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Enterococcal Endocarditis: Can We Win the War?

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Abstract

Treatment of enterococcal infections has long been recognized as an important clinical challenge, particularly in the setting of infective endocarditis (IE). Furthermore, the increase prevalence of isolates exhibiting multidrug resistance (MDR) to traditional anti-enterococcal antibiotics such as ampicillin, vancomycin and aminoglycosides (high-level resistance) poses immense therapeutic dilemmas in hospitals around the world. Unlike IE caused by most isolates of *Enterococcus*

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faecalis, which still retain susceptibility to ampicillin and vancomycin, the emergence and dissemination of a hospital-associated genetic clade of multidrug resistant *Enterococcus faecium*, markedly limits the therapeutic options. The best treatment of IE MDR enterococcal endocarditis is unknown and the paucity of antibiotics with bactericidal activity against these organisms is a cause of serious concern. Although it appears that we are winning the war against *E. faecalis*, the battle rages on against isolates of multidrug-resistant *E. faecium*.

Keywords

Infective endocarditis; *Enterococcus*; Therapy; Multi-drug resistant enterococci; Vancomycin resistance

Introduction

Enterococci are gram-positive commensal bacteria that form part of the normal gastrointestinal flora of humans and many animals. These organisms have been known to cause endocarditis since 1899, when the first detailed clinical and pathological description of a strain of what almost certain was *Enterococcus faecalis* (termed “*Micrococcus zymogenes*”) was published [1]. Apart from infective endocarditis (IE), enterococci are also known to cause several other diseases (especially in the nosocomial environment) including urinary tract infections, bacteremia and meningitis, among others.

Difficulties in the treatment of enterococcal IE have been recognized for many years and relate to the frequent lack of bactericidal activity of penicillin or ampicillin when used as monotherapy, the toxicity incurred with the recommended combination of penicillin plus an aminoglycoside, and the increased reports of high-level resistance to aminoglycosides. A more recent problem derives from the increase in the number of nosocomial infections caused by multidrug-resistant (MDR) *Enterococcus faecium* isolates belonging to a well characterized hospital-associated (HA) clade [2•, 3]; indeed, ampicillin and vancomycin, which formerly were the two most commonly used “first-line” antibiotics for the treatment of enterococcal IE, are now obsolete for *E. faecium* endocarditis due to the very high prevalence of resistance to these agents. Another important factor is the lack of reliable bactericidal options with well-established clinical activity against MDR *E. faecium*. This problem dramatically reduces the therapeutic alternatives for IE and clinicians are forced to make decisions based on in vitro activity and limited clinical data [4].

In this review, we will focus on the epidemiology and clinical aspects of enterococcal IE, with special emphasis on the limitations of available therapeutic options. We will divide this war in two battlefronts, one being fought against *E. faecalis*, in which we still seem to have the upper hand, and the other against *E. faecium*, in which we have lost considerable ground. Winning the “war” against enterococcal IE will depend on the development of novel therapeutic strategies in the future.

Pathogenesis of Enterococcal IE

Several pathogenicity factors have been described in enterococci. Table 1 summarizes determinants that have been shown to contribute to experimental pathogenesis of enterococcal endocarditis (for a more detailed description readers are directed to a recently published review [5•]). Among the best characterized are the cell surface adhesins, which are structures of the cell envelope of enterococci that mediate the attachment to tissues (e.g., the endothelium of the heart and blood vessels) and contribute to the production of biofilm: two critical steps in the pathogenesis of IE [6].

Aggregation substance (AS) comprises a family of enterococcal surface adhesins, one of which has been shown to have a role in *E. faecalis* IE. They are cell wall-anchored LPxTG proteins, encoded on pheromone-responsive plasmids, that can enhance adherence to proteins of the extracellular matrix as well as serum proteins, favor cell clumping and increase biofilm formation [7–9]. Although the presence of AS is not required for the development of IE, animals infected with *E. faecalis* strains containing a member of the AS family (Asc-10) produced larger vegetations and higher bacterial loads as compared with controls lacking Asc-10 [10]. The use of IgG antibodies against AS has not been useful in animal models of IE (in fact it could increase enterococcal aggregation), however, passive immunization of rabbits with the Fab fragment of IgG anti-AS attenuated the severity of *E. faecalis* IE; moreover, Fab fragments prevented enterococcal aggregation in vitro [11].

Several well-documented enterococcal surface adhesins belong to the MSCRAMM family (microbial surface components recognizing adhesive matrix molecules), a group of surface proteins involved in the attachment of bacteria to a wide range of proteins including collagen, fibrinogen, laminin and fibronectin. They also have LPxTG motifs and are thought to be important in early stages of infection. Two of the most extensively studied enterococcal MSCRAMMs are the collagen adhesin of *E. faecalis* (Ace) and its homolog in *E. faecium* (Acm). Both Ace and Acm deletion mutants were substantially attenuated in a rat enterococcal IE model compared with parental strains [12, 13]. Also, passive and active immunization against Ace significantly protected rats from acquiring the infection when compared to non-immunized controls [13].

Another important surface adhesin is the enterococcal surface protein (Esp) of *E. faecalis* and its homolog in *E. faecium* (Esp_{fm}, which shares 89 % amino acid identity with Esp). These are cell wall anchored LPxTG proteins frequently found in clinical strains that have been shown to be involved in biofilm formation and in the pathogenesis of experimental enterococcal infections [14], e.g., in a rat model of IE fewer colony-forming units (CFU) were recovered from the vegetations of animals infected with mutants of *E. faecium* lacking Esp_{fm}, as compared to those infected with wild-type strains [15].

Some enterococcal LPxTG proteins are known for their ability to form pili, which are filamentous structures protruding from the cell surface that have been described in both *E. faecalis* and *E. faecium*. The best characterized are the *E. faecalis* Ebp (endocarditis and biofilm-associated pili) proteins, which are important in cell adhesion, colonization and biofilm formation [16, 17]. Non-piliated mutants of *E. faecalis* were shown to be

significantly attenuated in a rat IE model. Similar results were obtained with mutants of *E. faecium* and *E. faecalis* when testing their ability to produce urinary tract infection in mice [18, 19].

Another important group of pathogenic determinants are factors that are secreted and released from the cell and may contribute to the pathogenesis of several enterococcal infections including IE. Among them, there is hemolysin/cytolysin, a molecule frequently encoded by *E. faecalis* pheromone-responsive plasmids that has been shown to act together with AS in animal models of IE [20]. Another secreted factor associated with pathogenesis of experimental IE is the gelatinase (GelE) enzyme, a protein that degrades host tissues and promotes the release of DNA [21] (extracellular DNA, eDNA), an important component of biofilm. Mutants lacking *gelE* show decreased biofilm production and attenuation of IE in rats and rabbits [22, 23]. A final protein that has been shown important in experimental IE is Gls24, a stress-response protein that mediates resistance of *E. faecalis* to bile salts as well as being important in a rat IE model [24].

Epidemiology and Clinical Characteristics of Enterococcal IE

Multiple publications, including a large international prospective cohort that included 2781 cases, rank *Enterococcus* spp. as the third most frequent etiologic agent of both native and prosthetic valve IE, after *Staphylococcus* spp. and *Streptococcus* spp. [6, 25, 26]. Recent studies suggest that the frequency of enterococcal IE is increasing [27, 28], especially in the subgroup of health-care associated IE, where enterococci are considered the second most frequent etiologic agents, surpassed only by staphylococci [29–31]. Moreover, enterococci are considered the second leading cause of nosocomial infections in the United States (after staphylococci), including catheter-associated bacteremias [32]. The frequency with which enterococcal bacteremia results in IE varies widely in different publications [33, 34]. Risk factors for the development of IE in patients with enterococcal bacteremia include a history of pre-existent valvular heart disease, prosthetic valve and infection with *E. faecalis* [35, 36]. Enterococcal IE often occurs in older patients with underlying diseases and prior valvular damage or a prosthetic valve, affects predominantly the aortic or mitral valve and is rarely seen in the setting of right-sided endocarditis [37]. A prior risk group was women of childbearing age but this situation has been rare during the last years, presumably because of improvements in perinatal care, in antimicrobial use and a decrease in rheumatic heart disease. The more commonly described sources of enterococcal bacteremia are indwelling catheters, the gastrointestinal and urinary tracts (with an important association with invasive procedures) and anatomical abnormalities, including the presence of malignant or inflammatory lesions [38–40].

The clinical presentation of enterococcal IE is usually subacute, with fever and the presence of a cardiac murmur as the most common findings in the physical examination. Classical signs of IE such as Osler nodes or Roth spots are less frequently found. The main complication of enterococcal IE is heart failure, which occurs in almost half of the patients and has an important impact on outcome. Despite this, mortality rates of enterococcal IE are lower than in other causes of endocarditis, especially when comparing to *S. aureus* [41].

An important aspect in the epidemiology of enterococcal IE is the increase in infection caused by MDR *E. faecium*. This species shift has important clinical consequences since most of the MDR enterococci are *E. faecium*, while over 90 % of the *E. faecalis* isolates remain susceptible to ampicillin and vancomycin. Indeed, the first cases of IE due to vancomycin-resistant enterococci (VRE) were published in the late 90s and since then the number of reports has risen [42, 43]. Clinical descriptions of the characteristics of VRE in patients with IE are scarce, but the history of organ transplantation (mainly liver), hemodialysis and the presence of a central venous catheter are considered important risk factors for the development of VRE IE [44, 45]. Patients with VRE IE are similar to those with endocarditis due to vancomycin-susceptible enterococci in terms of age of presentation, sex and clinical characteristics [44]. Forrest et al. compared the clinical characteristics and outcomes of patients with *E. faecium* and *E. faecalis* VRE IE, showing a higher mortality ($p=0.002$) and a longer duration of bacteremia ($p=0.002$) in patients with *E. faecium* IE [45], which may be due to the limited availability of effective antimicrobials to treat this MDR species.

Treatment of Enterococcal IE

The management of enterococcal IE has long been recognized as a challenging clinical problem. Endovascular infections, such as IE, are entities in which bactericidal therapy appears to be of paramount importance for eradication of infecting organisms and clinical cure. Indeed, unlike the clinical success initially observed with penicillin in the treatment of staphylococcal and streptococcal IE, failure rates with this compound in enterococcal IE were unacceptably high [46]. The poor performance of penicillin monotherapy has been attributed to the “natural” tolerance of many enterococcal isolates to β -lactams, which means that they do not achieve a bactericidal effect even though they inhibit enterococcal growth. The combination of penicillin plus streptomycin was empirically found to cure the patients who were not improving with penicillin alone [47] and was subsequently shown to have synergistic bactericidal activity in vitro [48]. The development of high-level resistance to streptomycin (which abolishes synergism) led to the use of gentamicin, an aminoglycoside for which resistance was rare at the time, and showed similar results in terms of bactericidal effect [49]. Treatment of enterococcal IE with the combination of penicillin plus streptomycin or gentamicin has been evaluated in several studies [50, 51] and became the standard of care many decades ago for patients with IE due to enterococci in the absence of high-level resistance to aminoglycosides (HLRAG) [52].

Treatment of *E. faecalis* IE: Winning the Battle?

Except for a few isolates of β -lactamase producers described in outbreak situations [53], most *E. faecalis* strains have remained susceptible to penicillin and ampicillin. Thus, these β -lactams continue to be part of the recommended regimens for the treatment of *E. faecalis* IE in combination with an aminoglycoside (Fig. 1). However, a pressing issue is the development of HLRAG in clinical isolates of *E. faecalis*, which is defined, for streptomycin, as an MIC > 1000 mg/L by broth microdilution and 2000 mg/L by agar dilution and, for gentamicin, as an MIC > 500 mg/L by any of the above-mentioned methods. The presence of HLRAG abolishes synergism of the aminoglycosides with β -lactams, precluding

the achievement of bactericidal therapy and, ultimately, reducing the likelihood of cure in IE. Isolates exhibiting HLR to streptomycin often harbor ribosomal mutations and/or have acquired an aminoglycoside nucleotidyltransferase [54]. On the other hand, the most common cause of HLR to gentamicin is the presence of a bifunctional aminoglycoside-modifying enzyme that confers resistance to all commercially available aminoglycosides, except for streptomycin. Testing for the presence of HLRAG to gentamicin and streptomycin should be routinely performed in all clinical enterococcal isolates causing an endovascular infection.

The widespread dissemination of aminoglycoside resistance determinants coupled with their important toxicity profile has limited the clinical use of these compounds in critically ill patients. Therefore, other regimens have been used in order to avoid the aminoglycosides and still obtain bactericidal therapy. The combination of ampicillin and cefotaxime has been shown to have enhanced bactericidal effect in vitro against an *E. faecalis* strain with HLRAG [55] and a similar combination was effective in vivo in a rabbit model of endocarditis with an *E. faecalis* isolate exhibiting HLRAG [56]. More importantly, a multicenter, non-randomized, open-label study evaluating the combination of ceftriaxone (2 g every 12 h) plus ampicillin (2 g every 4 h), in the treatment of IE caused by *E. faecalis* isolates with and without HLRAG showed that this combination produced clinical cure at the end of therapy in 71.4 % of the patients infected with isolates exhibiting HLRAG and in 72.7 % of those with IE due to strains without HLRAG [57•]. In the same study, the clinical cure rate at 3 months for all the episodes was 67.4 %. Of note, this synergistic effect has not been shown with *E. faecium*. Data about other therapeutic options are scarce and mainly come from case reports and in vitro studies. Successful treatment of a patient with IE caused by HLRAG *E. faecalis* has been reported with the combination of ampicillin, imipenem and vancomycin [58]. Additionally, the use of ampicillin plus ofloxacin was shown to be synergistic in vitro, achieving bactericidal activity, and to successfully clear the bacteremia in a patient with *E. faecalis* IE exhibiting HLRAG [59].

Treatment of *E. faecium* IE: The War is Still Raging

E. faecium infections pose very difficult therapeutic dilemmas for clinicians as treatment options have been reduced dramatically during the last decade. In contrast to *E. faecalis*, over 90 % of *E. faecium* clinical isolates in the USA, the vast majority of which belong to a HA clade, are reported to be ampicillin-resistant, making this antibiotic obsolete for the treatment of *E. faecium* IE. The mechanism of ampicillin resistance is related to differences in penicillin binding protein 5 (PBP5) of *E. faecium* strains of the HA clade, called PBP5R, which has a lower affinity for β -lactams compared with the PBP5S of strains of the community-associated clade, which are typically susceptible to ampicillin [2•, 60]. The HA strains frequently exhibit high-level resistance to ampicillin, with MICs >64 mg/L. In certain instances, isolates exhibiting lower MICs (< 64 mg/L) may still respond to therapy with higher doses of ampicillin (ca. 30 g/day) in combination with aminoglycosides (provided that the organism does not exhibit HLRAG) [61] (Fig. 2). Unfortunately, *E. faecium* isolates with ampicillin MICs > 64 mg/L are seen less frequently [62]. For many years, vancomycin was the alternative of choice when dealing with ampicillin-resistant *E. faecium* infections;

however, modern-day *E. faecium* isolates are often resistant to vancomycin, particularly in the USA (ca. 80 %), making this antibiotic useless for the majority of *E. faecium* IE patients.

Streptogramins: Quinupristin-Dalfopristin—Quinupristin-dalfopristin (Q/D) is composed of 30 % quinupristin (streptogramin B) and 70 % dalfopristin (streptogramin A), and has activity against most vancomycin-resistant *E. faecium*, but not *E. faecalis*, which are intrinsically resistant. Q/D inhibits protein synthesis by interacting with the 50 S ribosomal subunit and was the first agent to receive FDA approval for the treatment of VRE infections [63]. Its activity against vancomycin-resistant *E. faecium* was tested in non-comparative, multicenter, prospective studies enrolling patients with severe *E. faecium* infections, with an overall success rate of 65 % [64, 65]. Of note, the clinical success against VRE bacteremia of unknown origin was 72 % [64], however, the number of patients with IE was too low to extrapolate these results to this group of patients. One important limitation of this drug is the high frequency of secondary effects, particularly phlebitis, arthralgia and myalgia, which frequently leads to treatment interruptions [66, 67]. In addition, several mechanisms of *E. faecium* resistance to Q/D have been described including drug modification, inactivation and efflux pumps [68••]. Among these, ribosomal methylases encoded by the *erm* genes are frequently found in clinical isolates of *E. faecium* and have been shown to decrease Q/D bactericidal activity in vitro and in a rabbit model of IE [69]. Although Q/D is one of the American Heart Association recommended alternatives for the treatment of MDR *E. faecium* IE [52], evidence for its efficacy as a single agent is limited. Published reports suggest that Q/D is most useful when used in combination and monotherapy is discouraged. Indeed, treatment with Q/D alone was shown to be inferior to the combination of Q/D plus imipenem or levofloxacin in a rabbit model of *E. faecium* IE [70]. The combination of Q/D plus doxycycline and rifampin was able to clear the bacteremia in a patient with VRE *faecium* IE in which microbiological failure had been observed with Q/D alone [71]. Moreover, the combination of Q/D and high-dose ampicillin (24 g/day) was successfully used in a patient with persistent bacteremia with VRE and ampicillin-resistant (MIC>32 mg/L) *E. faecium* who had failed linezolid monotherapy [72] and in an immunocompromised patient with a relapse of VRE IE initially treated with doxycycline plus gentamicin and high-dose ampicillin [73]. Therefore, the above limited but compelling clinical data, suggest that Q/D, if used, should be part of a combination therapy in the treatment of *E. faecium* endocarditis (Fig. 2).

Oxazolidinones: Linezolid—Linezolid is a bacteriostatic compound that inhibits protein synthesis by interfering with the A site of bacterial ribosomes. It has activity against a wide range of Gram positive micro-organisms and has been FDA-approved for the treatment of VRE infections [68••]. Enterococcal resistance to linezolid remains rare, but it has been well described, mostly related to mutations in the genes encoding domain V of the 23 S rRNA [74]. Also, resistance due to the acquisition of the *cfr* gene, which encodes a methyltransferase that modifies the 23 S rRNA, has been reported in human isolates of *S. aureus* and, recently, in a clinical strain of *E. faecalis* [75, 76].

Together with Q/D, linezolid is one of the alternatives suggested for the treatment of MDR enterococcal IE; however, evidence supporting its use in endovascular infections is limited.

There are no randomized control trials and a small, open-label study published in 2003, reported the efficacy of linezolid for the treatment of VRE *faecium* bacteremia with rates of clinical and microbiological cure of 78 % and 85 %, respectively. In the subgroup of endocarditis, out of 13 patients with VRE IE, 10 (76.9 %) achieved clinical cure [77]. A systematic review published in 2006 attempted to evaluate the clinical efficacy of linezolid in the treatment of enterococcal IE. This study found that 7 out of 8 cases improved or were cured with linezolid [78]; four of the included cases were caused by *E. faecalis* (two VRE) [79–82] and the rest of them were cases of IE due to vancomycin-resistant *E. faecium* [83–86]. Conversely, four cases of linezolid failure in the treatment of VRE IE (two *E. faecalis* and two *E. faecium*) have recently been published [44, 87–89]. Therefore, with the available clinical data, it is very difficult to draw strong conclusions regarding the clinical efficacy of linezolid as monotherapy for *E. faecium* IE. Thus, treatment of *E. faecium* IE with linezolid should be reserved for cases in which no other therapeutic options are available, and, perhaps, as part of a combination regimen (Fig. 2).

Lipopeptides: Daptomycin—Daptomycin (DAP) is a cyclic lipopeptide whose bactericidal activity depends on its insertion into the cell membrane in a calcium-dependent manner. DAP has dose-dependent bactericidal activity against most Gram-positive agents, including vancomycin and ampicillin-resistant enterococci [90]. It is approved for the treatment of SSTI including vancomycin-susceptible *E. faecalis* and for *S. aureus* bacteremia and right-sided IE. The use of DAP for the management of *E. faecium* infections, regardless of vancomycin-susceptibility, is off-label. The great majority of enterococcal isolates remain DAP-susceptible; however, several reports of isolates developing DAP non-susceptibility during therapy have been documented [91, 92]. The mechanisms of DAP-resistance in enterococci remain to be completely elucidated, but mutations in two groups of genes that are likely to be involved in the bacterial cell envelope response to antibiotics and cell membrane phospholipid metabolism were recently shown to have a role in DAP-resistance in clinical isolates of both *E. faecalis* and *E. faecium* [93, 94].

DAP has been shown to have good penetration into endocardial vegetations [95], a property that, together with its bactericidal activity against enterococci, makes it attractive when dealing with MDR enterococcal IE. Indeed, DAP therapy was shown to be useful against VRE *faecium* in an in vitro endocardial simulated vegetation model [96] and has been successfully used as single therapy against *E. faecium* and *E. faecalis* [vancomycin-susceptible and VRE] in a rat IE model [97]. In addition, DAP monotherapy was shown to be superior to vancomycin and to the combination of ampicillin plus gentamicin for the treatment of rats with IE due to a penicillin-resistant *E. faecalis* with HLRAG [98].

Although there are no prospective randomized-controlled studies evaluating the efficacy of DAP for the treatment of IE, several reports of successful use for the treatment of MDR enterococcal IE have been published. Among 22 patients with enterococcal IE treated with DAP reported in a European registry (18 *E. faecalis* and 4 *E. faecium*), the success rate was 73 %, but no information regarding dosage or combination therapy was given [99]. Also, the combination of DAP and tigecycline was reported to be successful in three different patients with VRE *faecium* IE [100–102] and there are unpublished data of a patient with *E. faecalis* VRE IE and persistent bacteremia while on DAP 8 mg/kg, that was successfully treated with

the combination of DAP 9 mg/kg plus streptomycin. On the other hand, there are four cases of microbiological failure of DAP (one received 4 mg/kg and the rest 6 mg/kg) when treating DAP-susceptible VRE *faecium* IE [44, 89, 103, 104•, 105]. Clinical cure was achieved in three of these cases after increasing DAP dose and combining it with high-dose ampicillin in one case, gentamicin plus ampicillin in another and doxycycline in the third [103, 104•, 105]. Interestingly, Sakoulas et al. were able to clear the bloodstream of a patient with IE caused by an ampicillin-resistant VRE *faecium* IE by adding ampicillin (1 g every 6 h) to daptomycin (12 mg/kg every 48 h). The combination was shown to be synergistic in vitro in spite of the fact that the isolate exhibited ampicillin MICs >256 mg/L. Moreover, using fluorescent-labeled DAP, they were able to show that ampicillin increased the cell membrane binding of DAP to the enterococcal cells [104•]. As mentioned, all the reported failures were using DAP at a dose of 6 mg/kg (approved dose for *S. aureus* bacteremia and right-sided IE) and microbiological eradication was obtained when the dose used, in combination with another agent, was increased to 8 and 12 mg/kg [103, 104•]. This issue is of particular interest since the high protein binding of DAP in vivo (decreasing the free fraction of the drug) has been suggested to contribute to clinical failure and higher doses could potentially overcome this problem [89, 106]. Indeed, using a simulated model of endocardial vegetations, Hall et al., showed that DAP displayed a dose-dependent bactericidal effect and that high-dose daptomycin regimens demonstrated an enhanced pharmacodynamic profile and were the most bactericidal regimens against VRE [107]. Also, it is important to note, that the DAP MIC₉₀ for enterococci, especially *E. faecium*, is higher than that of staphylococci (4 mg/L and 0.5 mg/L, respectively), supporting the concept that higher doses of DAP may be needed for the management of enterococcal IE [108].

Thus, the limited data available suggest that daptomycin as single therapy should be used with caution and, perhaps, a dose of 8–12 mg/kg in combination with ampicillin, tigecycline or aminoglycosides may offer a clinical advantage. Prospective clinical studies to support the use of these combinations are warranted.

Glycylcyclines: Tigecycline—Tigecycline is a bacteriostatic, semi-synthetic tetracycline-analogue derived from minocycline that binds to the bacterial 30 S ribosomal subunit, inhibiting protein synthesis. It is active against a wide range of Gram-positive and Gram-negative bacteria and was approved for the treatment of intra-abdominal infections and skin and soft tissue infections (SSTI) including those where vancomycin-susceptible *E. faecalis* were present [109]. Tigecycline is active in vitro against VRE, but its use remains off-label for the management of these infections.

Enterococcal resistance to tigecycline is uncommon. The first resistant clinical isolate of *E. faecalis* was reported on 2008 [110] and 7 other tigecycline-resistant *E. faecalis* isolates were recently identified, although only four of them were recovered from humans (two from clinical samples) [111]. The mechanisms of enterococcal resistance to tigecycline are unknown.

Using a rat model of endocarditis, tigecycline monotherapy produced a 2-log₁₀ reduction in the bacterial CFU counts in cardiac vegetations, compared to untreated controls, for both vancomycin-susceptible and resistant *E. faecalis* [112]. Similarly, tigecycline produced a

4.2-log₁₀ reduction in CFU counts on the vegetations of rabbits infected with a tetracycline-resistant *E. faecium* isolate compared with start-of-therapy controls; however, no difference was detected when comparing tigecycline-treated and untreated animals with IE caused by tetracycline-susceptible strains of *E. faecalis* [113].

The combination of tigecycline with several drugs, including vancomycin, gentamicin, doxycycline and rifampin has been shown to be additive in vitro against *Enterococcus* spp. [114]. Of note, three patients with MDR *E. faecium* IE have been successfully treated with a combination of tigecycline plus daptomycin (DAP) [100–102]. In summary, although tigecycline has good and homogenous penetration into the cardiac vegetation, the use of this drug as monotherapy is discouraged because of the following: *i*) it is bacteriostatic, *ii*) the maximum serum concentrations achievable with the recommended doses are low (ca. 1 mg/L) which may be a significant shortcoming in the treatment of IE, *iii*) emergence of resistance during therapy is a concern since it has been well reported in Gram-negative bacteria and has also been documented in an *E. faecalis* strain [68••, 113], and *iv*) there is paucity of clinical data to support the use of tigecycline for IE. Therefore, the role of this compound in the treatment of IE is unclear but may offer promise when used as part of a combination regimen.

Conclusions

The treatment of MDR enterococci causing IE has become an important clinical challenge due mostly to the lack of effective therapies and the paucity of clinical data. Most worrisome is the increasing prevalence of MDR *E. faecium* isolates causing IE, since no standard therapy has been proven to work effectively. Anti-enterococcal antibiotics [i.e., ampicillin, aminoglycosides and vancomycin] used in the past for the treatment of enterococcal IE are now obsolete for *E. faecium* IE. The two antibiotics that are approved for the treatment of VRE infections and suggested in the endocarditis guidelines for therapy (i.e., linezolid and Q/D) have important limitations of activity against *E. faecium* and the emergence of side effects is common in prolonged course required for IE. The role of antibiotics such as daptomycin or tigecycline for the treatment of IE is still unclear but it is likely that, in order to win the war, novel strategies that include combinations of agents may be required. The search for the optimal therapy for MDR enterococcal IE continues and the battle rages on.

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Fig. 1.

Suggested therapeutic alternatives for the treatment of *E. faecalis* IE with isolates exhibiting different susceptibility patterns; authors preferred options are bolded and underlined. (1) Rare cases of β-lactamase producing strains. (2) Consider doses of 8–12 mg/kg. For penicillin allergy, vancomycin or desensitization is suggested. If unable to desensitize, high-dose daptomycin plus gentamicin or streptomycin (in the absence of HLRAG) or high-dose daptomycin plus another agent (if the organism exhibits HLRAG) should be considered. *HLRAG* high-level resistance to aminoglycosides

Fig. 2.

Suggested therapeutic regimens for the treatment of *E. faecium* IE with isolates exhibiting different susceptibility patterns, Authors' preferred choices are bolded and underlined. (1) Consider doses up to 30 g/day. (2) Consider doses of 10–12 mg/kg. (3) If imipenem MIC < 32 mg/L. (4) Recommended by the American Heart Association for the treatment of IE. (5) Agents with possible activity include ampicillin, doxycycline, rifampin, tigecycline and fluoroquinolones. *HLRAG* high-level resistance to aminoglycosides; *DAP* daptomycin; *Q/D* quinupristin-dalfopristin

Table 1

Pathogenic determinants shown to play a role in the in vivo pathogenesis of enterococcal IE

Pathogenic determinant	Description and role in enterococcal IE
<ul style="list-style-type: none"> Aggregation substance 	<ul style="list-style-type: none"> Cell surface determinant that enhances adherence, favors clumping and increases biofilm formation Not critical for IE development, but in animal models <i>E. faecalis</i> endocarditis showed larger vegetations and higher bacterial loads in the presence of AS
<ul style="list-style-type: none"> Esp and Esp_{fm} 	<ul style="list-style-type: none"> Affect biofilm formation An Esp_{fm} deletion mutant produced attenuated endocarditis in rats
<ul style="list-style-type: none"> Ace and Acm 	<ul style="list-style-type: none"> Belong to the family of MSCRAMMs and mediate adherence to collagen and laminin Deletion mutants of <i>ace</i> and <i>acm</i> were attenuated in endocarditis in rats and immunization against Ace and Acm protected animals from developing the infection
<ul style="list-style-type: none"> Ebp and Ebp_{fm} proteins 	<ul style="list-style-type: none"> Form pili and play a role in biofilm formation and adherence A non-piliated mutant of <i>E. faecalis</i> produced an attenuated form of endocarditis in rats
<ul style="list-style-type: none"> Gelatinase 	<ul style="list-style-type: none"> Secreted factor that degrades host tissues, promotes eDNA release and has a role in clearing misfolded proteins Affects translocation through intestinal cells and affects biofilm formation Rabbits and rats infected with mutants lacking gelatinase produced a milder form of endocarditis
<ul style="list-style-type: none"> Gls24 	<ul style="list-style-type: none"> Stress-response protein Mediates resistance of <i>E. faecalis</i> to bile salts Role in the pathogenesis of experimental endocarditis in a rat model