Clinical Infectious Diseases

STATE-OF-THE-ART REVIEW

State-of-the-Art Review: Persistent Enterococcal Bacteremia

Ralph Rogers and Louis B. Rice

Division of Infectious Diseases and Department of Medicine, Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA

Keywords. enterococcus; bacteremia; persistence; duration; review.

Enterococcus species, in particular *E. faecalis* and *E. faecium*, are now among the most prevalent causes of bacteremia, trailing behind only *Escherichia coli* as well as *Staphylococcus*, *Streptococcus*, and *Klebsiella* species [1]. Enterococcal bacteremia is associated with an imposing 20%–35% 30-day mortality rate, likely at least in some part due to the advanced age, multiple comorbid conditions, and/or underlying immunocompromised state typical among patients affected by enterococcal bacteremia [2–4]. Beyond the intrinsic antimicrobial resistance present in *Enterococcus* species, increasing rates of acquired resistance to multiple antimicrobials have further limited potential therapeutic options. Persistent enterococcal bacteremia despite seemingly appropriate antimicrobial treatment (based on in vitro antimicrobial susceptibilities) is a relatively frequent occurrence in clinical practice, at times due to an underlying inadequately addressed nidus of infection though frequently occurring without any such identified uncontrolled source. Current best practices for management of persistent enterococcal bacteremia are understudied and largely undefined.

DEFINING PERSISTENT ENTEROCOCCAL BACTEREMIA

There is no consensus definition for persistent enterococcal bacteremia. Ideally such a definition would neatly segregate those with a "normal" duration of bacteremia from those with an "atypically long" duration of bacteremia, with corresponding good and poor clinical outcomes among the respective groups, in order to facilitate efforts to understand and improve the care of those in the latter group. Even with such an ideal definition, those with persistent bacteremia would remain a heterogenous group given the multitude of potential contributing factors, including deficient host immunity, virulence factors specific to particular clinical isolates, presence or absence of ongoing focal source(s) of infection (eg, catheter, abscess, or endocarditis), and the timing and appropriateness of antimicrobial therapy. Of note, among these factors, beyond encouraging efforts at source control, only the choice of antimicrobials is typically modifiable in clinical practice.

One approach to defining persistent enterococcal bacteremia is to acknowledge that any duration of bacteremia beyond only transient detection may be associated with (or a marker of) a poor clinical outcome and thus define persistent bacteremia simply by the detection of an additional positive blood culture obtained after the first. Other approaches acknowledge the delays inherent to clinical care (ie, time from blood culture collection to microbiologic diagnosis and availability of antimicrobial susceptibility testing results) and suggest a definition of persistent enterococcal bacteremia that includes a positive blood culture collected after a certain amount of time from the initial positive culture and/or subsequent to the administration of a certain duration of appropriate antimicrobial therapy. A critique of the former approach is that it may include patients not yet receiving antimicrobials who respond quickly and appropriately to antimicrobials once started. Of 2 single-center studies that examined clinical outcomes in patients with only 1 positive culture, compared with those with >1 positive culture, one reported similar outcomes between groups (suggesting that a single positive blood culture may represent a significant infection), and the other described significantly higher infection-attributable mortality rate among those with >1 positive culture [5, 6].

When choosing a metric to best define persistent enterococcal bacteremia, it is helpful to consider various reports of the epidemiology of this increasingly common infection (Table 1) [7–55]. Among recent larger studies describing cohorts that include hospitalized patients with any episode of enterococcal bacteremia, one found a mean duration of bacteremia of 4 days, another found that 12.0% of patients had persistently positive blood cultures for ≥5 days, and

Received 02 May 2023; editorial decision 20 September 2023; published online 29 November 2023

Correspondence: R. Rogers, Division of Infectious Diseases and Department of Medicine, Warren Alpert Medical School of Brown University, 593 Eddy St, Providence, RI 02903 (rrogers@lifespan.org); L. B. Rice, Division of Infectious Diseases and Department of Medicine, Warren Alpert Medical School of Brown University, 593 Eddy St, Providence, RI 02903 (lrice@lifespan.org).

Clinical Infectious Diseases® 2024;78(1):e1–e11

https://doi.org/10.1093/cid/ciad612

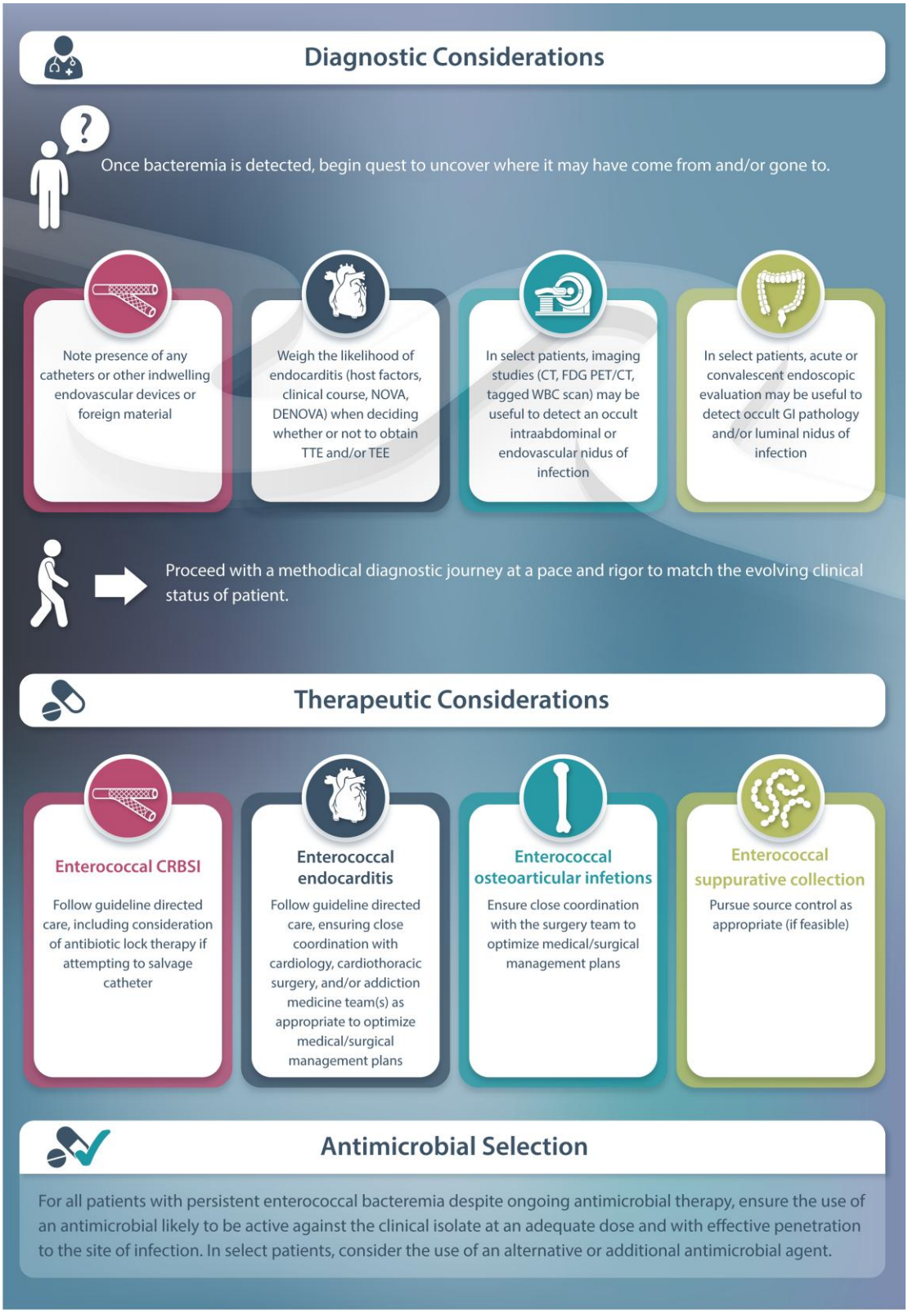

Table 1. Selected Reports Describing Cohorts of Patients With Enterococcal Bacteremia and Including Data on Bacteremia Duration

Reference No.	Population	Total No. in Cohort	Condition	Definition of Persistent Bacteremia	Persistent Bacteremia, No./Total Included (%)	Average Duration of Bacteremia
28	Adults	224	VRE bacteremia	Positive culture for ≥4 d or death within ≤7 d	68/153 (44.4)	…
37	Children	74	Bacteremia with sepsis	…	…	2.9 d
38	Adults	80	VRE (*Enterococcus faecium*) bacteremia	Positive culture for >48 h	13/80 (16.3)	2 d
39	Adults	106	VRE (*E. faecium*) bacteremia	Positive culture for ≥4 d or death within ≤7 d	26/106 (24.5)	…
9	Adults	244	Bacteremia	Positive culture after ≥72 h antibiotics	33/244 (13.5)	4–7 d
40	Adults	97	*E. faecium* bacteremia	…	…	2.5–3 d
8	Adults	250	Bacteremia	Positive culture for ≥5 d	30/250 (12.0)	68 h
35	Adults	113	CLABSI	2nd Positive blood culture	13/121 (10.7)	…
36	Adults	279	*E. faecalis* endocarditis	Positive culture for ≥3 d	19/256 (7.4)	2 d
16	Adults	138	VRE bacteremia	Positive culture after ≥ 4 d of antibiotics	24/108 (22.2)	1–7 d
49	Adults	145	PSE bacteremia	Positive culture for >7 d	28/104 (26.9)	…
7	Adults	263	Bacteremia	…	…	4 d
12	Adults	232	Bacteremia	Positive culture for ≥4 d and after ≥48 h of antibiotics	39/232 (16.8)	…
41	Adults	190	*E. faecalis* endocarditis	…	…	73–102 h
42	Adults	50	*E. faecalis* bacteremia	Positive culture after 48–72 h of antibiotics	5/50 (10.0)	…
43	Adults	109	*E. faecalis* endocarditis	Positive culture after >7 d antibiotics	16/109 (14.7)	…
13	Adults	516	endocarditis	Positive culture after >7 d antibiotics	69/516 (13.4)	…
44	Adults	186	Bacteremia	…	…	55–58 h
50	Adults	105	*E. faecium* bacteremia	Positive culture after >72 h antibiotics	2/56 (3.6)	…
15	Neutropenia	154	Bacteremia	Positive culture after >72 h antibiotics	6/100 (6.0)	…
51	SCT recipients	95	VRE bacteremia	Positive culture for >3 d	…	2 d
52	Adults	140	*E. faecium* bacteremia	…	…	3–4 d
45	Adults	78	*E. faecalis* endocarditis	Definition of persistence per modified Duke Criteria	6/78 (7.7)	…
46	Adults	210	VRE bacteremia	Positive culture for ≥5 d	18/210 (8.6)	…
47	Hematologic cancer	74	VRE bacteremia	Positive culture for >4 d	9/60 (15.0)	3–5 d
11	Adults	911	VRE bacteremia	Graph of clearance time	…	…
10	Adults	2630	VRE bacteremia	Positive culture for ≥7 d	91/1117 (8.1)	2–3 d
53	Adults	190	Bacteremia	…	…	3–4 d
48	Adults	644	VRE bacteremia	Lack of microbiologic clearance	38/390 (9.7)	3–4 d
14	Neutropenia	91	Bacteremia	Positive culture for ≥7 d	12/91 (13.2)	…
54	Adults	245	Bacteremia	Last culture positive	14/191 (7.3)	3 d
55	Adults	83	Bacteremia	Graph of clearance time	…	1–5 d

Abbreviations: CLABSI, central line–associated bloodstream infection; ISCVID, International Society for Cardiovascular Infectious Diseases; PSE, penicillin-sensitive enterococcal; SCT, stem cell transplant [16–34]; VRE, vancomycin resistant enterococcal.

another found that 13.5% of patients had persistently positive blood cultures after ≥72 hours of appropriate antimicrobials [7–9]. In the largest description in recent years of a cohort of patients with vancomycin-resistant enterococcal (VRE) bacteremia, 8.1% of patients had persistently positive blood cultures for ≥7 days [10]. A separate report describing a large subset of these same patients with VRE bacteremia who were treated with daptomycin provides a more detailed look at the distribution of duration of bacteremia among this group; notably absent is any natural grouping into "short" or "long" durations of bacteremia [Figure 1] [11].

A recent large multicenter prospective study directly compared the rates of persistent VRE and vancomycin-susceptible enterococcal (VSE) bacteremia (defined as persistent positive blood cultures for ≥4 days while receiving ≥48 hours of appropriate antimicrobials) and found slightly higher rates among patients with VRE compared with VSE bacteremia (21.4% vs 15.3%) [12]. One large study found no significant difference

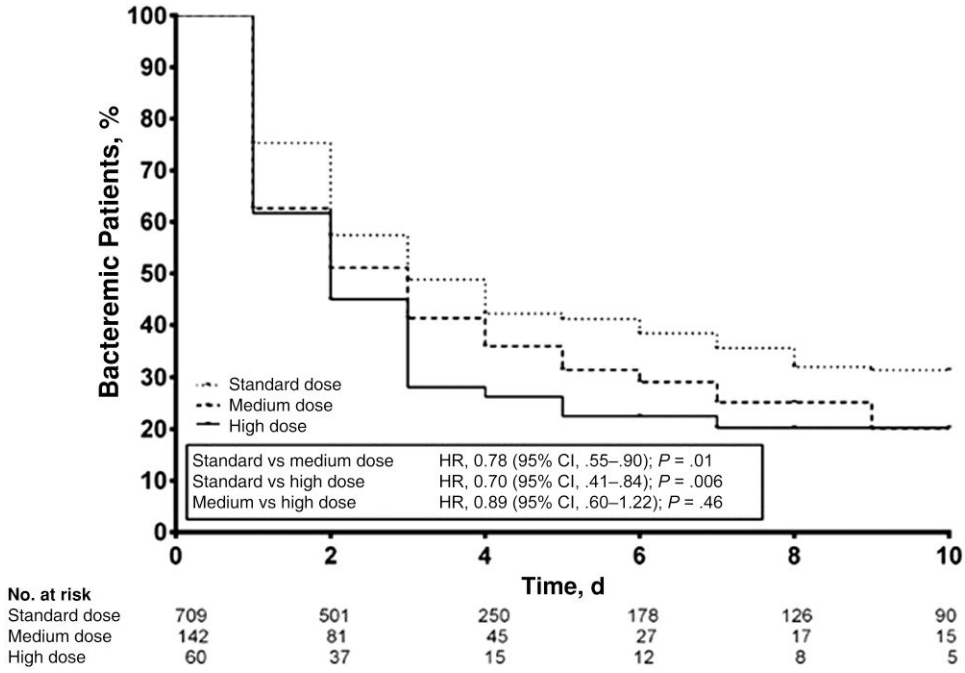

Figure 1. Comparison of microbiologic clearance for various doses of daptomycin among patients with vancomycin-resistant enterococcal bacteremia (modified from Britt et al [11]). Abbreviations: CI, confidence interval; HR, hazard ratio.

in rates of persistent bacteremia between individuals with *E. faecalis* or *E. faecium* or between nosocomial or community acquired infections [9]. Interestingly, the largest recent report describing a group of patients with enterococcal endocarditis found that only 13.4% of patients had persistent bacteremia after ≥7 days of antimicrobials, which was similar to the rate of persistent bacteremia (11.4%) among patients with all other causes of endocarditis (eg, *Staphylococcus* and *Streptococcus* spp.) in the entire cohort [13]. Two studies examining cohorts of neutropenic patients with enterococcal bacteremia describe persistent bacteremia among 13.2% (with bacteremia defined as positive blood cultures for ≥7 days) and 6.0% (with bacteremia defined as positive blood cultures after ≥72 hours of appropriate antimicrobials) [14, 15].

When synthesizing the descriptions of the various rates of persistent enterococcal bacteremia among these diverse reports, a few salient points emerge. There may be differences in the rates of persistent bacteremia dependent on specific host (eg, presence or absence of neutropenia), bacterial (eg, VRE vs VSE bacteremia), or clinical (eg, presence or absence of endocarditis) factors; however, these differences do not appear to be large. Any analysis examining the clinical relevance of only one of these factors to the duration of bacteremia may in turn be confounded by the remaining heterogeneity among these or other factors (eg, virulence or source control). Finally, given the continuous rather than discrete or bimodal distribution of bacteremia duration, it remains challenging to settle up an ideal clinically relevant definition for persistent enterococcal bacteremia. Moving forward, we would suggest that future studies consistently report the duration of bacteremia after active antimicrobial therapy is started (as opposed to after collection of blood cultures) to aid in the integration of various research findings and the implementation of these findings into clinical practice.

CLINICAL RELEVANCE OF PERSISTENT ENTEROCOCCAL BACTEREMIA

An association between persistent enterococcal bacteremia and adverse clinical outcomes, including death, has been repeatedly demonstrated, but this association is limited by the lack of clarity as to whether the persistent bacteremia is a primary driver of poor clinical outcomes or whether instead it serves only as a marker of poor host immune status and/or severity of infection. Further limiting any interpretation of the clinical relevance of persistent enterococcal bacteremia are the inconsistent definitions for persistent bacteremia used throughout the literature, as well as the diversity of host and clinical factors that may contribute to persistent bacteremia in any individual. One recent study that directly compared the clinical characteristics of patients with persistent (positive blood cultures after ≥72 hours of antimicrobials) compared with nonpersistent enterococcal bacteremia demonstrated a higher 30-day mortality rate among those with persistent bacteremia (32% vs 18%, respectively), but it also described significant differences in the clinical characteristics of the groups, including higher rates of active

hematologic cancer as well as endocarditis in the persistent bacteremia group [9].

Another study compared patients with persistent (positive blood cultures after ≥4 days of antimicrobials) versus nonpersistent VRE bacteremia and similarly found a higher in-hospital mortality rate (58% vs 40%, respectively); in that study the group with persistent VRE bacteremia was more likely to have neutropenia, 4 of 4 positive index blood cultures, and an uncontrolled source of infection, in that a higher number required a source control intervention, underwent an intervention less often, and experienced a significant delay in the timing of this intervention [56]. Concordant with these findings, a prospective multicenter study identified multiple risk factors for in-hospital mortality among patients with enterococcal bacteremia that included microbiologic failure (persistent positive blood cultures for ≥4 days and after ≥48 hours of antimicrobials), as well as elevated Pitt bacteremia score, neutropenia, urinary catheter, and VRE rather than VSE bacteremia [12]. Regardless of whether persistent enterococcal bacteremia is directly implicated as a contributing factor to adverse clinical outcomes per se, it is unequivocally associated with poor host immune status and complicated infections. Once detected, it should alert treating clinicians to the high risk for adverse clinical outcomes and the need for aggressive source control and optimization of antimicrobial therapy.

ANTIMICROBIAL SUSCEPTIBILITY AND TOLERANCE CONSIDERATIONS

Understanding susceptibility to antimicrobial agents is central to informed treatment of *E. faecalis* and *E. faecium* infections [57]. While on Gram stain these species may resemble commonly encountered streptococci like *Streptococcus pneumoniae* and *Streptococcus pyogenes*, their susceptibilities to commonly used antimicrobial agents are markedly different. Importantly, both *E. faecalis* and *E. faecium* exhibit reduced susceptibilities to β-lactam antimicrobials, including universal resistance to all cephalosporins (except for the susceptibility of *E. faecalis* to ceftaroline). For *E. faecalis*, this difference from streptococci is manifested by a reduced susceptibility without frank resistance to penicillin and ampicillin and resistance to the antistaphylococcal penicillins. For *E. faecium*, most strains express high-level resistance to all β-lactam antimicrobials, including ampicillin [58]. In both species, intrinsic resistance is associated with expression of a single, low-affinity penicillin-binding protein (PBP), PBP4 (*E. faecalis*) or PBP5 (*E. faecium*) [59, 60]. Clinically available antimicrobials for the treatment of susceptible enterococcal infections therefore include ampicillin, penicillin, piperacillin, vancomycin, daptomycin, linezolid, tigecycline, oritavancin, telavancin, and quinupristin-dalfopristin (*E. faecium* only) (Table 2). Linezolid is the only one of these agents approved by the Food and Drug Administration for the treatment of VRE bacteremia, and clinical experience with newer agents is sparse. None of these agents are free of enterococcal resistance, and in some cases (eg, ampicillin and vancomycin with *E. faecium*) acquired resistance is quite common [58].

Table 2. Commonly Used Antimicrobials Effective Against Susceptible *Enterococcus* Species

Antimicrobial Agent or Class	Comments
Ampicillin	First-line treatment of choice for susceptible enterococcal infections in patients without a penicillin allergy; may have some bactericidal activity against some *Enterococcus faecalis* strains; inactive against most clinical *Enterococcus faecium* isolates;
Penicillin	Less potent than ampicillin against most strains of *E. faecalis,* with increasing reports of *E. faecalis* strains resistant to penicillin and sensitive to ampicillin
Piperacillin	In vitro activity/potency mirroring that of penicillin
Ceftaroline	Active in vitro against *E. faecalis*; unclear role in treatment of clinical infections at present
Ceftriaxone/cefotaxime	Useful in treating *E. faecalis* endocarditis, in combination with ampicillin
Vancomycin	Active against strains lacking acquired vancomycin-resistance operons; activity is strictly bacteriostatic; *Enterococcus gallinarum* and *Enterococcus casseliflavus* strains intrinsically resistant
Daptomycin	Broadly active against most *E. faecalis* and *E. faecium* strains, as well as less common enterococci; bactericidal activity; emergence of resistance during therapy is an issue, and such strains may also exhibit greater resistance to vancomycin despite lack of exposure
Linezolid	Despite strictly bacteriostatic activity, observational studies have shown benefit in some serious enterococcal infections
Tigecycline	Achievable serum levels preclude use in the treatment of patients with bacteremia
Quinupristin-dalfopristin	Active only against *E. faecium*; local vascular toxicity and muscle toxicity have limited its use

E. faecalis and *E. faecium* also exhibit a clinically important tolerance to cell-wall active antimicrobials like ampicillin and vancomycin. "Tolerance" has had a variety of technical definitions over the years but in general can by defined as a large disparity between the antimicrobial concentration required to inhibit growth of a bacterial strain in vitro and that required to kill the strain (often defined as >99.9% reduction of the initial inoculum at 24 hours) [61]. While some level of in vitro tolerance to different antimicrobials can be demonstrated in individual strains of a variety of bacterial species, significant clinical consequences of tolerance have only been demonstrated in enterococci. Early studies of *E. faecalis* endocarditis confirmed that cure rates using penicillin alone approximated 40% [62]. Once it was recognized that combining penicillin with streptomycin resulted in in vitro synergistic bactericidal activity, the clinical use of cell wall active agents and

aminoglycosides has resulted in cure rates of 70% or greater for enterococcal endocarditis [13, 63]. The clinical utility of cell wall active agents and aminoglycoside combinations has been limited by the intrinsic toxicity of aminoglycosides as well as by the spread of high-level resistance conferred by acquired aminoglycoside-modifying enzymes.

More recently, it has been shown that the use of ceftriaxone-ampicillin combinations results in cure rates similar to those of cell wall agent–aminoglycoside combinations when treating *E. faecalis* endocarditis [64]. The mechanism for achieving this result is unclear but may be the result of more complete inhibition of all PBPs than can be achieved with either agent alone [65]. The success of this strategy opens the possibility that other β-lactam combinations may also prove useful in treating enterococcal endocarditis [66]. It remains unclear whether combination antimicrobial therapy provides any clinical benefit for the treatment of serious enterococcal infections apart from endocarditis, with clinical data limited to case reports and observational studies [15, 67, 68].

Acquired resistance is quite common in enterococci. Resistance to tetracyclines (except tigecycline) and erythromycin is widespread, owing to the presence of resistance determinants on transposons, transferable plasmids and mobilizable chromosomal regions [69, 70]. Resistance to oxazolidinones most commonly occurs through mutations in ribosomal RNA genes selected by exposure to these antimicrobials in the clinical setting, though plasmid-mediated linezolid resistance can also occur [71, 72]. Resistance to daptomycin can be selected by exposure to this antimicrobial through mechanisms that appear to alter membrane charge [73]. Resistance to ampicillin in *E. faecalis* remains rare and results most often from combinations of amino acid substitutions in low-affinity PBP4 and increased expression of this protein [60]. Rarely, ampicillin resistance in *E. faecalis* may be caused by acquired β-lactamase production. Resistance to ampicillin in *E. faecium* is most commonly mediated through amino acid substitutions in low-affinity PBP5, while resistance to vancomycin is generally the result of expression of acquired vancomycin resistance transposons [35, 36, 59]. The majority of clinical *E. faecium* strains in many series are resistant to high concentrations of both vancomycin and ampicillin. For reasons that remain unexplained, vancomycin resistance continues to be relatively rare in *E. faecalis* [58].

PATHOGENICITY AND VIRULENCE CONSIDERATIONS

Enterococci are commonly considered pathogens of "lower" virulence than more aggressive pathogens like *S. pyogenes*, *S. pneumoniae,* and *Staphylococcus aureus*. Still, there are defined mechanisms by which enterococci move from commensal to pathogen, which include their ability to multiply in the gastrointestinal (GI) tract, their ability to attach to epithelial cells of the GI tract, the urinary tract, heart valves, and prosthetic material. A delineation of these factors is beyond the scope of this discussion and the reader is referred to excellent recent reviews of the subject [74, 75]. One virulence characteristic that is particularly relevant to this discussion is the formation of biofilm. Biofilm formation is important in many different types of infections [76]. It is likely that enterococci can enter a "persister state" when present in a biofilm, making them less susceptible to antimicrobials. In addition, in vitro experiments have shown that minimum inhibitory concentrations for some antimicrobials are higher in biofilm cells than in planktonic cells and increase with the duration of the biofilm (which in many clinical infections is prolonged). Finally, gene exchange between enterococci is promoted by some of the same factors that are involved in biofilm generation, increasing the risk of the emergence of new resistant variants. Currently, there are no pharmaceutical interventions proved to attenuate the impact of biofilms on antimicrobial therapy, emphasizing the importance of debridement and removal of prosthetic devices whenever possible.

The relationship between virulence and antimicrobial resistance in human pathogenic bacteria is complex. There are clear examples where, using in vitro or in vivo techniques, acquisition of antimicrobial resistance reduces the "fitness" or virulence of a bacterial strain. In general, explanations proffered for this increased cost have included compromise of function caused by changing amino acids in target proteins when resistance results from target mutations or the extra metabolic load created by the additional DNA and gene expression associated with acquired resistance elements [77]. In the clinical setting, it is difficult to confirm that antimicrobial resistance is associated with reduced virulence, since mutational resistance may be followed by compensatory mutations lessening the burden, acquired resistance elements may be accompanied by new virulence determinants, and regulatory elements within resistance determinants may reduce the metabolic load to minimal levels or serve to activate otherwise quiescent virulence factors [78]. In the case of *E. faecium*, one could posit that vancomycin and ampicillin resistance were themselves virulence determinants, since their emergence in the clinical setting was associated with percentages of enterococcal infections caused by this species rising from around 10% in the era before ampicillin and vancomycin resistance to 25%–35% after they emerged [79]. Of course, this increase was associated with a specific clade that may also have important virulence determinants, but that remains a matter of speculation since the clinical relevance of most putative virulence determinants in this species remains largely unexplored [37].

A sometimes-overlooked consequence of enterococcal resistance is the impact antimicrobials have on GI colonization by enterococci. Enterococci are present in the normal human GI flora in substantial numbers, but they represent a relatively

small percentage of bacteria in the gut. Under the influence of antimicrobials, especially those that achieve high concentrations in the GI tract, enterococci can become predominant, leading to increased translocation into the bloodstream and increased contamination of the perineal region, predisposing to infections, particularly in immunocompromised patients and in those with instrumented urinary tracts. In particular, cephalosporins secreted by the GI tract, such as ceftriaxone (which achieves biliary concentrations exceeding 5000 μg/mL with normal dosing), and drugs with potent activity against anaerobic bacteria have been associated with enterococcal colonization and infection [38, 39].

DIAGNOSTIC CONSIDERATIONS

From a clinical standpoint, identifying those who will develop persistent enterococcal bacteremia at the outset of their infection when any intervention would presumably be most helpful can be challenging; once persistent bacteremia (however defined) has been demonstrated days later, the therapeutic window for optimal aggressive clinical management may have already passed. As previously described, there is not a single point in time when ongoing enterococcal bacteremia should abruptly trigger concern for persistent bacteremia and/or complicated infection; instead, appropriate diagnostic and therapeutic maneuvers should begin once bacteremia is detected and methodically proceed so long as the bacteremia persists and/or a focal source of infection has not been identified and addressed. Knowledge of the characteristics of local blood culture systems may be helpful to assess the relevance of late or persistent culture growth despite appropriate antimicrobial therapy.

Certain host factors may help predict persistent enterococcal bacteremia, including neutropenia, active hematologic cancer, and ongoing intermittent hemodialysis. Enterococcal bacteremia attributed to a central venous catheter infection does not seem to be associated with persistent bacteremia per se, perhaps because this is an easily and frequently addressed source of infection during typical clinical care, and thus ongoing attention to appropriate management of central venous catheters in patients with enterococcal bacteremia should not be neglected [9]. The most efficient diagnostic strategy to Identify all patients with enterococcal endocarditis remains unsettled. The NOVA and DENOVA scores were developed to help "rule out" endocarditis and avoid the need for transesophageal echocardiography (TEE) in patients at very low risk for endocarditis; the diagnostic performance of these scores is good but not perfect, so a cautious approach to this algorithmic diagnostic strategy, considering additional relevant clinical features of individual patients, seems prudent [40–42] (Table 3).

The Duke–International Society for Cardiovascular Infectious Diseases (ISCVID) criteria for the diagnosis of infective endocarditis were recently updated and now newly include *E. faecalis* as a typical pathogen for endocarditis [43]. It is important to note that enterococcal endocarditis is primarily due to *E. faecalis* rather than *E. faecium* or other enterococci, with one large cohort finding *E. faecalis* as the cause of 91% of enterococcal endocarditis cases [13]. The accurate identification of all patients with enterococcal endocarditis is paramount, as the recommended management typically will include 2 antimicrobial agents rather than a single agent [44]. One group assessed a large cohort of patients with *E. faecalis* bacteremia (defined as ≥1 positive culture) and found that 26% had definite endocarditis; in that study, TEE was used in the diagnostic workup in 74% of the patients [45].

The updated Duke-ISCVID criteria also describe the use of alternate imaging studies (cardiac computed tomography, fluorodeoxyglucose positron emission tomography/computed tomography) to complement echocardiography for the diagnosis of endocarditis [43]. Attempts to identify occult sources for enterococcal bacteremia are also crucial. Consideration of endoscopic evaluation (in particular colonoscopy) may help identify luminal GI pathology responsible for translocation of GI flora; importantly, this can also serve to identify occult noninfectious processes (eg, GI cancer) in need of management. Despite a thorough evaluation, in many cases an underlying nidus of infection is not found. One recent large study described a cohort of patients with persistent enterococcal bacteremia (defined as positive blood cultures after ≥72 hours of antibiotics) and found that 39% had no identifiable source of infection beyond primary bacteremia, though it is unclear how extensive the diagnostic evaluations were in these cases [9]. Regardless of whether or not a source of persistent enterococcal bacteremia is immediately apparent, infectious disease consultation should be considered to assist with diagnostic and management efforts, as this has been consistently associated with a decrease in mortality rate [46].

THERAPEUTIC CONSIDERATIONS

Patients with persistent enterococcal bacteremia are frequently eventually found to have an underlying nidus of infection. Optimal management strategies for enterococcal catheter-related bloodstream infections (CRBSIs) and enterococcal endocarditis are well described in clinical practice guidelines covering these topics [44, 48]. Of note, if attempting salvage therapy for an enterococcal CRBSI as opposed to prompt removal of the offending catheter, one should strongly consider antimicrobial lock therapy as an adjunct to systemic antimicrobial therapy. A 2022 report suggests that a 7-day course of antimicrobials after catheter removal may be adequate treatment for enterococcal CRBSI; updated Infectious Diseases Society of America CRBSI guidelines are expected soon [48, 49]. Regarding the treatment of enterococcal endocarditis, beyond

Table 3. Diagnostic Criteria and Scoring Systems for Enterococcal Infective Endocarditis

Clinical Data	2023 Duke-ISCVID Criteria[a]	NOVA[a]	DENOVA[a]
Positive blood culture	Major criteria: *E. faecalis* bacteremia in ≥2 blood culture sets OR other enterococcal bacteremia in ≥3 blood culture sets	N represents *number* of positive blood cultures suggestive of continuous bacteremia (3 of 3 or majority of >3); O, *origin* of bacteremia unknown	N represents *number* of positive blood cultures suggestive of continuous bacteremia (2 of 2 or majority of >2); O, *origin* of bacteremia unknown
Evidence of endocardial involvement	Major criteria: echocardiogram and/or cardiac CT showing vegetation, perforation or other suppurative complication, or significant new regurgitation OR PET/CT showing abnormal metabolic activity involving valve	V represents prior *valve* disease, including native valve disease, previous endocarditis, or presence of a valve prosthesis	V represents prior *valve* disease, including native valve disease, previous endocarditis, or presence of a valve prosthesis
Predisposition	Minor criteria: prior endocarditis, prosthetic valve or valve repair, CHD or HOCM, more than mild stenosis or regurgitation, endovascular CIED, or injection drug use	A represents *auscultation* of a heart murmur	A represents *auscultation* of a heart murmur
Fever	Minor criteria: temperature >38.0°C	…	D represents *duration* of any symptoms compatible with endocarditis for ≥7 d
Vascular phenomena	Minor criteria: major arterial emboli, septic pulmonary infarcts, cerebral or splenic abscess, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, or Janeway lesions	…	E represents *embolization* as determined with clinical examination or imaging
Immunologic phenomena	Minor criteria: glomerulonephritis, Osler nodes, Roth spots, or rheumatoid factor	…	…
Microbiologic evidence	Minor criteria: positive enterococcal blood cultures that do not meet major criteria OR positive enterococcal culture from other sterile site	…	…
Imaging criteria	Minor criteria: abnormal PET/CT metabolic activity at prosthetic valve within 3 mo of implantation	…	…

Abbreviations: CHD, congenital heart disease; CIED, cardiovascular implantable electronic device; CT, computed tomography; *E. faecalis*, *Enterococcus faecalis*; HOCM, hypertrophic obstructive cardiomyopathy; ISCVID, International Society for Cardiovascular Infectious Diseases; PET, positron emission tomography.

[a]The 2023 Duke-ISCVID criteria describe definite infective endocarditis as the presence of 2 major, 1 major and 3 minor, or 5 minor clinical criteria [43]. The NOVA score assigns points to clinical criteria (N, 5 points O, 4 points; V, 2 points; A, 1 point) and describes a very low risk for endocarditis with total scores <4 points [40]. The DENOVA score assigns points to clinical criteria (1 point for each of the 6 DENOVA criteria) and describes a very low risk for endocarditis with total scores <3 points [42].

the perennially controversial choice of optimal antimicrobial therapy reviewed in depth elsewhere, arguably the most important factor in a successful outcome for these complicated patients is clear communication among the multidisciplinary team of providers typically involved in their care. In particular, highlighting attributes specific to enterococcal endocarditis—such as increased rates of recurrent infection and similar morbidity and mortality rates despite a less frequent overt septic appearance compared with nonenterococcal endocarditis—may help guide decision making surrounding individualized medical and/or surgical treatment strategies [13, 50].

Enterococcal osteoarticular infections may also serve as a nidus for persistent enterococcal bacteremia, as well as a source of clinical management challenges. In particular, the optimal treatment of enterococcal prosthetic joint infections remains uncertain. Again, a collaborative medical and surgical approach with clear communication among providers surrounding planned management strategies is paramount. At issue is the choice between debridement with implant retention or 1- or 2-stage implant exchange, optimal choice of antimicrobial therapy (single vs combination therapy), and whether there is a role for subsequent suppressive antimicrobial therapy in some or all cases. The evidence addressing the optimal management of enterococcal prosthetic joint infections in particular is limited to retrospective cohort studies. The unique pathogenicity, antimicrobial tolerance, and biofilm formation attributes intrinsic to enterococcal infections suggest that an optimal approach to the management of enterococcal prosthetic joint infections may differ from management strategies for other more commonly implicated bacteria, such as *S. aureus* or Enterobacteriaceae [51, 52].

Persistent enterococcal bacteremia without an evident underlying nidus of infection despite an appropriate or exhaustive workup is also a relatively common diagnostic end point. On encountering such a clinical scenario, beyond consideration of interventions to improve the patient's immune status if possible or relevant, the only remaining modifiable treatment strategy is typically a change in directed antimicrobial therapy.

When considering such a change, it is prudent to be cautious, as "more" antimicrobials (combination therapy) may not necessarily provide additional efficacy and "different" or "stronger" antimicrobials may also be associated with additional direct and indirect adverse effects. No change to antimicrobial therapy, particularly in a clinically stable or improving patient, should also be entertained as an appropriate therapeutic option.

Among patients with persistent bacteremia and ongoing sepsis, embolic phenomena, or other clinical complications attributable to their ongoing infection, a limited number of choices for alternate or additional antimicrobial therapy are available, including gentamicin or other aminoglycosides, vancomycin, daptomycin, linezolid, tigecycline, and/or quinupristin-dalfopristin (for *E. faecium*). Evidence addressing the clinical benefit of transitioning to any of these agents or combination therapy in the absence of antimicrobial resistance is lacking and at present limited to preclinical and observational data [15, 66–68]. Of note, given concerns regarding the current daptomycin susceptibility breakpoint for enterococci and prior observational studies demonstrating that higher daptomycin doses may improve clinical outcomes, attention to appropriate dosing is imperative when using this antimicrobial [11, 53, 54] (Figure 1). Among severely immunocompromised patients, persistent and/or recurrent enterococcal bacteremia may be difficult to eradicate without a return of or improvement in host immunity. Antimicrobial treatment of these patients without effective eradication of bacteremia for weeks or months (in the setting of the extensive prior antimicrobial exposure common in many of these patients) may lead to the emergence of clinically relevant antimicrobial resistance; in these patients, even more than in others, it is important to plan ahead and preserve alternative antimicrobial therapies until they are needed [55, 80].

FUTURE RESEARCH DIRECTIONS/QUESTIONS

Ongoing research is needed to further elucidate specific factors intrinsic to host immunity or enterococcal virulence that contribute to persistent bacteremia and severe infections. Additional efforts to unravel mechanisms of antimicrobial synergism (and/or antagonism) with respect to *Enterococcus* species may help direct (or discourage) novel treatment strategies. Several newer antimicrobials (eg, oritavancin, dalbavancin, eravacycline, omadacycline, tedizolid, ceftaroline, fosfomycin) have demonstrated activity against *Enterococcus* isolates, though their role in clinical care, as single agents or in combination, has yet to be defined. Combination antimicrobial therapy or early antimicrobial escalation strategies for severe enterococcal infection (without endocarditis) may provide a clinical benefit to some patients, although this has not yet been demonstrated in any interventional study. Despite extensive investigation, the ideal antimicrobial for the initial treatment of VRE bacteremia is not yet well defined. The role of rifampin or other biofilm active agents for use in enterococcal infections involving prosthetic materials needs further exploration. Given the poor clinical outcomes associated with many severe or persistent enterococcal infections, there remains much work yet to be done.

Note

Potential conflicts of interest. The authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Kontula KSK, Skogberg K, Ollgren J, Järvinen A, Lyytikäinen O. Population-based study of bloodstream infection incidence and mortality rates, Finland, 2004–2018. Emerg Infect Dis **2021**; 27:2560–9.
2. Pinholt M, Østergaard C, Arpi M, et al. Incidence, clinical characteristics and 30-day mortality of enterococcal bacteraemia in Denmark 2006–2009: a population-based cohort study. Clin Microbiol Infect **2014**; 20:145–51.
3. Suzuki H, Hase R, Otsuka Y, Hosokawa N. A 10-year profile of enterococcal bloodstream infections at a tertiary-care hospital in Japan. J Infect Chemother **2017**; 23:390–3.
4. Verway M, Brown KA, Marchand-Austin A, et al. Prevalence and mortality associated with bloodstream organisms: a population-wide retrospective cohort study. J Clin Microbiol **2022**; 60:e0242921.
5. Jindai K, Strerath MS, Hess T, Safdar N. Is a single positive blood culture for *Enterococcus* species representative of infection or contamination? Eur J Clin Microbiol Infect Dis **2014**; 33:1995–2003.
6. Claeys KC, Zasowski EJ, Lagnf AM, Rybak MJ. Comparison of outcomes between patients with single versus multiple positive blood cultures for *Enterococcus*: infection versus illusion? Am J Infect Control **2016**; 44:47–9.
7. Ali GA, Goravey W, Najim MS, et al. Epidemiology, microbiological and clinical characteristics of *Enterococcus* species bloodstream infections: a 10-year retrospective cohort study from Qatar. Ann Med Surg (Lond) **2022**; 80:104258.
8. Shephard EA, Mondy K, Reveles KR, Jaso T, Rose DT. A comparison of outcomes with and without infectious diseases consultation for enterococcal bacteraemia in a multicenter healthcare system. Int J Antimicrob Agents **2022**; 60:106665.
9. Bussini L, Rosselli Del Turco E, Pasquini Z, et al. Risk factors for persistent enterococcal bacteraemia: a multicentre retrospective study. J Glob Antimicrob Resist **2022**; 29:386–9.
10. Britt NS, Potter EM, Patel N, Steed ME. Effect of continuous and sequential therapy among veterans receiving daptomycin or linezolid for vancomycin-resistant *Enterococcus faecium* bacteremia. Antimicrob Agents Chemother **2017**; 61:e02216-16.
11. Britt NS, Potter EM, Patel N, Steed ME. Comparative effectiveness and safety of standard-, medium-, and high-dose daptomycin strategies for the treatment of vancomycin-resistant enterococcal bacteremia among Veterans Affairs patients. Clin Infect Dis **2017**; 64:605–13.
12. Contreras GA, Munita JM, Simar S, et al. Contemporary clinical and molecular epidemiology of vancomycin-resistant enterococcal bacteremia: a prospective multicenter cohort study (VENOUS I). Open Forum Infect Dis **2022**; 9:ofab616.
13. Pericàs JM, Llopis J, Muñoz P, et al. A contemporary picture of enterococcal endocarditis. J Am Coll Cardiol **2020**; 75:482–94.
14. Cho SY, Lee DG, Choi SM, et al. Impact of vancomycin resistance on mortality in neutropenic patients with enterococcal bloodstream infection: a retrospective study. BMC Infect Dis **2013**; 13:504.
15. Jent P, Thalmann L, Pabst T, Droz S, Sendi P. Adjunctive gentamicin did not improve outcome of enterococcal bacteraemia in neutropenic patients: a propensity scored matched study. Infect Dis (Lond) **2019**; 51:409–16.
16. Bizot E, Truong J, Mariani-Kurkdjian P, Bonacorsi S, Faye A, Caseris M. Pediatric enterococcal bacteremia: a 12-year retrospective study in a French pediatric center. Pediatr Infect Dis J **2022**; 41:e346–e50.
17. Lopez-Luis BA, Ponce-De-León A, Ortiz-Brizuela E, et al. Risk factors associated with failure of linezolid therapy in vancomycin-resistant *Enterococcus faecium* bacteremia: a retrospective cohort study in a referral center in Mexico. Microb Drug Resist **2022**; 28:744–9.
18. Chuang YC, Tseng TC, Wang JT, et al. Influence of daptomycin dose and fosfomycin susceptibility on outcome of vancomycin-resistant *Enterococcus faecium*

bloodstream infections treated with daptomycin and fosfomycin combination. J Antimicrob Chemother **2022**; 77:1436–43.
19. Ha S, Huh K, Chung DR, et al. Efficacy of teicoplanin in bloodstream infections caused by *Enterococcus faecium*: posthoc analysis of a nationwide surveillance. Int J Infect Dis **2022**; 122:506–13.
20. Shah NH, Shutt KA, Doi Y. Ampicillin-ceftriaxone vs ampicillin-gentamicin for definitive therapy of *Enterococcus faecalis* infective endocarditis: a propensity score-matched, retrospective cohort analysis. Open Forum Infect Dis **2021**; 8: ofab102.
21. Oldberg K, Rasmussen M. *Enterococcus faecalis* in blood cultures—a prospective study on the role of persistent bacteremia. Diagn Microbiol Infect Dis **2021**; 101: 115433.
22. Ramos-Martínez A, Pericàs JM, Fernández-Cruz A, et al. Four weeks versus six weeks of ampicillin plus ceftriaxone in *Enterococcus faecalis* native valve endocarditis: a prospective cohort study. PLoS One **2020**; 15:e0237011.
23. Fletcher JM, Kram SJ, Sarubbi CB, Anderson DJ, Kram BL. Effectiveness of vancomycin or beta-lactam therapy in ampicillin-susceptible *Enterococcus* spp. bloodstream infections. J Pharm Pract **2019**; 32:375–81.
24. Pericàs JM, Cervera C, Moreno A, et al. Outcome of *Enterococcus faecalis* infective endocarditis according to the length of antibiotic therapy: preliminary data from a cohort of 78 patients. PLoS One **2018**; 13:e0192387.
25. Ye JJ, Shie SS, Cheng CW, et al. Clinical characteristics and treatment outcomes of vancomycin-resistant *Enterococcus faecium* bacteremia. J Microbiol Immunol Infect **2018**; 51:705–16.
26. Herc ES, Kauffman CA, Marini BL, Perissinotti AJ, Miceli MH. Daptomycin nonsusceptible vancomycin resistant *Enterococcus* bloodstream infections in patients with hematological malignancies: risk factors and outcomes. Leuk Lymphoma **2017**; 58:2852–8.
27. Britt NS, Potter EM, Patel N, Steed ME. Comparison of the effectiveness and safety of linezolid and daptomycin in vancomycin-resistant enterococcal bloodstream infection: a national cohort study of Veterans Affairs patients. Clin Infect Dis **2015**; 61:871–8.
28. Hemapanpairoa J, Changpradub D, Santimaleeworagun W. Clinical impact of vancomycin treatment in ampicillin-susceptible enterococci bloodstream infections. Antibiotics (Basel) **2022**; 11:1698.
29. Echeverria-Esnal D, Sorli L, Prim N, et al. Linezolid vs glycopeptides in the treatment of glycopeptide-susceptible *Enterococcus faecium* bacteraemia: a propensity score matched comparative study. Int J Antimicrob Agents **2019**; 54:572–8.
30. Kamboj M, Cohen N, Huang YT, et al. Impact of empiric treatment for vancomycin-resistant *Enterococcus* in colonized patients early after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant **2019**; 25: 594–8.
31. Kohler P, Eshaghi A, Kim HC, et al. Prevalence of vancomycin-variable *Enterococcus faecium* (VVE) among vanA-positive sterile site isolates and patient factors associated with VVE bacteremia. PLoS One **2018**; 13:e0193926.
32. Zasowski EJ, Claeys KC, Lagnf AM, Davis SL, Rybak MJ. Time is of the essence: the impact of delayed antibiotic therapy on patient outcomes in hospital-onset enterococcal bloodstream infections. Clin Infect Dis **2016**; 62:1242–50.
33. Casapao AM, Kullar R, Davis SL, et al. Multicenter study of high-dose daptomycin for treatment of enterococcal infections. Antimicrob Agents Chemother **2013**; 57: 4190–6.
34. DiazGranados CA, Jernigan JA. Impact of vancomycin resistance on mortality among patients with neutropenia and enterococcal bloodstream infection. J Infect Dis **2005**; 191:588–95.
35. Arthur M, Molinas C, Depardieu F, Courvalin P. Characterization of Tn1546, a Tn3-related transposon conferring glycopeptide resistance by synthesis of depsipeptide peptidoglycan precursors in *Enterococcus faecium* BM4147. J Bacteriol **1993**; 175:117–27.
36. Carias LL, Rudin SD, Donskey CJ, Rice LB. Genetic linkage and cotransfer of a novel, vanB-containing transposon (Tn5382) and a low-affinity penicillin-binding protein 5 gene in a clinical vancomycin-resistant *Enterococcus faecium* isolate. J Bacteriol **1998**; 180:4426–34.
37. Galloway-Peña JR, Nallapareddy SR, Arias CA, Eliopoulos GM, Murray BE. Analysis of clonality and antibiotic resistance among early clinical isolates of *Enterococcus faecium* in the United States. J Infect Dis **2009**; 200:1566–73.
38. Donskey CJ, Chowdhry TK, Hecker MT, et al. Effect of antibiotic therapy on the density of vancomycin-resistant enterococci in the stool of colonized patients. N Engl J Med **2000**; 343:1925–32.
39. Fridkin SK, Edwards JR, Courval JM, et al. The effect of vancomycin and third-generation cephalosporins on prevalence of vancomycin-resistant enterococci in 126 U.S. adult intensive care units. Ann Intern Med **2001**; 135: 175–83.
40. Bouza E, Kestler M, Beca T, et al. The NOVA score: a proposal to reduce the need for transesophageal echocardiography in patients with enterococcal bacteremia. Clin Infect Dis **2015**; 60:528–35.
41. Dahl A, Lauridsen TK, Arpi M, et al. Risk factors of endocarditis in patients with *Enterococcus faecalis* bacteremia: external validation of the NOVA score. Clin Infect Dis **2016**; 63:771–5.
42. Berge A, Krantz A, Östlund H, Nauclér P, Rasmussen M. The DENOVA score efficiently identifies patients with monomicrobial *Enterococcus faecalis* bacteremia where echocardiography is not necessary. Infection **2019**; 47:45–50.
43. Fowler VG, Durack DT, Selton-Suty C, et al. The 2023 Duke-ISCVID criteria for infective endocarditis: updating the modified Duke criteria. Clin Infect Dis **2023**; 77:518–26.
44. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation **2015**; 132:1435–86.
45. Dahl A, Iversen K, Tonder N, et al. Prevalence of infective endocarditis in *Enterococcus faecalis* bacteremia. J Am Coll Cardiol **2019**; 74:193–201.
46. Tholany J, Kobayashi T, Marra AR, Schweizer ML, Samuelson RJ, Suzuki H. Impact of infectious diseases consultation on the outcome of patients with enterococcal bacteremia: a systematic literature review and meta-analysis. Open Forum Infect Dis **2022**; 9:ofac200.
47. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis **2000**; 30:633–8.
48. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis **2009**; 49:1–45.
49. Rosselli Del Turco E, Pasquini Z, Scolz K, et al. Treatment duration for central line-associated infection caused by *Enterococcus* spp.: a retrospective evaluation of a multicenter cohort. Eur J Clin Microbiol Infect Dis **2022**; 41:1203–6.
50. Danneels P, Hamel JF, Picard L, et al. Impact of *Enterococcus faecalis* endocarditis treatment on risk of relapse. Clin Infect Dis **2023**; 76:281–90.
51. Thompson O, Rasmussen M, Stefánsdóttir A, Christensson B, Åkesson P. A population-based study on the treatment and outcome of enterococcal prosthetic joint infections: a consecutive series of 55 cases. J Bone Jt Infect **2019**; 4:285–91.
52. Renz N, Trebse R, Akgün D, Perka C, Trampuz A. Enterococcal periprosthetic joint infection: clinical and microbiological findings from an 8-year retrospective cohort study. BMC Infect Dis **2019**; 19:1083.
53. Chuang YC, Lin HY, Chen PY, et al. Effect of daptomycin dose on the outcome of vancomycin-resistant, daptomycin-susceptible *Enterococcus faecium* bacteremia. Clin Infect Dis **2017**; 64:1026–34.
54. Avery LM, Kuti JL, Weisser M, et al. Pharmacodynamic analysis of daptomycin-treated enterococcal bacteremia: it is time to change the breakpoint. Clin Infect Dis **2019**; 68:1650–7.
55. Munita JM, Mishra NN, Alvarez D, et al. Failure of high-dose daptomycin for bacteremia caused by daptomycin-susceptible *Enterococcus faecium* harboring LiaSR substitutions. Clin Infect Dis **2014**; 59:1277–80.
56. Fox E, Ha D, Bounthavong M, et al. Risk factors and outcomes associated with persistent vancomycin resistant enterococcal bacteremia. BMC Infect Dis **2022**; 22:855.
57. Khan A, Miller WR, Axell-House D, Munita JM, Arias CA. Antimicrobial susceptibility testing for enterococci. J Clin Microbiol **2022**; 60:e0084321.
58. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014. Infect Control Hosp Epidemiol **2016**; 37:1288–301.
59. Rice LB, Carias LL, Hutton-Thomas R, Sifaoui F, Gutmann L, Rudin SD. Penicillin-binding protein 5 and expression of ampicillin resistance in *Enterococcus faecium*. Antimicrob Agents Chemother **2001**; 45:1480–6.
60. Rice LB, Desbonnet C, Tait-Kamradt A, et al. Structural and regulatory changes in PBP4 trigger decreased β-lactam susceptibility in *Enterococcus faecalis*. mBio **2018**; 9:e00361-18.
61. Dörr T. Understanding tolerance to cell wall-active antibiotics. Ann N Y Acad Sci **2021**; 1496:35–58.
62. Geraci JE, Martin WJ. Antibiotic therapy of bacterial endocarditis. VI. Subacute enterococcal endocarditis; clinical, pathologic and therapeutic consideration of 33 cases. Circulation **1954**; 10:173–94.
63. Herrera-Hidalgo L, Fernández-Rubio B, Luque-Márquez R, López-Cortés LE, Gil-Navarro MV, de Alarcón A. Treatment of *Enterococcus faecalis* infective endocarditis: a continuing challenge. Antibiotics (Basel) **2023**; 12:704.
64. Fernández-Hidalgo N, Almirante B, Gavaldà J, et al. Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for treating *enterococcus faecalis* infective endocarditis. Clin Infect Dis **2013**; 56:1261–8.

65. Mainardi JL, Gutmann L, Acar JF, Goldstein FW. Synergistic effect of amoxicillin and cefotaxime against *Enterococcus faecalis*. Antimicrob Agents Chemother **1995**; 39:1984–7.
66. Beganovic M, Luther MK, Rice LB, Arias CA, Rybak MJ, LaPlante KL. A review of combination antimicrobial therapy for *Enterococcus faecalis* bloodstream infections and infective endocarditis. Clin Infect Dis **2018**; 67:303–9.
67. Chuang YC, Wang JT, Yang JL, et al. The combination of daptomycin with β-lactam antibiotics is more effective than daptomycin alone for vancomycin-resistant *Enterococcus faecium* bloodstream infection. J Infect Public Health **2022**; 15:1396–402.
68. Tseng TC, Chuang YC, Yang JL, et al. The combination of daptomycin with fosfomycin is more effective than daptomycin alone in reducing mortality of vancomycin-resistant enterococcal bloodstream infections: a retrospective, comparative cohort study. Infect Dis Ther **2023**; 12:589–606.
69. Manson JM, Hancock LE, Gilmore MS. Mechanism of chromosomal transfer of *Enterococcus faecalis* pathogenicity island, capsule, antimicrobial resistance, and other traits. Proc Natl Acad Sci U S A **2010**; 107:12269–74.
70. Rice LB. Tn916 family conjugative transposons and dissemination of antimicrobial resistance determinants. Antimicrob Agents Chemother **1998**; 42:1871–7.
71. Marshall SH, Donskey CJ, Hutton-Thomas R, Salata RA, Rice LB. Gene dosage and linezolid resistance in *Enterococcus faecium* and *Enterococcus faecalis*. Antimicrob Agents Chemother **2002**; 46:3334–6.
72. Lazaris A, Coleman DC, Kearns AM, et al. Novel multiresistance *cfr* plasmids in linezolid-resistant methicillin-resistant *Staphylococcus epidermidis* and vancomycin-resistant *Enterococcus faecium* (VRE) from a hospital outbreak: co-location of *cfr* and *optrA* in VRE. J Antimicrob Chemother **2017**; 72:3252–7.
73. Mishra NN, Bayer AS, Tran TT, et al. Daptomycin resistance in enterococci is associated with distinct alterations of cell membrane phospholipid content. PLoS One **2012**; 7:e43958.
74. Fiore E, Van Tyne D, Gilmore MS. Pathogenicity of enterococci. Microbiol Spectr **2019**; 7:10.1128/microbiolspec.GPP3-0053-2018.
75. Goh HMS, Yong MHA, Chong KKL, Kline KA. Model systems for the study of enterococcal colonization and infection. Virulence **2017**; 8:1525–62.
76. Ch'ng JH, Chong KKL, Lam LN, Wong JJ, Kline KA. Biofilm-associated infection by enterococci. Nat Rev Microbiol **2019**; 17:82–94.
77. Starikova I, Al-Haroni M, Werner G, et al. Fitness costs of various mobile genetic elements in *Enterococcus faecium* and *Enterococcus faecalis*. J Antimicrob Chemother **2013**; 68:2755–65.
78. Foucault ML, Depardieu F, Courvalin P, Grillot-Courvalin C. Inducible expression eliminates the fitness cost of vancomycin resistance in enterococci. Proc Natl Acad Sci U S A **2010**; 107:16964–9.
79. Miller WR, Murray BE, Rice LB, Arias CA. Vancomycin-resistant enterococci: therapeutic challenges in the 21st century. Infect Dis Clin North Am **2016**; 30: 415–39.
80. Messina JA, Sinha R, Starr K, et al. Clinical and genomic characterization of recurrent enterococcal bloodstream infection in patients with acute leukemia. Open Forum Infect Dis **2018**; 5:ofy107.