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CARDIOVASCULAR INFECTIONS (D LEVINE, SECTION EDITOR)

What's New in the Treatment of Enterococcal Endocarditis?

Masayuki Nigo · Jose M. Munita · Cesar A. Arias · Barbara E. Murray

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Abstract *Enterococcus* spp. are among the common pathogens causing infective endocarditis (IE). Despite major medical advances and new potent antimicrobial agents, the mortality has not significantly improved for several decades. The usual lack of bactericidal activity of penicillin or ampicillin, the toxicity from the combination of penicillin plus aminoglycosides, and the increased reports of high-level resistance to aminoglycosides have led to the exploration of other regimens for treatment of *Enterococcus faecalis* IE. As an example, ampicillin plus ceftriaxone is now a well-recognized regimen for this organism. However, the emerging of new drug resistances in *Enterococcus faecium* dramatically reduces the therapeutic alternatives for this organism in IE which continues to be an immense challenge for clinicians even with the availability of newer antimicrobial agents. This article summarizes the current treatment options for enterococcal endocarditis and reviews of recent publications on the topic.

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M. Nigo · J. M. Munita · C. A. Arias · B. E. Murray
Division of Infectious Diseases, Department of Internal Medicine, University of Texas Medical School at Houston, Houston, TX, USA

C. A. Arias · B. E. Murray
Department of Microbiology and Molecular Genetics, University of Texas Medical School at Houston, Houston, TX, USA

C. A. Arias
Molecular Genetics and Antimicrobial Resistance Unit, Universidad El Bosque, Bogotá, Colombia

J. M. Munita
Clinica Alemana de Santiago, Universidad del Desarrollo, Santiago, Chile

B. E. Murray (✉)
University of Texas Medical School at Houston, 6431 Fannin St. MSB 2.112, Houston, TX 77030, USA
e-mail: bem.asst@uth.tmc.edu

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Introduction

The earliest description of infective endocarditis (IE) as a distinct clinical entity is attributed to Sir William Osler in 1885. However, the pathological description of an endocardial vegetation dates from centuries before in a manuscript by Lazarus Riverius and others in the seventeenth century [1]. Despite major medical advances and important efforts to improve antimicrobial prophylaxis in high-risk patients and the availability of potent antibiotics, the prevalence and associated mortality of IE have not markedly improved over the last several decades [2, 3]. Gram-positive bacteria are, by far, the most important causes of IE and, among them, *Enterococcus* spp. play a significant role, ranking third within the most frequent causes of both native and prosthetic valve IE, after *Staphylococcus* spp. and *Streptococcus* spp. [2, 3]. Furthermore, some recent data suggest that the frequency of enterococcal IE is actually increasing, a phenomenon that is associated with a rise in hospital-associated (HA) infections caused by these organisms. Indeed, *Enterococcus* spp. cause as much as 30 % of HA endocarditis and it is second behind *Staphylococcus* spp. as a cause of IE acquired in this setting [4, 5].

The treatment of enterococcal endocarditis has long been recognized as an important clinical challenge due to the lack of reliable bactericidal activity of most antimicrobials against these bacteria. This problem was first identified over 60 years ago when failure rates of penicillin monotherapy for the treatment enterococcal IE were found to be much higher than those caused by staphylococci or streptococci [6]. It was later found that the addition of streptomycin to penicillin in patients who were failing penicillin therapy improved the clinical

outcome. Improvement correlated with in vitro bactericidal synergism of the combination of a cell wall agent with an aminoglycoside compared with either of these drugs alone [7]. These findings prompted clinicians to adopt the combination of a beta-lactam with an aminoglycoside as the standard of care for enterococcal IE, a regimen that has only recently come under challenge for IE caused by *E. faecalis*.

Unfortunately, most *E. faecium* seen in the modern-day hospital exhibit resistance to the historically most active cell wall agents (beta-lactams and vancomycin) and also have acquired high-level resistance (HLR) to both gentamicin and streptomycin, the two aminoglycosides most commonly used in clinical practice against enterococci. Additionally, toxicity, particularly in the elderly and critically ill patients, has become a limiting factor when using aminoglycosides for prolonged periods of time (as used to treat IE). A dramatic example of this issue is the description of a patient in 1959 who became deaf after a treatment course of penicillin plus neomycin for recurrent *E. faecalis* aortic valve IE [8].

The two main species of enterococci that are responsible for IE in humans are *E. faecalis* and *E. faecium*. In this review, we will summarize the available literature regarding treatment of IE caused by these organisms, with special emphasis on the most recent drugs and therapeutic combinations. Since *E. faecalis* and *E. faecium* present different clinical challenges, largely due to differences in their antimicrobial susceptibility and resistance mechanisms, we will discuss them separately.

Treatment of IE caused by *Enterococcus faecalis*

The vast majority of clinical *E. faecalis* isolates remain susceptible to penicillin and ampicillin and, consequently, these antibiotics continue to be a very important part of the therapeutic armamentarium against this species. A more challenging issue has been the development of high-level resistance to aminoglycosides (HLRAG), which is defined as minimal inhibitory concentrations (MICs) measured by agar dilution higher than 500 μg/mL and 2,000 μg/mL for gentamicin and streptomycin, respectively. High-level resistance (HLR) to streptomycin is mediated by ribosomal mutations or enzymatic modification and HLR to gentamicin is usually due to the acquisition of a gene encoding a bi-functional enzyme that modifies all commercially available aminoglycosides, but not streptomycin; these different mechanisms can occur together in the same strain. Whichever the mechanism, the presence of HLRAG abolishes the synergism of the combination with cell wall agents, reducing the likelihood of obtaining a favorable clinical outcome in IE. Therefore, if using an aminoglycoside for synergism against enterococci, it is of paramount importance to test for the presence of HLR to gentamicin and streptomycin in order to choose the appropriate antimicrobials to treat endovascular infections caused by *E. faecalis* (Table 1).

Treatment of *E. faecalis* IE with an Aminoglycoside-Containing Regimen

In the absence of HLARG, the abovementioned combination of ampicillin/penicillin (or vancomycin for patients with severe penicillin allergy) and an aminoglycoside was long the combination of choice for IE. Among the aminoglycosides, gentamicin has usually been the drug of choice since measurement of plasma levels is more readily available than for streptomycin. The American Heart Association (AHA)/Infectious Diseases Society of America (IDSA) endocarditis guidelines of 2005 recommended gentamicin in a dose of 3 mg/kg/day divided three times daily (combined with penicillin or ampicillin) [9]. The most important limitation for the use of aminoglycosides is the development of nephrotoxicity during therapy. In order to decrease aminoglycoside-related nephrotoxicity, two main strategies have been utilized, (i) changing the frequency of administration to a once-daily dosing and (ii) decreasing the duration of the administration of the aminoglycoside. The rationale for the first strategy originated from clinical data that suggested that once daily administration of aminoglycosides reduced the toxicity of aminoglycosides while maintaining the therapeutic efficacy [10]. However, this approach has not been systematically evaluated when aminoglycosides are used for synergism against enterococcal IE. The second strategy (shortening the length of aminoglycoside therapy) was tested in Sweden. In a retrospective study of 93 episodes of *E. faecalis* IE, Olaison et al. found that outcomes of patients receiving 2 weeks of gentamicin combined with 6 weeks of a cell wall-active antimicrobial agent were similar to those of patients receiving the aminoglycoside for the entire 4–6 weeks course [11]. This finding was further supported by a recent study from Denmark which retrospectively compared the outcomes of 84 patients with *E. faecalis* (without HLRAG) IE treated with 4–6 weeks of gentamicin plus ampicillin (41 subjects) vs. the same regimen but stopping gentamicin after two weeks (43 subjects) [12]. Although the authors found no differences in clinical outcomes, nephrotoxicity was significantly higher (estimated GFR; median, 45 versus 66 mL/min; $p=0.008$) in patients who were treated with gentamicin during the full course of the therapy. In the above studies, the mean duration of symptoms was 21 and 25 days, respectively. Of note, the AHA/IDSA guidelines recommend 6 weeks of treatment if symptoms have been present for more than 3 months, based on the study conducted by Wilson et al. and 4 weeks otherwise [13]. Comparative prospective evaluation of such regimens has not been performed but 2 weeks of the combination followed by ampicillin monotherapy may be beneficial in a sub-population of patients with less severe presentations of IE including those with

Table 1 Therapeutic options for the treatment of *Enterococcus faecalis* infective endocarditis

Agent (s)	Comments
PEN[b] or AMP[a,b] plus an aminoglycoside (GEN or SM)[c]	• 4–6 weeks for the treatment of *E. faecalis* without HLR to aminoglycosides [9]. • Shorter duration of the aminoglycoside (2 weeks) may be considered in selected patients in order to decrease toxicity [11, 12].
AMP plus CRO[d]	• Recommended for *E. faecalis* exhibiting HLR to aminoglycosides [9]. • May be considered as first choice for *E. faecalis* without HLR to aminoglycosides, especially in patients at high risk of renal toxicity [14•].
VAN plus AG[c]	• To be considered for patients with severe allergy to β-lactams who cannot be desensitized.
DAP[e]±AMP[b] or CPT	• Combinations may have a synergistic effect and may also prevent emergence of DAP resistance during therapy [21, 23].
DAP[e] plus GEN	• Could be considered in cases of β-lactam allergy.

PEN penicillin, *AMP* ampicillin, *GEN* gentamicin, *SM* streptomycin, *HLR* high-level resistance, *CRO* ceftriaxone, ampicillin/sulbactam, *VAN* vancomycin, *DAP* daptomycin, *CPT* ceftaroline

[a] For rare case of β-lactamase-producing *E. faecalis*, ampicillin/sulbactam12 g IV q24 h in four equally divided doses can be used, instead of AMP

[b] PEN: 18–30 million U q24 h IV by continuous infusion or in six equally divided doses; AMP, 12–20 g q24 h IV in six equally divided doses

[c] GEN is more often used due to the availability of serum level tests. GEN dose is 3 mg/kg per day IV in three equally divided doses

[d] A CRO dose of 2 g q12 h should be used

[e] Consider DAP doses of 8–12 mg/kg IV daily

shorter duration of symptoms. A large study of the use of ampicillin plus ceftriaxone, which was initially intended for *E. faecalis* exhibiting HLRAG, has been published recently and will be discussed in the following section [14•].

Treatment of *E. faecalis* IE with a Non-Aminoglycoside-Containing Regimen

The emergence and increased frequency of HLRAG among modern-day *E. faecalis* isolates coupled with the abovementioned toxicity issues related to the use of aminoglycosides prompted the study of alternative regimens with similar efficacy and a better safety profile to treat enterococcal IE. In vitro studies have demonstrated that the combination of cefotaxime or ceftriaxone with ampicillin exhibited bactericidal activity against *E. faecalis* with HLRAG, despite the fact that enterococci are intrinsically resistant to cephalosporins [15, 16]. This effect is explained by the differential targeting of the penicillin binding proteins (PBPs) (i.e., cell wall synthesis enzymes) by each beta-lactam compound. Indeed, total saturation (100 %) of PBP 2 and 3 by cefotaxime (or ceftriaxone) plus partial saturation (25 %) of PBPs 4 and 5 by amoxicillin appears to explain the synergistic effect [15]. Furthermore, the combination of ceftriaxone and ampicillin was effective in animal models of IE caused by *E. faecalis* with and without HLRAG [16, 17] and was successfully used as rescue therapy in a patient with relapsing IE after therapy with ampicillin plus gentamicin [18]. Subsequently, two observational prospective multicenter studies have analyzed the efficacy of this regimen. The first one was an open-label study that evaluated 43 patients with IE due to *E. faecalis* with and without HLRAG (21 and 22, respectively) treated with ceftriaxone (2 g every 12 h) plus ampicillin (2 g every 4 h) for 6 weeks [19]. This study reported clinical cure rates of 71.4 % at the end of therapy for patients infected with isolates exhibiting HLRAG and 72.7 % for subjects infected without HLRAG. The overall success rate at 3 months was 67.4 % with a relapse rate of 5 % and overall mortality of 23.3 %. The second study, recently published by Fernandez-Hidalgo et al., was a nonrandomized, open-label, observational study in which the combination of ampicillin-ceftriaxone was compared with a "control" group treated with the standard of care (ampicillin plus gentamicin) [20]. There were 159 patients in the ampicillin plus ceftriaxone arm and 87 in the ampicillin (or penicillin, 3 patients) plus gentamicin arm. The most important finding was that the authors found no differences in mortality, clinical failure, or relapse rates between the two treatment arms. However, interruption of antibiotic treatment due to adverse events was much higher in the ampicillin plus gentamicin group (25 % vs. 1 %, $p<0.001$) mainly driven by a higher incidence of acute renal injury. Although this study provided compelling clinical evidence for the use of the double beta-lactam combination as the treatment of choice for *E. faecalis* IE, several caveats need to be taken into consideration: (i) the study was nonrandomized, (ii) the definition of renal failure was rather liberal (increase of>25 % of the basal serum creatinine) and it could have overestimated the rates of kidney injury, (iii) only a subset of patients in the gentamicin group received the drug three times daily as recommended (37 patients), (iv) gentamicin levels were not

reported, and (v) the duration of ceftriaxone containing treatment is 2 weeks longer than for a gentamicin containing regimen (for symptoms less than 3 months), which may give a higher risk of complications from long term intravenous therapy. A question also remains as to what therapy to use in patients who relapse after receiving the ceftriaxone plus ampicillin combination; in one reported failure (ampicillin plus ceftriaxone 1 g every 12 h), daptomycin plus ceftaroline was successfully used [21].

Treatment of Ampicillin and Vancomycin-Resistant *E. faecalis* IE

Resistance to ampicillin and vancomycin is rare and uncommon, respectively, in isolates of *E. faecalis*. The frequency of vancomycin resistance among isolates of *E. faecalis* is much lower than that observed in *E. faecium*, and these isolates have to date remain ampicillin susceptible. If confronted with a patient presenting with IE caused by an ampicillin and vancomycin-resistant *E. faecalis*, there are some data supporting the use of the lipopeptide daptomycin (DAP). Carugati et al. recently published the results of a prospective, observational, multicenter cohort of patients with left-sided IE in which they compared patients with *E. faecalis* IE treated with DAP (9 patients) vs. standard of care therapy (ampicillin or vancomycin plus gentamicin, 43 cases). Although the patients treated with DAP had a higher proportion of prosthetic-valve IE, they were no differences in time to clearance of the bacteremia or mortality and a shorter length-of-stay (17.5 vs. 19.5, $p=0.02$). The median dose of DAP used in that cohort was 8.3 mg/kg/day [22]. Also, the combination of DAP (8 mg/kg/day) plus ceftaroline was successfully used to treat a patient with left-sided IE due to ampicillin susceptible *E. faecalis* with HLRAG that failed therapy with ampicillin plus ceftriaxone (see above). Furthermore, this regimen was found to have synergistic activity in vitro and to increase DAP binding to the bacterial cell membrane [21]. In another report, the combination of DAP plus ampicillin was successfully used for treatment of IE due to ampicillin-susceptible *E. faecalis* with HLRAG [23]. A more detailed summary of the evidence for the use of drugs with activity against vancomycin-resistant enterococci (VRE) will be presented in the section dealing with *E. faecium* endocarditis.

Ampicillin resistance in *E. faecalis* has been reported and has been mediated mostly by the presence of the staphylococcal penicillinase [24]. However, isolates of penicillinase producing *E. faecalis* currently appear to be quite rare, although the presence of this enzyme is not detected by standard testing. Since this enzyme is inhibited by beta-lactamase inhibitors, ampicillin-sulbactam should suffice in place of ampicillin [25].

Treatment of IE caused by *Enterococcus faecium*

Treatment of *E. faecium* IE poses an even more complex challenge. In contrast to *E. faecalis*, most clinical isolates of *E. faecium* in the USA are resistant to ampicillin and vancomycin, markedly reducing the therapeutic alternatives with reliable in vitro bactericidal activity or established clinical efficacy. The resistance problem correlates with the emergence and widespread dissemination of multidrug-resistant (MDR) *E. faecium* isolates belonging to a hospital-associated (HA) genetic subclade that is responsible for most of the infections caused by this species [26••, 27]. Genomic analyses have shown that isolates belonging to this genetic lineage frequently harbor pathogenicity islands and genes encoding potential virulence and resistance determinants. Indeed, the allelic variant of the gene encoding the penicillin-binding protein 5 (associated with high-level resistance to ampicillin and designated *pbp5-R*) [28] and genes coding for aminoglycoside modifying enzymes are more frequently found in *E. faecium* isolates belonging to this genetic lineage (clade A).

The only two compounds that have been granted FDA approval for the treatment of vancomycin-resistant *E. faecium* infections are quinupristin/dalfopristin (Q/D) and linezolid. Consequently, the AHA/IDSA guidelines suggests these agents for treatment of vancomycin and ampicillin-resistant *E. faecium* IE. Despite this, the clinical evidence supporting their use as reliable agents in *E. faecium* IE is scarce. We will summarize the available alternatives for the management of MDR *E. faecium* and the evidence supporting their use and/or concerns about their efficacy (Table 2).

Streptogramins: Quinupristin-Dalfopristin

Q/D is a combination of 30 % quinupristin (streptogramin B) and 70 % dalfopristin (streptogramin A) that has in vitro bactericidal activity against *E. faecium* through the inhibition of protein synthesis by interacting with the 50S ribosomal subunit. Importantly, Q/D has no activity against *E. faecalis* (due to intrinsic resistance) and was the first compound to receive FDA approval for the management of vancomycin-resistant (VR) *E. faecium* infections. The best clinical evidence supporting the use of Q/D against VR *E. faecium* in deep-seated infections originates from a prospective study in which 72 % of the subjects with bacteremia of unknown origin were successfully treated with Q/D [29]. However, the number of patients with IE was too low to draw any meaningful conclusion for this infection. Additionally, Q/D has three important limitations: (i) its safety and tolerability profile is far from ideal with a high frequency of secondary effects (e.g.,

Table 2 Therapeutic options for the treatment of vancomycin-resistant *Enterococcus faecium* infective endocarditis

Agents	Comments
Linezolid	• Suggested by the AHA/IDSA guidelines for IE [9]
	• Bacteriostatic agent
	• Toxicities (hematological and neurological) may be a problem when used for IE that requires ca. 6 weeks of therapy
	• Efficacy uncertain
Q/D	• Suggested by the AHA/IDSA guidelines for IE [9]
	• Bactericidal in vitro, however, such activity may be compromised in vivo by the presence of *erm* genes that confer resistance to quinupristin (common in clinical isolates of *E. faecium*) [30]
	• Frequent reports of side effects including infusion site (needs central venous access), myalgias, drug interactions
	• High likelihood of failures when used as monotherapy
	• Combination with other agents may be of clinical benefit (see text)
Daptomycin	• Bactericidal in vitro but not FDA approved for *E. faecium*
	• Potential of developing resistance during therapy.
	• Higher doses (8–10 mg/kg/day) generally recommended against *E. faecium* [60]
	• Patients infected with DAP-susceptible isolates with MICs close to the breakpoint (3–4 μg/mL) may be at high risk of therapeutic failure and recurrence [57••].
	• Combination with other agents such as β-lactams (ampicillin or ceftaroline) or tigecycline or aminoglycosides (when not exhibiting HLRAG) may be of clinical benefit to increase likelihood of microbiological eradication and decrease development of DAP resistance during therapy.

AHA American Heart Association, *IDSA* Infectious Disease Society of America, *IE* infective endocarditis, *HLARG* high-level resistance to aminoglycosides, *Q/D* quinupristin/dalfopristin, *DAP* daptomycin

phlebitis, arthralgia and myalgia) often resulting in treatment interruptions; (ii) many *E. faecium* have *erm*(B) which eliminates the bactericidal activity of Q/D [30]; and iii) the available evidence suggests that its use as monotherapy should be discouraged in IE. Indeed, using a rabbit model of MDR *E. faecium* IE, Pérez-Salmerón and colleagues found that Q/D alone was inferior to the combination of Q/D with imipenem or levofloxacin. Moreover, in a patient with VR *E. faecium* IE and persistent bacteremia while on Q/D monotherapy, the bloodstream was successfully sterilized after the addition of doxycycline and rifampin to Q/D [31]. Furthermore, the combination of Q/D and ampicillin achieved microbiological eradication and clinical cure in a patient with an ampicillin-resistant (MIC>32 μg/mL) and vancomycin-resistant *E. faecium* bacteremia after initial failure of linezolid monotherapy [32]. Therefore, the available clinical evidence suggests that Q/D be reserved for recalcitrant cases of IE when other alternatives have been exhausted and as part of a combination regimen.

Oxazolidiones: Linezolid

Linezolid, an oxazolidinone antibiotic with broad spectrum activity against Gram-positive bacteria, is a bacteriostatic agent that inhibits protein synthesis by interacting with the A site of bacterial ribosomes [33]. Although linezolid resistance among enterococci continues to be rare, it has been well described and increasingly reported [34]. The most important mechanism of resistance involves mutations affecting the 23S rRNA, followed by the acquisition of a methyltransferase encoded by the *cfr* gene [35]. Although linezolid has been recommended for treatment of VRE endocarditis [9, 36], it is not often used due to its bacteriostatic nature, limited clinical data, and a high rate of adverse events when used for prolonged periods of time (particularly bone marrow toxicity). There are no randomized, controlled trials evaluating linezolid for the treatment of enterococcal IE. Birmingham et al. published the experience of a compassionate-use program of linezolid for the treatment of vancomycin-resistant (VR) *E. faecium* bacteremia in a small, open-label study and reported that rates of clinical and microbiological cure were 78 and 85 %, respectively [37]. The efficacy in the subgroup of patients with IE was similar with a clinical cure rate of ca. 77 %, which is a very good cure rate for *E. faecium* IE, although the number of concomitant antimicrobial use in this specific subgroup was not reported. A systematic review published by Falagas and collaborators included eight patients with enterococcal IE (two vancomycin-susceptible *E. faecalis*, two VR *E. faecalis*, and four VR *E. faecium*) [38]. Only one of the eight cases was labeled as a clinical failure, while all the others improved or were cured with linezolid monotherapy or with other concomitant other antibiotics (five cases and three cases, respectively). Also, a recent retrospective, multicenter, and observational study conducted in Denmark analyzed the use of linezolid as rescue therapy in 38 patients (out of a cohort of 550) with left-sided IE [22]. Among these patients, 19 cases corresponded to enterococcal IE (18 *E. faecalis* and 1 *E. durans*, while no *E. faecium* were included and the majority of cases were native valve infections). The authors reported that only 1 of the 19 patients who received linezolid had a clinical failure, but it is important to note that it was used as monotherapy in only three cases. Moreover, the main reason to use linezolid in that report was due to allergy, pharmacological interactions, and nephrotoxicity of other regimens that had already achieved initial clinical success [39]. On the other hand, several case reports of therapeutic failure with linezolid have been published for both *E. faecium* and *E. faecalis* [40–43]. Thus, the paucity of robust clinical data supporting the use of linezolid for the management of MDR enterococcal

IE suggests that this antibiotic should be used with caution and reserved for cases for which a bactericidal alternative is not available.

Lipopeptides: Daptomycin

DAP is a cyclic antimicrobial lipopeptide that targets the cell membrane in a calcium-dependent fashion. This compound is one of the few antibiotics that show reliable in vitro bactericidal activity against VR *E. faecium*, a property that was found to be concentration-dependent [44]. For enterococcal infections, DAP is FDA-approved only for skin and soft tissue infection due to *E. faecalis*, not for enterococcal bacteremia or endocarditis, although it is approved for the management of bacteremia and for right-sided IE due to *Staphylococcus aureus*. However, due to the paucity of other reliable therapeutic alternatives, many clinicians use DAP off-label as their first-line option to treat VR E. *faecium* IE, despite the fact that most of the evidence supporting the use of DAP for the management of *E. faecium* IE originated only from retrospective studies and from in vitro studies and animal models. For example, using a simulated endocardial vegetation (SEV) model, DAP showed greater than 99.9 % kill against VR *E. faecium* with simulated dosing of 6 and 8 mg/kg [45]. Two other studies from the same group reported higher and more sustained bactericidal activity in SEVs against VR *E. faecalis* and *E. faecium* using DAP simulating 10–12 mg/kg than with 6–8 mg/kg [46, 47]. In addition, using a rat IE model, 82 to 91 % of vegetations were sterilized with DAP monotherapy for vancomycin-susceptible and VR *E. faecium* and *E. faecalis*, respectively [48, 49]. Furthermore, a case series from a European registry indicated that among 22 cases of enterococcal IE treated with DAP (18 *E. faecalis* and 4 *E. faecium*), the clinical success rate was 73 %, although no details regarding treatment doses or concomitant antimicrobial agents were provided [50]. There are also several retrospective studies analyzing the use of DAP against VRE bacteremia and comparing this compound with the activity of linezolid, but most of them do not include patients with IE or have very few of such infections. For example, Mave et al. presented a retrospective analysis of 98 patients with VRE bacteremia, 68 of whom received linezolid while 30 were treated with DAP. The authors found no differences in outcomes between the two antibiotics, but only five cases of IE were included in the series (three treated with linezolid and two with DAP, two patients failed, one with each drug) [51]. In another retrospective analysis of 201 patients with VRE bacteremia (138 treated with linezolid and 63 with DAP), no differences in mortality or clinical/microbiological cure were found; however, recurrence was higher in the DAP group (3 vs. 12 %, $p=0.032$). In this study, patients with IE were again underrepresented, with only seven cases fulfilling the criteria for IE [52•]. Recently, meta-analyses attempted to improve the available evidence regarding the ideal treatment of VRE bacteremia. Balli et al. published a systematic review and meta-analysis comparing linezolid vs. DAP for the treatment of VRE bacteremia with a primary outcome of 30-day mortality. They included 10 studies, all of them retrospective, with a total of 967 patients. A higher overall and infection-related mortality was reported for the DAP group, but no statistical differences in relapse or clinical/microbiological cure rates were found [53]. Importantly, the median daily dose of DAP was 6 mg/kg/day in six studies and 5.5 mg/kg/day in one, and it was not reported in the other three studies. Also, DAP susceptibility was provided in only two studies. Another recent meta-analysis published by Whang et al. addressing the same question found no differences in clinical or microbiological cure rates between DAP and linezolid. The authors reported a trend toward increased survival in the group treated with linezolid, but it did not reach statistical significance ($p=0.054$) [54].

A relevant concern when using DAP monotherapy for the management of IE is the development of DAP resistance during therapy leading to both clinical and microbiological failures [55, 56], as seen in reports of DAP failure when treating DAP-susceptible enterococcal isolates. It is important to note that *Enterococcus* spp. typically exhibit higher DAP MICs than staphylococci and other Gram-positive bacteria. Indeed, the current CLSI susceptibility breakpoint for enterococci is 4 μg/mL, which is fourfold higher than that of *S. aureus* (1 μg/mL). It was recently shown that a high proportion of clinical *E. faecium* isolates with DAP MICs close to the breakpoint (3–4 μg/mL, interpreted as DAP susceptible) harbored genetic changes related to DAP resistance. In *E. faecalis*, a single gene mutation increased the MIC from 1 to 4 μg/mL and was sufficient to abolish the bactericidal activity to DAP [57••]. Thus, these data challenge the current CLSI breakpoint of DAP of 4 μg/mL and suggest that a breakpoint of 2 μg/mL is likely more predictive of "true" susceptibility (particularly in endovascular infections), although clinical data to support this notion are still lacking.

In order to overcome these problems, two strategies are the subject of active research. *First* is the use of higher doses of DAP of 8–12 mg/kg/day (FDA-approved doses are 4 and 6 mg/kg/day for skin and soft tissue infections and *S. aureus* bacteremia and right-sided endocarditis, respectively). The rationale for this approach originates from in vitro studies, an MIC_{90} of 2 μg/mL, and a theoretical concern about the high protein binding in vivo which may markedly decrease the free fraction of the drug at the site of infection [43, 58, 59]. As mentioned above, data using the SEV model reported higher and more sustained killing with a regimen simulating DAP 10–12 mg/kg/day compared to 6–8 mg/kg/day. Moreover, the only dosing scheme which did not select for resistance mutants in *E. faecalis* was 12 mg/kg/day, suggesting that higher dosing could influence the efficacy of DAP and also prevent development of DAP resistance although stains with reduced

susceptibility were not detected in *E. faecium* with any dosing scheme [47]. The clinical effectiveness and safety of DAP used in high doses (8–12 mg/kg) was evaluated in two recent retrospective studies and one safety study using healthy volunteers. Casapao et al. analyzed a multicenter cohort of 245 subjects with enterococcal infections (175 *E. faecium* and 49 *E. faecalis*); overall, 204 (83 %) cases were due to VRE isolates and 173 (71 %) had enterococcal bacteremia (15 patients fulfilled criteria for IE). The median dose of DAP was 8.2 mg/kg/day, and the clinical and microbiological success rates were 89 and 93 %, respectively [60]. Although seven patients (3.2 %) experienced CPK elevation from their baseline (one patient; ×5 upper normal limit (UNL), six patients; ×3 UNL), no apparent relationship between high-dose DAP and CPK elevation was observed. In another retrospective and multicenter evaluation, Kullar et al. evaluated the use of high-dose DAP for the management of IE caused by Gram-positive organisms [61]. Among 70 patients with IE, DAP was used as rescue therapy in 65 and the median dose used was 9.8 mg/kg/day. Only six patients had enterococcal IE (five VR *E. faecium* and one*E. faecalis*). The overall success rate was 85.9 %, but no specific details were provided for patients with enterococcal infections. Only two patients (2.9 %) had mild or moderate adverse events, such as hyperkalemia and thrombocytosis. No patient experienced abnormal CPK elevation in this study. Lastly, DAP safety was evaluated in 36 healthy volunteers given four different dosing regimen, placebo, 6, 8, 10, and 12 mg/kg/daily, for up to 14 days [62]. Despite mild adverse events (such as headache), serious adverse events leading to termination of DAP therapy did not occur.

The *second* approach to increase efficacy or decrease development of DAP resistance is to use DAP combined with other agents. The most promising appears to be the combination of DAP with beta-lactams. Interestingly, the addition of ampicillin to DAP (12 mg/kg/day) was able to clear the bacteremia in a patient with ampicillin-resistant VR *E faecium* IE who was failing DAP (6 mg/kg/day) plus linezolid [63]. Furthermore, the combination was found to be synergistic in vitro even though the ampicillin MIC for the clinical isolate was 256 μg/mL. Of note, the addition of ampicillin increased the binding of DAP to the cell membrane target [63]. Gentamicin and rifampin were each successfully used for VR *E. faecium* as a third agent added to DAP and ampicillin after initial treatment failure [64, 65]. Another beta-lactam that has been used in combination with DAP in recalcitrant cases of VR *E. faecium* IE is ceftaroline, a recently FDA-approved cephalosporin (skin and soft tissue infections and community-acquired pneumonia, including methicillin-resistant *S. aureus*). The combination of DAP with ceftaroline had a synergistic effect against an endocarditis isolate of VR *E. faecium* and, similar to ampicillin, it was found to increase DAP binding to the bacterial cell membrane [66]. The combination of DAP with another agent may also decrease development of DAP resistance. In an in vitro study, *E. faecium* and *E. faecalis* were serially exposed to stepwise increasing concentration of DAP with or without a fixed 0.25×MIC concentration of a second agent, such as ampicillin, gentamicin, or rifampicin [67]. Emergence of resistance was delayed by ampicillin, but not by gentamicin and rifampin.

Finally, there are three reports of patients with VR *E. faecium* IE treated with a combination of DAP and tigecycline [68–70]. One patient had mitral IE due to an MDR VR *E. faecium* resistant to ampicillin, linezolid and exhibiting HLRAG. The DAP and tigecycline MICs were 4 and 0.06 μg/mL, respectively, and the bacteremia was successfully cleared with tigecycline plus DAP 6 mg/kg/day [68]. In another patient, DAP (8 mg/kg/day) plus tigecycline eradicated the infection in a patient with history of a tricuspid valve replacement who had 19 days of recurrent VR *E. faecium* bacteremia before the initiation of the combination therapy. Of note, the isolate was linezolid resistant; the DAP MIC was 3 μg/mL; and the tigecycline MIC was 0.032 μg/mL [69]. MICs of tigecycline for *E. faecium* (MIC_{90}, 0.12 μg/mL) are generally lower than for *E. faecalis* and *S. aureus* (MIC_{90}; 0.12–0.25 μg/mL, and 0.25 μg/mL, respectively) [71] and the combination might overcome the concern of the low serum concentration of tigecycline for patients with bacteremia.

In summary, although DAP has interesting properties in vitro against VR *E. faecium*, the microbiological and clinical evidence suggest that the current FDA-approved doses are likely to be suboptimal for this organism in IE. The use of higher doses or the combination of DAP with other compounds (particularly β-lactams) may offer clinical benefit, and these strategies deserve to be studied in prospective and controlled clinical trials.

Conclusion

In conclusion, the treatment of enterococcal IE has long been recognized as a complicated clinical challenge, and the appearance and dissemination of MDR *E. faecium* harboring a wide-range of resistance mechanisms has complicated the picture even further, leaving clinicians with very limited therapeutic alternatives. Furthermore, data supporting the use of the few antimicrobials with activity against drug-resistant enterococci are scarce and prospective, controlled trials are urgently needed.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Murray reports grants from Johnson & Johnson, grants from Cubist, grants and personal fees from Theravance, grants from Forest, personal fees and non-financial support from Rib-X, personal fees and non-financial support from Durata Therapeutics, personal

fees and non-financial support from Achaogen, personal fees and non-financial support from The Medicines Co., personal fees and non-financial support from GlaxoSmithKline. Dr. Arias reports grants and consulting fees from Pfizer, grants from Forest Pharmaceuticals, grants and consulting fees from Theravance Inc., consulting fees from Novartis, consulting fees from Cubist and consulting fees from Astra Zeneca and he has served as a speaker for Pfizer, Forest Pharmaceutics, Novartis, Cubist and Astra Zeneca. Drs. Nigo and Munita have not conflicts of interest to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- • Of importance
- •• Of major importance

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