of 22 VRE BSI studies showed that a duration of 11 to 15 days was prescribed in most studies (90). More recently, a retrospective multicenter study of uncomplicated VRE BSI (predominantly VRE*fm*) compared the clinical outcomes of patients receiving short-course ($<$9 days) to those of patients receiving long-course ($>$10 days) VRE-active therapy (197). The majority of the included patients (78.1%) received monotherapy, of which linezolid was the most commonly used. A short course (median of 7 days) was not associated with an increase in 30-day or 90-day mortality or BSI relapse compared to long-course therapy (median of 15 days) (197). These findings suggest that there may be a role for shorter durations of therapy for the management of uncomplicated VRE BSIs; however, further research is required to confirm this.

Persistent VRE Bloodstream Infections: Infective Endocarditis and Osteoarticular Infections

Persistent positive blood cultures with *Enterococcus* spp. ($\geq$72 h) despite appropriate antimicrobial therapy are associated with an increased 30-day mortality rate (72). In patients with persistent VRE BSIs, it is essential to assess for a source and actively manage as well as seeding of the infection to other sites such as the heart valves and bones.

Infective endocarditis. *Enterococcus* spp. are the third most common cause of IE, with *E. faecalis* being the most common causative enterococcal species (198). In patients with *E. faecalis* BSIs, a prevalence of confirmed IE of 26.1% $\pm$ 4.6% (95% confidence interval) has been reported (199). Predictors of IE in this cohort included $\geq$3 positive blood culture bottles, community acquisition, immunosuppression, and the presence of a prosthetic heart valve. VRE IE is relatively uncommon and, as for BSI, is most commonly caused by *E. faecium*. Very little data exist to support recommendations for the treatment of VRE IE. The European Society for Cardiology does not provide

recommendations for VRE IE and refers readers to seek expert advice (200). The American Heart Association recommends the use of linezolid or daptomycin (class IIb, level of evidence C), or for patients with persistent BSIs with enterococcal strains with high MICs of daptomycin (e.g., $\geq$3 μg/mL), combination therapy with daptomycin plus ampicillin or ceftaroline is recommended (class IIb, level of evidence C) (198). A multidisciplinary team approach is recommended, including ID, cardiology, cardiovascular surgery, and clinical pharmacy (198).

The evidence to support daptomycin use for VRE IE is relatively limited. A retrospective review of 70 patients with Gram-positive IE, of whom 7.8% had VRE, demonstrated successful clinical outcomes with a median daptomycin dose of 9.8 mg/kg/day (201). Daptomycin has been shown to penetrate vegetations in *in vitro* PD models with simulated endocardial vegetations (202, 203). Luther et al. demonstrated that the addition of gentamicin (1.3 mg/kg q12h) to daptomycin (dosed at either 6 mg/kg/day or 10 mg/kg/day) in the first 24 h improved bactericidal activity against biofilm-forming VRE*fm*, whereas rifampicin antagonized the activity of daptomycin (203). Hall et al. demonstrated that daptomycin had a dose-dependent effect against VRE*fm* and VRE*fs* isolates, with 10-mg/kg/day and 12-mg/kg/day doses having more significant and sustained killing than a 6-mg/kg/day dose (202).

Combination therapy is often considered in the context of persistent VRE BSI and IE. There is an overall paucity of data; however, some evidence exists for daptomycin combination therapy, and an even smaller amount exists for linezolid. Daptomycin plus a β-lactam antibiotic (BLA) such as ampicillin, ceftaroline, or ertapenem has shown promise in both clinical and *in vitro* studies (204–206), including for a daptomycin-susceptible VRE*fm* strain with LiaFSR substitutions (118). LiaFSR is a three-component regulatory system that is involved in the cell envelope stress response to antibiotics and has been linked to reduced daptomycin susceptibility in *Enterococcus* spp. (207, 208). Clinically, the use of combination BLA therapy with daptomycin was shown to have greater treatment success for patients with VRE BSIs (with higher daptomycin MICs of 3 to 4 μg/mL) than for patients treated with daptomycin without a BLA (116). Moreover, a retrospective review of 114 patients with VRE*fm* BSIs showed that patients receiving high-dose daptomycin ($\geq$9 mg/kg) plus a BLA had better survival than those receiving low-dose daptomycin ($<$9 mg/kg), low-dose daptomycin plus a BLA, or high-dose daptomycin alone (209). A more recent study by the same group observed a 28-day mortality benefit in patients with VRE*fm* BSIs prescribed the combination of a BLA and daptomycin upon multivariate analysis; however, this finding must be interpreted carefully as the study was not designed to assess outcomes related to BLA combination therapy (78). Possible explanations for the observed synergy between daptomycin and BLAs include BLAs reducing the surface charge of *Enterococcus* spp., resulting in the increased binding of daptomycin (204), and/or different affinities of BLAs for enterococcal PBPs (118). For *Enterococcus* spp., daptomycin-resistant strains can demonstrate an increase in β-lactam susceptibility because of cell membrane remodeling and alterations in PBPs essential for β-lactam resistance (210). This "seesaw effect" is a phenomenon classically used to describe susceptibility to β-lactams increasing with declining vancomycin or daptomycin susceptibility in *S. aureus*.

Alternative agents have also been combined with daptomycin, including tigecycline, chloramphenicol, and fosfomycin. The evidence for the addition of tigecycline or chloramphenicol is limited to case reports for the treatment of VRE IE as last-line salvage therapy (211–213), while the evidence for the addition of fosfomycin includes both *in vitro* evidence (214, 215) and clinical evidence (216). A recent single-arm, prospective study evaluated the outcomes of the combination of daptomycin and i.v. fosfomycin (16 g/day) in 106 patients with VRE BSIs and showed that higher doses of daptomycin and susceptible fosfomycin MICs ($\leq$64 μg/mL) independently reduced 28-day mortality (216). The proposed mechanism for this combination is that fosfomycin reduces the surface charge (through disruption of the membrane potential) of VRE, enabling enhanced daptomycin binding (216). For linezolid combination therapy, only a small number of clinical cases related to VRE infection have been published, including gentamicin for persistent VRE*fm*

BSI (217) and VRE*fm* meningitis (218), rifampicin for VRE*fm* meningitis (219), and doxycycline for a daptomycin-resistant VRE*fm* BSI (220).

Osteoarticular infections. *Enterococcus* spp., both vancomycin susceptible and resistant, are an uncommon cause of osteoarticular infections, and when they are implicated, they are predominantly involved in prosthetic joint infections (221, 222). Key considerations for the successful management of osteoarticular infections are adequate source control where possible and antimicrobial penetration to the site of the infection. Daptomycin has been shown to achieve mean concentrations of 3.3 $\pm$ 1.5 μg/g bone and 3.4 $\pm$ 1.9 μg/g bone in healthy thighbone and shinbone, respectively, following a single preoperative 8-mg/kg dose (223). The median bone penetration of 11.1% (interquartile range [IQR], 6.6% to 17.3%) suggests that daptomycin is likely suitable for osteoarticular infections where VRE isolates with lower MICs are involved. Higher daptomycin doses (>10 mg/kg) are warranted for the treatment of VRE osteoarticular infections, which should ultimately yield higher bone concentrations; however, further research is needed to quantify this. Linezolid has been shown to achieve median bone concentrations of 5.7 mg/L (95% CI, 3.9 to 8.6 mg/L), equivalent to a median bone penetration of 35.9%, 30 min following a single dose of linezolid at 600 mg in patients undergoing routine hip replacement (224). A second study showed mean linezolid steady-state concentrations of 8.49 mg/kg (standard deviation [SD], $\pm$3.92 mg/kg) in cancellous bone and 18.51 mg/kg (SD, $\pm$6.55 mg/kg) in the synovium of patients undergoing primary total knee arthroscopy (225). Importantly, the concentrations reported by Rana et al. reflect steady-state concentrations following linezolid dosing at 600 mg twice a day (BD) for 48 h and a further dose 1 h prior to surgery (225). These studies suggest that linezolid is suitable for VRE osteoarticular infection treatment; however, adverse effects are a limitation due to the likely prolonged duration of therapy.

Where an osteoarticular infection involves prosthetic material, the use of an antimicrobial agent with biofilm activity may be considered. Daptomycin as a single agent has been shown in an *in vitro* biofilm model to have activity against VRE biofilms associated with a strain without an LiaFSR mutation (S447); however, combination therapy with ampicillin, ceftaroline, ertapenem, or rifampicin resulted in enhanced activity, including a strain with an LiaFSR mutation (HOU503) (226). Daptomycin has demonstrated evidence of biofilm activity against *S. aureus*; in contrast, linezolid has been shown to have limited biofilm activity (227, 228). The data are less clear for *Enterococcus* spp., with *in vitro* data suggesting that standard doses of linezolid are insufficient to inhibit *E. faecalis* and *E. faecium* biofilms (229); however, potential synergy with linezolid in combination with rifampicin has been reported for *E. faecalis* biofilms (230).

Due to the low incidence of VRE osteoarticular infections, evidence to guide management is generally limited to case reports and case series. A case series of 81 Italian cases of vertebral osteomyelitis reported that 17.3% of cases were caused by VRE (equally distributed across VRE*fm* and VRE*fs* isolates) (231) Of note, approximately one-third of these cases were postsurgical. Daptomycin was the predominant antibiotic used, at doses of 8 to 10 mg/kg. All patients ultimately achieved clinical cure (with a mean follow-up of 16.9 months); however, first-line therapeutic failure occurred in 42.9% (n = 6) (231). Various alternative treatment regimens have been utilized in case reports, including pristinamycin (232), quinupristin-dalfopristin for VRE*fm* vertebral osteomyelitis (233), and oritavancin plus ampicillin for salvage therapy of a VRE lumbar spine infection involving metalware (234).

Persistent VRE BSIs with or without IE or osteoarticular infections represent a difficult area for clinical management, with a risk of poor patient outcomes. Attainment of source control is critical (including referral to the appropriate surgical specialty unit, e.g., cardiothoracic surgical intervention in the case of IE or orthopedic surgery in the case of osteoarticular infections) to ensure the best possible outcome for patients. High-dose daptomycin (12 mg/kg) or linezolid remains the recommended first-line treatment for persistent VRE BSI with or without IE, with alternative treatment options including daptomycin combined with a BLA for salvage therapy. High-dose daptomycin or linezolid

also remains the first-line treatment for osteoarticular infections; however, it may require the use of a concurrent biofilm-active agent when prosthetic material is involved. Further research is required in this patient cohort to determine the best treatment outcomes.

ROLE OF DOSE OPTIMIZATION AND THERAPEUTIC DRUG MONITORING

TDM is well established for certain antimicrobial agents, including vancomycin and aminoglycosides. Antimicrobial TDM enables the optimization of dosing for patients with variable PK and has been utilized for maximizing the efficacy and minimizing the toxicity associated with many drugs (235). Given the importance of antimicrobial exposure (or the concentration of the drug available at the site of infection) for clinical infection management, there is established evidence demonstrating a relationship between antimicrobial dosing, PK/PD exposure, and patient outcomes (236). The consequences of underdosing antimicrobial therapy include the emergence of antimicrobial resistance, clinical failure, and increased mortality (237). Conversely, the use of supratherapeutic antimicrobial dosing may lead to patient toxicity, which can lead to the early cessation of therapy or may necessitate a switch to a combination of antimicrobials with less evidence of efficacy (237).

Each antimicrobial agent has a PK/PD index that best describes its efficacy, and all are expressed in relation to the MIC of the causative pathogen. It is important to note that there are accepted inherent assay variations in MIC determinations, with a $\pm$1-$\log_2$ dilution variation possible (238). As such, to minimize potential harm associated with MIC-based dose adjustments, Mouton et al. proposed the use of the ECOFF when the MIC is lower than or equal to the ECOFF or the MIC plus two 2-fold dilutions when the MIC is higher than the ECOFF (238). Studies are still required to evaluate the clinical outcomes of using the proposed ECOFF approach for PD target evaluation.

The patient populations at risk of VRE BSI often fall outside those included in the licensing trials for key antimicrobial treatment agents. Obesity, critical illness, renal impairment, renal replacement therapies, and life-saving modalities such as extracorporeal membrane oxygenation compound the dosing uncertainty. TDM offers a number of advantages for clinicians; however, a number of barriers across the TDM process must be navigated (237, 239, 240). Here, we present the current evidence to support TDM for the three most commonly used agents for VRE BSIs: daptomycin, linezolid, and teicoplanin.

Daptomycin

Daptomycin has been shown to have a dose-dependent effect on VRE BSIs; however, uncertainty remains about the appropriate dose in this setting. Despite daptomycin concentrations being measured and reported in the literature since the late 2000s, daptomycin TDM studies have been reported from only a small number of countries to date. A recent systematic review identified no published studies comparing the clinical outcomes of patients with a Gram-positive infection who had daptomycin TDM with subsequent dose adjustment with the outcomes of those who did not (241). The included studies reported a variety of clinical outcomes and were not pathogen specific, instead focusing on a broad range of Gram-positive organisms, including *S. aureus*, coagulase-negative staphylococci, *Enterococcus* spp., and *Streptococcus* spp. (242–250). Most studies were not limited to BSIs, instead including a variety of infection types such as prosthetic joint infections, cSSTIs, and IE (242–250).

The AUC/MIC ratio is the key PK/PD index for daptomycin efficacy, but at this stage, there is limited clinical evidence to support a target AUC/MIC ratio for VRE BSIs. A 2003 PD model with simulated endocardial vegetations observed AUC/MIC ratios of 502 and 705 with daptomycin dosing at 6 mg/kg/day and 8 mg/kg/day, respectively (251). Given that both regimens achieved $>$99.9% kill by 8 h, these data provide some insight into the optimal daptomycin PK/PD index. A later 2012 *in vitro* PK/PD model also utilizing endocardial vegetations identified that the minimum $AUC_{0–24}$ required for sustained bactericidal activity was 1,540, and the corresponding $AUC_{0–24}$/MIC ratio was 214 to 1,715 (202). A 2019 classification and regression tree (CART) analysis using pooled data from seven observational

studies demonstrated that a daptomycin free-drug AUC (*f*AUC)/MIC ratio of >27.43 (using Etest MIC determination) was associated with improved 30-day survival rates in low-acuity patients with enterococcal BSIs (86% had VRE) (252). A separate 2022 CART analysis identified that *f*AUC/MIC ratios of >75.07 and >81.87 using BMD and Etest determinations of daptomycin MICs, respectively, significantly predicted reduced 28-day mortality in patients with VRE*fm* BSIs treated with daptomycin at ≥8 mg/kg (117). At this time, there is a paucity of real-world clinical data to support these PK/PD targets, and further studies are required.

Despite the AUC/MIC ratio being the best predictor of efficacy, Galar et al. examined the association between trough concentrations (C_{min}) and clinical outcomes in patients with Gram-positive infections (242). The included patients had a variety of pathogens (including *S. aureus*, *Staphylococcus epidermidis*, *E. faecalis*, and *E. faecium*) and a broad range of infections (including BSIs, cSSTIs, IE, and osteoarticular infections). Those authors found that a C_{min} of 3.18 to 16.84 mg/L had a correlation with a favorable outcome, fewer adverse events, and less related mortality (242). It was not stated if these levels were total drug or unbound drug concentrations, which is relevant given the high protein binding (>90%) of daptomycin. Multivariate analysis showed that a C_{min} of <3.18 mg/L was independently related to a poor outcome (242).

The key toxicity that has been associated with daptomycin is CPK elevation, with the risk being increased with high doses. There have been conflicting results linking daptomycin trough concentrations with CPK elevation and muscle toxicity. Trough concentrations of ≥19.5 mg/L (253) or ≥24.3 mg/L (254) have been associated with an increased probability of CPK elevation, while at least three other studies have found no association (242, 255, 256).

Taken together, there are enough preliminary data to support further research to assess the utility of daptomycin TDM for the clinical management of challenging infections such as VRE BSI or IE, especially in complex patient groups (236).

Linezolid

Despite standard approved dosing of 600 mg q12h, linezolid exposure is highly variable (139–145). In certain patient populations, including those with extremes of body weight, those with renal impairment, those with critical illness, and those receiving prolonged treatment courses, linezolid TDM is warranted. Numerous PK/PD targets have been proposed for linezolid TDM, including the AUC/MIC ratio, C_{min}, and the percentage of time above the MIC (%$T_{>MIC}$), and these are summarized in Table 5. Expert consensus suggests that the C_{min} is the most practical indicator of linezolid therapeutic efficacy given the good correlation with the AUC_{0-24} and the logistical challenges associated with taking multiple drug levels required for other PK/PD targets (257). C_{min} does not take the MIC of the causative pathogen into consideration, and PK simulations have suggested that in order to achieve a therapeutic target of an AUC/MIC ratio of >100, C_{min} values of 2 to 5 mg/L and 5 to 8 mg/L may be required for pathogens with MICs of 1 μg/mL and 2 μg/mL, respectively (258). Importantly, to achieve the therapeutic target for an organism with an MIC of 4 μg/mL, linezolid concentrations would need to be in the toxic range (>8 mg/L) (258). Proportional dose adjustments for linezolid have been proposed by expert consensus (257), while a recent publication by Gatti et al. provided recommendations for linezolid dose adjustments in critically ill patients according to C_{min} and MIC values (259).

Linezolid TDM is relatively well established in some international centers, with a recent expert consensus statement being published on linezolid TDM and dose individualization (260). Despite this statement, there is a lack of data on the role of linezolid TDM in predicting efficacy for VRE BSIs. A 2003 retrospective analysis of patients prescribed linezolid under the manufacturer's compassionate use program, of which VRE*fm* BSIs represented 29% of infections, showed that a median linezolid AUC/MIC ratio of 128.1 and a median %$T_{>MIC}$ of 98.6% were associated with bacterial eradication from the blood (261). Clinical studies have been undertaken in various mixed infection types caused by a variety of Gram-positive pathogens, with conflicting clinical outcome results. (142, 262, 263). Pea et al. demonstrated that TDM

TABLE 5 Summary of recommended adult antimicrobial doses and available TDM targets for antibiotics commonly used for VRE BSIs

Drug at recommended dose (CrCl[i] of >90 mL/min) and PK/PD index	Efficacy target value(s) (reference[s])	Toxicity target value(s) (reference[s])
Daptomycin at 10–12 mg/kg/day		
*f*AUC/MIC ratio	>27.43[a,b] (252), >75.07[a,c] (117), >81.87[a,b] (117)	NA
AUC_{0-24}/MIC ratio	≥502[d] (251), ≥705[d] (251), 214–1,715[d] (202)	NA
C_{min} (mg/L)	3.18–16.84[e] (242)	≥19.5 (253), ≥24.3 (254)
Linezolid at 600 mg q12h		
$T_{>MIC}$ (%)	>98.6[f] (261)	NA
AUC_{0-24}		≥400 mg/L (262), 280.74 mg/L · h (262)
AUC/MIC ratio	128.1[f] (261)	
C_{min} (mg/L)	2–7[g] (263)	>7–8 (262, 265–267)
Teicoplanin at 12 mg/kg q12h for 5 doses, followed by 12 mg/kg/day		
C_{min} (mg/L)	NA	31.47[h] (154); thrombocytopenia, >40 (273); nephrotoxicity, >60 (236)

[a]Efficacy target from a CART analysis. Not supported by clinical studies.
[b]MIC determined by Etest.
[c]MIC determined by BMD.
[d]Efficacy target from an *in vitro* PD model with simulated endocardial vegetations. Not supported by clinical studies.
[e]Efficacy from mixed-pathogen studies, including *Enterococcus* spp.
[f]Median value provided.
[g]Efficacy from a mixed-infection study with no identification of the pathogen.
[h]Mean value provided.
[i]CrCl, creatinine clearance.

guided dose reductions of linezolid when $C_{min} \geq 10$ mg/L and/or an estimated $AUC_{0-24} \geq 400$ mg/L · h enabled patients to recover from linezolid induced toxicity (thrombocytopenia) and to continue therapy until the planned end of treatment with a good clinical outcome (262). The same group further demonstrated in a later study that linezolid TDM and subsequent dose adjustments were associated with very high rates of favorable clinical outcomes (98%), albeit these were assessable in only ~58% of the cohort, as well as significant cost savings (263). In contrast to those two previous studies, Galar et al. showed a lack of a correlation between linezolid levels and clinical outcomes, including in-hospital mortality and adverse events, in 90 patients receiving linezolid (with dose adjustments) for the empirical or directed treatment of a mixture of pathogens and infectious syndromes (142). As for daptomycin, future research on the role of linezolid TDM for challenging infections like VRE BSI and IE is warranted.

The majority of evidence supporting the role of linezolid TDM is in the prevention of toxicity, specifically exposure thresholds for the development of hematological toxicities. Linezolid-induced inhibition of mitochondrial protein synthesis is associated with toxicities including anemia and neutropenia, lactic acidosis, and peripheral and optic neuropathy (264). Song et al. demonstrated that linezolid concentrations correlate with mitochondrial function levels (and, therefore, the risk of mitochondrial toxicity) in patients with extensively drug-resistant tuberculosis (TB) (264). Linezolid-induced thrombocytopenia usually occurs after 14 days of treatment, with a C_{min} of >7.5 mg/L being associated with a significantly higher incidence (265). Additional clinical studies in patients with mixed Gram-positive infections have shown an increased risk of thrombocytopenia when the C_{min} values are higher than 6.3 mg/L (266), 6.53 mg/L (262), and 8.2 mg/L (267). An AUC_{0-24} of 280.74 mg/L · h has also been associated with an increased thrombocytopenia risk (262). Cojutti et al. demonstrated that linezolid TDM with subsequent dose adjustments is beneficial for both the prevention of and recovery from thrombocytopenia (268). Exposure thresholds for adverse effects other than thrombocytopenia are poorly defined (257). A 2020 retrospective review of multidrug-resistant TB patients treated with linezolid found no association between linezolid trough levels and neurotoxicity (269), whereas Song et al.

identified that patients with an average linezolid trough concentration of >2 mg/L developed an adverse event, including peripheral neuropathy, optic neuropathy, and myelosuppression (264). From a toxicity point of view, linezolid TDM using a trough level (C_{min}) should be considered for certain patients being treated for complex VRE infections where treatment is planned for a more prolonged period (e.g., >14 days).

Teicoplanin

The AUC/MIC ratio and the time that the free concentration of the drug remains above the MIC ($fT_{>MIC}$) are important PK/PD indices for predicting teicoplanin efficacy (270). These targets are not well defined for teicoplanin, and trough concentrations (C_{min}) are used as a surrogate marker of efficacy (270). Teicoplanin is a highly protein-bound drug (approximately 90%), with the unbound fraction of the drug being responsible for its therapeutic effect. Significant interpatient variability in teicoplanin has been reported (152), with factors including hypoalbuminemia (270) and alterations of renal function (either augmented renal clearance or acute kidney injury/end-stage renal disease) implicated (150). Calculations have been published to enable estimations of the free concentration of teicoplanin (271); however, there are no validated targets for unbound levels available (270). Roberts et al. hypothesize that a lower therapeutic range of 1 to 2 mg/L may be appropriate as an unbound teicoplanin target trough concentration; however, this is not pathogen specific (270).

There is limited literature available regarding teicoplanin TDM to support the treatment of any VRE infections, which likely reflects the lack of approval for use in the United States. Much of the evidence for TDM of teicoplanin is reported for MRSA, and it is unclear whether this is able to be extrapolated to VRE BSIs. Teicoplanin has an ECOFF of 2 μg/mL for *S. aureus*, *E. faecalis*, and *E. faecium* (115). Japan has developed national TDM guidelines for teicoplanin; however, this is specific for MRSA infections (272). A C_{min} of ≥10 mg/L or ≥15 mg/L is recommended in the product information for most Gram-positive infections when measured by high-performance liquid chromatography (HPLC) or a fluorescence polarization immunoassay (FPIA), respectively (149). Higher trough concentrations of 15 to 30 mg/L and 30 to 40 mg/L measured by HPLC and FPIA, respectively, are recommended for serious infections, including IE and bone and joint infections (149). More recently, Ueda et al. identified that an initial C_{min} of ≥20 mg/L was an independent predictor (adjusted OR, 3.95 [95% CI, 1.25 to 12.53]) of an early clinical response (at 72 to 96 h) in patients with complicated MRSA infections, including BSIs (152). The use of an enhanced loading dose regimen (12 mg/kg q12h for 5 doses) was required to achieve this target (152). Interestingly, no significant difference in clinical success (that is, survival or resolution/improvement of the infection, requiring no further antibacterial therapy) was observed at the conclusion of teicoplanin therapy between patients who did and those who did not achieve the initial C_{min} of ≥20 mg/L. Those authors hypothesize that this may be due to teicoplanin dose modifications during therapy, which highlights the importance of TDM with subsequent dose adjustment (152). It is unclear whether total or unbound drug concentrations were measured in this study, which is of importance due to the high protein binding of teicoplanin (>90%).

Consensus exists linking teicoplanin TDM with significant adverse effects, which have been reported to occur at a mean teicoplanin C_{min} of 31.47 mg/L (154). Teicoplanin-induced thrombocytopenia has been reported with levels of >40 mg/L (273). Despite being a glycopeptide, the rates of teicoplanin-associated nephrotoxicity are relatively low, generally observed with trough levels of >60 mg/L (236). Overall, the literature supports the regular measurement of the teicoplanin C_{min} to assist with dose optimization (150) and the identification of adverse effects (154). The role of TDM, including therapeutic targets and clinical outcomes, in patients with *vanB* VRE BSIs and IE represents an important area for future research.

CONCLUSION

Vancomycin-resistant *Enterococcus* spp. are a common cause of BSIs, with high morbidity and mortality rates. They are pathogens of increasing global concern, with a limited treatment pipeline. The introduction of daptomycin and linezolid to the market in the early 2000s transformed the treatment of these difficult-to-treat pathogens, with current evidence supporting the use of either high-dose daptomycin (≥10 mg/kg) or

linezolid for the best patient clinical outcomes. Despite this, significant challenges remain, including limiting the emergence of resistance to ensure the longevity of these treatment options and for managing persistent VRE BSIs and IE. The use of combination antimicrobial regimens with daptomycin or linezolid as the key backbone agent is being increasingly investigated in both *in vitro* studies and clinical studies, with a role becoming apparent in patients with higher MIC values. The introduction of personalized antimicrobial dosing for both the patient and the pathogen through the use of TDM is emerging for VRE agents, and presently, there are significant gaps in the literature for TDM to predict the efficacy of daptomycin, linezolid, and teicoplanin in the management of VRE BSIs. More promisingly, evidence to support TDM to predict the toxicity of these agents has greater evidence and is increasing in utilization globally. Well-designed, prospective clinical studies specific to VRE BSIs are required to determine the most effective treatment regimen, duration of therapy, and role of daptomycin, linezolid, and teicoplanin TDM in optimizing patient outcomes.

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Kelly A. Cairns is an Antimicrobial Stewardship and Infectious Diseases Clinical Pharmacist at The Alfred Hospital, Melbourne, Australia, and is currently undertaking a Ph.D. through the Department of Infectious Diseases, The Alfred Hospital and Central Clinical School, Monash University, Melbourne, Australia. Her research interests include antimicrobial dose optimization for VRE bloodstream infections and the role and impact of antimicrobial stewardship teams within the hospital setting.

Andrew A. Udy is a full-time intensive care clinician and researcher at The Alfred ICU, Melbourne, Australia. He completed his undergraduate medical education at the University of Auckland, followed by ICU training in New Zealand, the United Kingdom, and Australia. After an award of Fellowship, he worked as a consultant for many years in Queensland while also completing a Ph.D. in antibiotic pharmacokinetics. His major academic interests include optimized drug prescribing for the critically ill, hemodynamic management in severe sepsis, acute kidney injury and renal replacement therapy, the management of subarachnoid hemorrhage and traumatic brain injury, and critical care nutrition. Professor Udy is involved in critical care research internationally as an Executive Member of the ANZICS Clinical Trials Group (CTG). He is also a keen educator, instructing on many ICU courses, and is Chair of the Neurocritical Care Special Interest Group, CICM. Professor Udy is Co-Deputy Director of the Australian and New Zealand Intensive Care Research Centre, Monash University.

Trisha N. Peel is an infectious diseases clinician-researcher. Professor Peel's clinical and research interests focus on health care-associated infections and antimicrobial stewardship. She completed her medical degree (M.B.B.S.) with honors at the University of Melbourne before training as an Infectious Diseases Physician (F.R.A.C.P.). She completed her Ph.D. at the University of Melbourne in 2013 before completing a postdoctoral fellowship at Mayo Clinic, Rochester, MN. She is the current Deputy Director (Research), Department of Infectious Diseases, Faculty of Medicine, Nursing and Health Sciences, Monash University, and is the Clinical Lead of the Antimicrobial Stewardship Services at Alfred Health and Epworth Healthcare.

Iain J. Abbott is an Infectious Diseases Physician and Clinical Microbiologist at The Alfred Hospital and Central Clinical School, Monash University, Melbourne, Australia. He completed his Ph.D. at Monash University in 2021, examining the *in vitro* modeling of urinary tract infections. He currently leads the Pharmacology Research Group within the Department of Infectious Diseases, examining the optimization of antimicrobials using dynamic antimicrobial PK/PD *in vitro* models. He sits on the Australian National Antimicrobial Susceptibility Testing Committee (AusNAC) and is the scientific editor of the Australian Society for Antimicrobials *Breakpoint* newsletter.

Michael J. Dooley holds a joint appointment as Director of Pharmacy at Alfred Health and Professor of Clinical Pharmacy, Centre for Medicine Use and Safety, Monash University, Melbourne, Australia. He is also an Adjunct Professor in the Department of Epidemiology and Preventative Medicine at Monash University. His career has focused on the acute health care sector and has spanned special clinical roles in oncology through to senior leadership positions within health services. He has led a wide range of initiatives progressing improvements in medication use and clinical pharmacy practice in Australia, including the development of professional standards of practice and formal residency training programs. He has been actively involved in a range of research activities from practice-based undergraduate projects to competitively funded collaborative initiatives and postgraduate programs. His work has included over 200 journal publications and nearly 500 invited or scientific presentations at conferences and meetings locally and internationally.

Anton Y. Peleg is a Professor of Infectious Diseases and Microbiology, Australian National Health and Medical Research Council Practitioner Fellow, and Director of the Department of Infectious Diseases at The Alfred Hospital and Monash University, Melbourne, VIC, Australia. He is Theme Leader for Infection and Immunity at the Monash Academic Health Research and Translational Centre and has recently been elected as a Fellow of the Australian Academy of Health and Medical Sciences. He completed his infectious diseases clinical training in Australia in 2005 and then went to the United States for 4 years and worked at the Harvard-affiliated hospitals Beth Israel Deaconess Medical Center and Massachusetts General Hospital. He completed a master's of Public Health at the Harvard School of Public Health and also completed a Ph.D. in Infectious Diseases and Microbiology with a focus on antimicrobial resistance (AMR) and microbial genomics in 2010. His research interests are in hospital-acquired infections, AMR and novel solutions, bacterial genomics, and mechanisms of pathogenesis and infections in immunocompromised hosts, and he has received numerous national and international awards for his advanced research and contribution to Infectious Diseases and Microbiology.