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Daptomycin for the treatment of bacteraemia due to vancomycin-resistant enterococci

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Abstract

Treatment of severe infections caused by vancomycin-resistant enterococci (VRE) is challenging due to the scarcity of reliable therapeutic alternatives. In this context, daptomycin (DAP), a lipopeptide antibiotic, has emerged as an interesting alternative as it is one of the few compounds that retain in vitro bactericidal activity against VRE isolates, although it has not been approved for this purpose by regulatory agencies. In this review, we will summarise the clinical, animal and in vitro evidence evaluating the efficacy of DAP for the management of deep-seated VRE infections. In addition, we will address important clinical concerns such as the emergence of DAP resistance during therapy and reports of therapeutic failure with DAP monotherapy. Finally, we will discuss possible future strategies (such as the use of higher doses and/or combination therapies) to optimise the use of this antibiotic against VRE.

Keywords

Daptomycin; VRE; Enterococcal bacteraemia; Enterococci

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1. Introduction

Enterococci are among the leading causes of nosocomial infections in the USA and are an increasing clinical problem in various other parts of the world [1,2]. These organisms are particularly important as causative agents of infective endocarditis (IE), catheter-related bloodstream infections (BSIs), urinary tract infections (UTIs) and bacteraemia of unknown source. Enterococcal infections have long been recognised as a therapeutic challenge, mainly due to their intrinsic resistance or tolerance to antibiotics (e.g. β-lactams). This observation was first reported to have clinical relevance in the 1950s, when patients with enterococcal IE treated with penicillin monotherapy were found to have a higher rate of clinical failure than those infected with other Gram-positive bacteria [3]. Subsequent reports of improved clinical outcomes of patients with enterococcal IE treated with penicillin plus streptomycin, coupled with findings showing in vitro synergism of that combination [4,5], led to the recommendation to use a cell-wall-active agent plus an aminoglycoside in severe enterococcal infections, particularly IE [6,7]. A more recent and pressing problem has been the emergence and dissemination of multidrug-resistant (MDR) enterococci exhibiting resistance to ampicillin, vancomycin and aminoglycosides [2], which precludes the use of the standard combination therapy. Consequently, the emergence of these MDR strains has dramatically reduced the number of therapeutic alternatives with reliable bactericidal activity, further complicating the management of severe enterococcal infections.

In this context, daptomycin (DAP), a cyclic lipopeptide that retains in vitro bactericidal activity against MDR enterococci, has emerged as an interesting alternative for the management of deep-seated infections caused by these micro-organisms. Here we will review the available data evaluating the efficacy of DAP against vancomycin-resistant enterococci (VRE). In addition, we will address some concerning issues such as clinical failures and the development of DAP resistance (DAP-R) and tolerance during therapy. Finally, we will discuss current research and future directions directed towards preserving the effectiveness of DAP against VRE, including alternative dosing strategies and innovative combination regimens.

2. The problem of vancomycin-resistant enterococci

The first reports of VRE were published in 1988 in Europe, mostly found as community commensals with a limited role as human pathogens. Their appearance was associated with the use of a glycopeptide called avoparcin in animal husbandry, which was banned from the European Community shortly after identification of the first VRE strains. Soon thereafter, VRE isolates were described in the USA, where avoparcin was never approved for animal or food purposes. Since then, the proportion of healthcare-related VRE infections has steadily increased (especially *Enterococcus faecium*), a phenomenon that is mostly explained by the preceding successful dissemination of a hospital-associated clade of *E. faecium* that often harbours determinants mediating resistance to ampicillin and aminoglycosides, which subsequently acquired vancomycin resistance. A recent US survey determined that the prevalence of VRE among *E. faecium* recovered from BSI isolates increased from 57.1% in 2000 to 80.7% in 2010 [8]. Similarly, a study analysing vancomycin susceptibility among more than 6500 enterococcal isolates recovered from US medical centres found an overall

VRE prevalence of 30.4%, with important differences between species: 76% and 4.5% for *E. faecium* and *Enterococcus faecalis*, respectively [9]. The frequency of VRE has also increased in other parts of the world; however, its relevance varies widely within different regions. For instance, VRE prevalence continues to be low in countries such as France and Finland (ca. 5%), whereas in other regions of Europe, such as Portugal and Greece, the frequencies of VRE isolation are closer to those reported in the USA [10].

Invasive enterococcal infections are frequently seen in patients with co-morbidities, immunosuppression and/or severe medical conditions that prompt their admission to the intensive care unit. Importantly, the mortality rate of patients who develop a VRE BSI has been reported as being 2.5 times higher than those infected with vancomycin-susceptible isolates [11]. In this context, use of antimicrobials with bactericidal activity is thought to be paramount to ensure bacteriological eradication and improve clinical outcomes. However, as previously mentioned, therapeutic alternatives with reliable bactericidal activity are limited and robust clinical data supporting their use are scarce. The only agents approved by the US Food and Drug Administration (FDA) to treat VRE infections are quinupristin/dalfopristin (only active against *E. faecium*) and linezolid. Use of quinupristin/dalfopristin is hindered by the high frequency of side effects and the need for central venous access. Linezolid, on the other hand, has good activity against VRE, is approved to treat BSIs and has an acceptable safety profile for short-term use. However, the bone marrow suppression and neurological toxicity observed with prolonged linezolid therapy (i.e. endocarditis or atypical mycobacterial infections) are important clinical challenges. Moreover, linezolid is a bacteriostatic agent, a characteristic that has raised concerns about its ability to eradicate bacteria in deep-seated VRE infections. Another compound with activity against VRE is tigecycline; however, its bacteriostatic nature and the low plasma levels achieved with this drug are serious concerns that limit its use against VRE. Furthermore, clinical data suggesting that the outcome of patients treated for severe bacterial infections with tigecycline monotherapy may be worse than those treated with alternative regimens make this antibiotic less attractive as a single agent for endovascular VRE infections [12]. Lastly, DAP is the only currently available compound that exerts reliable in vitro bactericidal activity against VRE with an acceptable pharmacokinetic and toxicity profile (even in long-term therapies) and it has become a key front-line antibiotic against VRE despite the lack of robust prospective clinical data or formal approval by regulatory agencies [13].

3. History of daptomycin and mechanism of action

DAP is a lipopeptide antibiotic produced by *Streptomyces roseosporus* that was initially studied for clinical use in the 1980s. However, the high frequency of muscle-related toxicity observed in phase 1 and 2 trials with doses of 4 mg/kg every 12 h halted its further development [14]. During the late 1990s, further studies using a dog model indicated that the muscular toxicity was strongly associated with the dosing interval and that the use of a once-daily dosing approach greatly reduced this side effect [14]. Consequently, DAP was developed as a once-daily agent and clinical trials were performed with this dosing strategy. DAP was granted FDA approval in 2003 for the treatment of complicated skin and soft-tissue infections caused by Gram-positive organisms, including vancomycin-susceptible *E. faecalis* (4 mg/kg), and in 2006 for *Staphylococcus aureus* bacteraemia and right-sided IE (6

mg/kg). In 2006, the European regulatory agency approved DAP for the same clinical indications [15].

The mechanism of action of DAP involves interaction of the antibiotic with the bacterial cell membrane in a calcium-dependent manner. Although the exact mechanism by which DAP causes bacterial death is yet to be clarified, a crucial step appears be the ability of the antibiotic to oligomerise within the cell membrane, a process that appears to depend on interactions with cell membrane phospholipids, specifically with the negatively charged phospholipid phosphatidylglycerol. Following oligomerisation, DAP molecules reach the inner leaflet of the cell membrane, disrupting its architecture and function in a process that appears to be dependent on the amount of cardiolipin present at the sites of antibiotic binding [16]. Using *Bacillus subtilis*, Pogliano et al. provided further insights into the mechanism of action of DAP. Indeed, it was shown that DAP preferentially binds the cell membrane at the level of the bacterial division septum, and that whenever the antibiotic binds to other parts of the membrane it triggers the localisation of cell division proteins and de novo synthesis of peptidoglycan in the affected area. These effects appear to affect not only cell membrane physiology but also cell division and peptidoglycan synthesis, eventually leading to bacterial cell death [17]. DAP is active against a wide-range of Gram-positive bacteria such as *S. aureus*, coagulase-negative staphylococci (CoNS), *Enterococcus* spp. and *Streptococcus* spp., retaining activity against all clinically relevant MDR Gram-positive bacteria, including meticillin-resistant *S. aureus* (MRSA), penicillin-resistant *S. pneumoniae* and VRE.

4. In vitro and animal studies

Different surveillance studies have shown that the vast majority of enterococcal isolates, including VRE strains, remain susceptible to DAP [18,19]. However, the MIC_{90} (minimum inhibitory concentration required to inhibit 90% of the isolates) for these micro-organisms (especially for *E. faecium*) is higher than that for other Gram-positive organisms. For instance, the DAP MIC_{90} values for *S. aureus, E. faecalis* and *E. faecium* are usually 0.5, 2 and 4 μg/mL, respectively [18], which correlate with the established breakpoints (1 μg/mL for *S. aureus* and 4 μg/mL for *Enterococcus* spp.) [20]. As will be discussed below, this difference may be particularly important when dealing with deep-seated infections since there is evidence that DAP-susceptible isolates with MICs within the higher range of susceptibility frequently harbour mutations related to DAP-R and tolerance that could compromise the killing ability of DAP.

An interesting characteristic of DAP is its ability to penetrate biofilms, an important feature in the pathogenesis of enterococcal infections. A study comparing different antibiotics against vancomycin-resistant *E. faecium* in an in vitro biofilm assay reported than DAP was significantly more active than linezolid or minocycline, with the greatest reduction in biofilm colonisation [21]. Similar results were obtained when analysing various compounds to eradicate staphylococci embedded in biofilm in a model simulating antibiotic-lock therapy [22]. In addition, DAP has been shown to penetrate cardiac vegetations homogeneously achieving high tissue concentrations, a property not shared by vancomycin, which was mostly found in the periphery of the vegetations [23–25]. Although the ability of

DAP to penetrate biofilm and to diffuse within cardiac vegetations is promising, the clinical relevance of these observations remains to be established.

Whilst most of the studies in the literature evaluate the efficacy of DAP against *S. aureus*, several publications have also investigated the use of this compound against enterococci. In the following section, we will summarise the data analysing the efficacy of DAP for the eradication of enterococci both using in vitro and animal models.

4.1. In vitro models

Using a model of simulated endocardial vegetations (SEVs), Cha and Rybak reported that DAP exerted rapid bactericidal activity at 8 h against a vancomycin-resistant *E. faecium* isolate using doses equivalent to 6 mg/kg/day and 8 mg/kg/day, without major differences between the regimens [26]. However, in a similar study with the same model, DAP exhibited concentration-dependent killing with more rapid and greater bacterial killing using doses simulating 10 mg/kg compared with 6 mg/kg [27]. Similarly, Hall et al. found more sustained killing both of vancomycin-resistant *E. faecalis* and *E. faecium* at 96 h with higher doses of DAP (10 mg/kg and 12 mg/kg) compared with lower doses (6–8 mg/kg) using a SEV model [28]. Furthermore, a DAP dose of 12 mg/kg was the only regimen that did not result in selection of *E. faecalis* strains with reduced susceptibility to the antibiotic [28].

4.2. Animal models

Using a rat model of IE, Ramos et al. showed that DAP monotherapy (20 mg/kg twice daily) was superior to vancomycin (and to the combination of ampicillin plus gentamicin for the treatment of penicillin-resistant *E. faecalis* with high-level resistance to aminoglycosides) [29]. Similarly, DAP (dosed at 25 mg/kg/day; peak levels 44 μg/mL) was superior to vancomycin and ampicillin/sulbactam in reducing bacterial titres of cardiac vegetations in a rat model of IE caused by a β-lactamase-producing and gentamicin-resistant *E. faecalis* [30]. In another study using a rabbit model of IE caused by a vancomycin-resistant and gentamicin-susceptible *E. faecium*, DAP 12 mg/kg every 8 h was found to be effective versus untreated controls ($P < 0.05$), and the combination with gentamicin was shown to enhance the killing ability of DAP [23]. Of note, in the same study the use of DAP 10 mg/kg twice daily had poor efficacy, failing to reduce bacterial titres or sterilise cardiac vegetations [23]. In two other studies using animal models of IE due to vancomycin-susceptible *E. faecalis*, DAP was found to be as effective as vancomycin or β-lactams [31,32]. Furthermore, DAP was more effective than teicoplanin against a vancomycin-susceptible *E. faecalis* and a vancomycin-resistant *E. faecium* (VanB) [31], and it was superior to ampicillin plus gentamicin for the prevention of *E. faecalis* IE [32]. It is important to note that in the above studies, although the in vivo activity was clearly evident, the dose schemes used did not necessarily correlate with human doses.

5. Clinical data

5.1. Bacteremia

There are no randomised controlled studies evaluating the efficacy of DAP for the management of VRE infections. None the less, the scarcity of therapeutic alternatives

coupled with DAP's favourable in vitro activity and pharmacologic profile have prompted its off-label use for the management of deep-seated VRE infections. Several publications have retrospectively gathered the experience with DAP for the treatment of VRE bacteraemia. For instance, Segreti et al. analysed 31 patients who received DAP for Gram-positive bacteraemia, reporting clinical success rates of 55% for the subgroup infected with VRE (9 subjects) [33]. Of note, all patients treated with DAP received the antibiotic as rescue therapy after failing treatment with vancomycin or linezolid, and DAP daily doses were ≤6 mg/kg in all cases [33]. Another retrospective study analysing 30 patients with VRE bacteraemia treated with DAP at a median daily dose of 6 mg/kg (range 3.7–8 mg/kg) reported successful microbiological eradication in 80% of the cases and a favourable clinical outcome in 59% [34]. Similarly, using a retrospective multinational registry known as CORE (Cubicin Outcomes Registry and Experience), Mohr et al. reported 120 bacteraemic patients with *E. faecium* (91% VRE) and 39 with *E. faecalis* (23% VRE) in which, overall, DAP was used as first-line therapy in only 17% [35]. Clinical success rates in this cohort were 87% and 90% for *E. faecium* and *E. faecalis*, respectively [35]. Likewise, a previous study utilising the same registry analysed 45 patients with enterococcal bacteraemia (34 VRE) and reported an overall success rate of 93% (42/45) [36].

Data on DAP for the management of enterococcal infections in patients with neutropenia are scarce. Using the CORE registry, Rolston et al. retrospectively analysed the outcomes of 96 neutropenic patients with VRE bacteraemia (87 *E. faecium* and 9 *E. faecalis*) treated with DAP and reported an overall clinical success of 81%, similar to other series of non-neutropenic patients [37]. On the other hand, an open-label study analysing the use of DAP in nine neutropenic subjects with BSI due to VRE found that only four patients (44%) achieved clinical success. Importantly, two of these patients received a DAP dose of only 4 mg/kg and the rest were treated with 6 mg/kg [38]. We found one retrospective study that specifically analysed the use of DAP for the management of critically ill patients. In that report, which included 22 patients infected with VRE, the clinical success rates were 67% for *E. faecium* (12/18) and 75% for *E. faecalis* (3/4) [39].

Several other publications have retrospectively analysed the efficacy of DAP compared with that of linezolid for the management of VRE bacteraemia (Table 1). Mave et al. analysed 98 adult patients (30 treated with DAP and 68 with linezolid) and reported no differences in microbiological success rates (90% vs. 88%). The authors did find a trend towards higher mortality (26.7% vs. 20%), longer duration of bacteraemia (3 days vs. 2 days) and higher relapse rate (6.7% vs. 2.9%) in the DAP group; however, none of these differences reached statistical significance [40]. McKinnell et al. reported similar findings in a larger study that described the outcomes of 235 patients with VRE bacteraemia (96% *E. faecium*) [41]. Linezolid was the primary therapy in 104 (44%) and DAP in 86 (37%); microbiologic failure occurred in 18 (17%) and 25 (29%) patients in the linezolid and DAP group, respectively (*P*-values were non-significant). There was a trend towards increased mortality in the DAP group (37% vs. 27%), but this difference did not reach statistical significance in the multivariate analysis. Of note, patients in the DAP group had a significantly higher proportion of neutropenia (29% vs. 7.7%; $P < 0.001$), and consultation with an infectious diseases specialist was more common in patients receiving linezolid (24.0% vs. 8.1%; $P =$

0.003) [41]. Another study retrospectively analysed a multicentric cohort of 101 patients with VRE BSI treated with DAP (n = 67) or linezolid (n = 34) and found no differences in in-hospital mortality between the two groups, despite the fact that patients treated with DAP had a higher proportion of shock and of previous treatment with vancomycin or linezolid [42]. Twilla et al. reported a retrospective analysis of 201 cases of VRE bacteraemia treated with DAP (63 patients) or linezolid (138 patients), in which no differences in clinical (75% vs. 74%) or microbiological cure (94% vs. 94%) were found, and mortality was also similar between the groups. However, patients in the DAP group had a higher rate of recurrence of bacteraemia (12% vs. 3%; P = 0.032). In this cohort, the DAP treatment group had a higher proportion of haematological malignancies (33% vs. 14%; P = 0.002) and liver transplantation (13% vs. 4%; P = 0.02) [43]. Another study included 72 patients with haematological malignancies and/or stem cell transplant and VRE bacteraemia treated with DAP (n = 43) or linezolid (n = 29) [44]. Outcomes between both groups were similar, with an overall success rate at Day 7 of 81% and 82% (P = 0.57) for DAP and linezolid, respectively. Similarly, all-cause 30-day mortality was also comparable between groups (23% vs. 24%; P = 0.93) [44]. Finally, a recently published study retrospectively analysed the outcomes of 225 patients with VRE bacteraemia treated with DAP, linezolid or β-lactams [45]. Among these, 139 (62%) were infected with *E. faecium* and 86 (38%) with *E. faecalis*; overall, 56 cases received DAP, 112 linezolid and 57 were treated with β-lactams. Importantly, only patients who received a DAP dose ≥6 mg/kg were included in the analysis. The bivariate analysis showed a higher in-hospital mortality for the DAP group (45% vs. 25% and 19% for linezolid and β-lactams, respectively). However, this difference disappeared after performing a propensity score analysis and matching for time to effective therapy, VRE species and length of stay (LOS) prior to VRE isolation. Furthermore, the only result that remained significant after a multivariate analysis was higher LOS in patients treated with linezolid compared with the β-lactam group. In this study, patients in the DAP group were more likely to be immunosuppressed, to have haematological malignancies and indwelling devices, and to require invasive procedures. After a cost analysis, DAP was associated with a higher cost during the hospitalisation compared with linezolid and β-lactam therapy (P = 0.01 and P = 0.03, respectively) [45].

Two systematic reviews and meta-analyses have used some of the above data to compare the clinical effectiveness of DAP versus linezolid. In the first study, Whang et al. analysed nine retrospective studies (including two abstracts) for a total of 1074 patients with VRE bacteraemia and reported no differences in clinical or microbiological success between DAP and linezolid [46]. A non-significant trend towards increase survival with linezolid therapy was found; however, it is noteworthy that the mortality time points varied widely among studies [46]. A second systematic review and metaanalysis analysed ten retrospective studies (including four abstracts) with a total of 967 patients [47]. In this report, the DAP-treated group had a higher 30-day all-cause mortality [odds ratio (OR) = 1.61, 95% confidence interval (CI) 1.08–2.40) and infection-related mortality (OR = 3.61, 95% CI 1.42–9.20) [47]. Of note, the median daily dose of DAP was 5.5 mg/kg in one study, 6 mg/kg in six studies and it was not reported in the other three publications.

Therefore, after analysing the clinical data available to date, it is clear that it is very difficult to draw conclusions regarding the clinical or comparative effectiveness of DAP for severe VRE infections. Indeed, the retrospective nature of all the studies, the intrinsic possibility of treatment bias and what many would consider suboptimal dosing preclude a balanced interpretation of the data. This situation is compounded by the fact that, in a high proportion of the studies, patients treated with DAP were often sicker and more patients in the DAP arms had important co-morbidities such as haematological malignancies, shock, neutropenia and solid organ transplantation. Prospective clinical data to evaluate the efficacy of DAP are urgently needed.

5.2. Infective endocarditis

Similar to the situation described for bacteraemia, data on the efficacy of DAP for the treatment of VRE IE mainly come from case series and retrospective cohorts. Case reports using DAP in association with other antibiotic(s) will not be included here as they will be summarised in a following section (see Section 7.2). In 2007, an analysis of the CORE registry found 49 patients with IE treated with DAP (11 right-sided). Among them, 14 were infected with enterococci and 6 were labelled as VRE. The median DAP dose was 6 mg/kg (range 4–7 mg/kg) and the overall success rate was 71% (10/14). Failure occurred in two cases and the other two patients were classified as non-evaluable due to missing data. A total of 32 patients (65%) received a concomitant antibiotic, the most frequent being an aminoglycoside (26%); however, no specific information regarding the patients infected with VRE was provided [48]. Similarly, the DAP success rate among 22 patients with enterococcal IE found in the European CORE registry (18 *E. faecalis* and 4 *E. faecium*) was 73%, but no specific information regarding VRE status, DAP dose or combination therapy was provided [49]. In a more recent study, Cerón et al. performed a 5-year retrospective analysis that included 32 patients with enterococcal IE (30 *E. faecalis* and 2 *E. faecium*) and evaluated the efficacy of DAP (6 patients; 5 *E. faecalis* and 1 *E. faecium*), ampicillin plus ceftriaxone (21 cases; all *E. faecalis*) and conventional therapy with ampicillin/vancomycin plus gentamicin (5 patients; 4 *E. faecalis* and 1 *E. faecium*) [50]. No information regarding the frequency of vancomycin-resistant strains was provided and the mean DAP dose was 8.5 mg/kg (range 6–10 mg/kg). In that study, patients treated with DAP had a longer duration of bacteraemia (median of 6 days vs. 1 day in the other two groups; $P = 0.01$) and a higher rate of complications (5 vs. 3 and 1 for the DAP, ampicillin/ceftriaxone and conventional therapy groups, respectively; $P < 0.001$), but no differences in LOS or mortality were found. Importantly, five of the six patients treated with DAP received a median of 8 days of another initial therapy [50]. In addition, a retrospective analysis of 70 patients with IE due to staphylococci or enterococci (VRE isolated in only 7.8%) who received ≥8 mg/kg of DAP reported overall clinical and microbiological success rates of 85.9% and 89%, respectively. Unfortunately, the incidence of VRE isolates was low and no specific information regarding their outcome or use of combination therapies was provided [51].

Carugati et al. prospectively gathered information in a multicentre observational cohort [International Collaboration on Endocarditis (ICE)] and analysed the outcomes of patients with definite IE due to *S. aureus*, CoNS or enterococci treated with either DAP (49 cases) or with the standard of care (SOC) according to the current IE guidelines (392 patients) [6,52].

Among 52 cases of enterococcal IE (all *E. faecalis*; no data on VRE were provided), 9 patients received DAP therapy (no information regarding the concomitant use of other antibiotics was available), whilst the rest were treated with the SOC. No differences in 6-month mortality or time to clearance of bacteraemia were found. Furthermore, patients in the DAP group had a shorter LOS (17.5 days vs. 31 days; $P = 0.02$) despite the fact that they had a higher rate of prosthetic valve infection (7 patients vs. 15 patients; $P = 0.03$) and of previous IE [52]. Interestingly, the median daily dose of DAP in this prospective cohort was 9.2 mg/kg (range 7.7–10 mg/kg), which is higher than in previous reports. This study suggests that higher DAP doses might be associated with better clinical outcomes in IE, a concept that will be discussed in depth in a following section.

Thus, similar to the situation discussed above in bacteraemia, most of the information analysing the efficacy of DAP for the treatment of IE is derived from retrospective studies, precluding reliable interpretation of the data. Furthermore, the amount of data specifically addressing the use of DAP for the management of IE caused by VRE is much more scarce than that for bacteremia, as most of the above mentioned publications consider enterococci in general and lack a separate analysis of the outcomes of patients infected with VRE.

6. Resistance, tolerance and failures

Although the majority of Gram-positive micro-organisms, including MRSA and VRE isolates, remain susceptible to DAP, DAP-R emerging during therapy or as a de novo phenomenon has rapidly become an important concern [53–55]. The mechanisms of DAP-R in enterococci are complex and remain to be fully elucidated, but detailed studies suggest that there are several genetic pathways that can lead to development of DAP-R and that the mechanism and phenotypic expression of resistance may differ between *E. faecium* and *E. faecalis*, although some common determinants may be shared [56,57].

From a genetic point of view, a crucial step towards DAP-R in *E. faecalis* and *E. faecium* appears to be the occurrence of mutations in genes encoding one of two groups of proteins: (i) bacterial regulatory systems that control cell envelope homeostasis and orchestrate the response to the attack by antibiotics and antimicrobial peptides; and (ii) enzymes involved in phospholipid metabolism [56,57]. An important consideration is that a high proportion of DAP-susceptible *E. faecium* isolates with DAP MICs close to the clinical breakpoint (3–4 μg/mL) harbour mutations in genes associated with DAP-R [58]. Moreover, these mutations have also been shown to abolish the in vitro bactericidal activity of DAP [59], raising important concerns and suggesting that the current DAP enterococcal breakpoint of 4 μg/mL may be too high (of note, *E. faecium* with DAP MICs of ≤2 μg/mL lack these mutations). Although the clinical relevance of these findings has not been confirmed, it is tempting to postulate that the efficacy of DAP against ‘susceptible’ isolates harbouring the abovementioned mutations may be severely compromised. Indeed, the following characteristics appear to be commonly found in patients who have failed DAP therapy: (i) the DAP MIC of the isolates was typically close to the breakpoint (between 3 μg/mL and 4 μg/mL) [60–64]; (ii) the daily dose of DAP was usually ≤6 mg/kg [60–62,65,66]; and (iii) the infection was successfully managed after increasing the DAP dose and/or adding a second antimicrobial [60-62,64,65]. Furthermore, we recently reported a neutropenic patient

with bacteraemia due to DAP-susceptible vancomycin-resistant *E. faecium* who failed DAP therapy whose first recovered isolate (DAP MIC = 3 μg/mL) already harboured genetic changes associated with DAP-R/tolerance. Specifically, these changes involved genes encoding the LiaFSR system, a three-component regulatory system that controls cell envelope homeostasis. Moreover, the in vitro bactericidal activity of DAP against the first isolate was lacking and the mutational changes in *liaFSR* were maintained during the course of therapy. In this patient, the bacteraemia was ultimately cleared with a combination of DAP plus ampicillin and tigecycline [64].

7. Higher doses, combination therapy, or both?

7.1. Higher daptomycin doses

The approved daily DAP doses are 4 mg/kg for skin infections and 6 mg/kg for *S. aureus* bacteraemia/IE. However, the ideal dosing strategy for the management of severe enterococcal infections has not been established. As already mentioned, the DAP breakpoint for enterococci is four-fold higher than that for staphylococci (and streptococci), which could have an impact on clinical efficacy when using the same dosing regimen. Furthermore, many experts postulate that higher doses might be needed to avoid clinical failures in this setting. Some of the data supporting the use of higher doses are derived from in vitro studies indicating that, for both *E. faecalis* and *E. faecium* (including VRE isolates), DAP doses of 10 mg/kg or 12 mg/kg provide significantly higher killing activity than lower doses (6 mg/kg or 8 mg/kg) [27,28]. Moreover, in two different in vitro studies of DAP monotherapy using a SEV model, the only regimen that did not select for DAP-resistant mutants was 12 mg/kg, suggesting that higher doses may also prevent the development of DAP-R during therapy [28,67]. From a clinical perspective, there are several reports of successful rescue therapy with DAP at ≥8 mg/kg for *E. faecalis* and *E. faecium* infections that had failed other antimicrobial regimens or DAP at lower doses. As will be addressed below, in many of these reports the increase in DAP dose was accompanied by the addition of another antimicrobial agent(s), making it difficult to dissect the relevance of these interventions separately.

Data extracted from series of cases and larger cohorts have provided further insights into the safety and efficacy of higher DAP doses. Kullar et al. retrospectively analysed a multicentre cohort that included 250 patients with Gram-positive infections receiving DAP doses ≥8 mg/kg, with a median daily dose of 8.9 mg/kg (range 8–10 mg/kg) [68]. Among them, 218 (87%) had bacteraemia, of which 53 (24%) were infected with vancomycin-resistant *E. faecium*. The overall clinical and microbiological success rates were 83.6% and 89%, respectively, but no specific information regarding the outcomes of VRE-infected patients was provided. Importantly, no severe adverse events were reported with the use of DAP at high doses [68]. Also, a small, single-centre retrospective study evaluating 46 cases of VRE bacteraemia treated with DAP at ≤6 mg/kg (*n* = 24) and >6 mg/kg (*n* = 22) reported no differences among groups when analysing time to microbiological cure as the primary outcome [69]. However, patients in the low-dose DAP group were more likely to have had the central venous catheter removed (52% vs. 22.7%; *P* = 0.04) and subjects treated with high-dose DAP had a higher incidence of catheter-related bacteraemia, hampering the

comparisons among groups [69]. More recently, a large retrospective study reported the outcomes of adult patients with documented enterococcal infections (173 cases of bacteraemia) treated with DAP at >6 mg/kg, with a median daily dose of 8.2 mg/kg (interquartile range, 7.7– 9.7 mg/kg) [70]. Among the 245 patients included, 204 (83%) were infected with VRE (175 *E. faecium*, 49 *E. faecalis* and 21 *Enterococcus* spp.). The overall clinical success rate was 89% and microbiological eradication was attained in 93%, with a median time to clearance of blood cultures of 3 days. Only 7 patients (3%) had creatinine phosphokinase elevation and none of them were symptomatic or required discontinuation of therapy [70]. Of interest, the reported efficacy of high-dose DAP (≥8 mg/kg) for the management of patients with IE is ca. 86% [51], and the 9 patients with IE infected with VRE from the ICE cohort reported by Carugati et al. had shorter LOS compared with the group treated with the SOC [52]. Therefore, the limited clinical evidence available suggests that higher DAP doses (8–12 mg/kg) should be seriously considered when dealing with deep-seated enterococcal infections.

7.2. Combination therapy

Another interesting strategy to optimise the effectiveness of DAP against VRE is the use of combination therapy with other antimicrobial agents. Among these, combination of DAP with β-lactams appears to be of particular interest since the latter are safe and inexpensive drugs and clinicians have decades of experience with these compounds. In one study, the addition of ampicillin (0.25×o DAP was able to prevent the emergence of DAP-resistant mutants in an in vitro model after serial passages of the antibiotic (both *E. faecalis* and *E. faecium*) [71]. Similarly, addition of ceftriaxone to DAP in a SEV model using vancomycin-resistant *E. faecalis* and *E. faecium* significantly enhanced the activity of DAP 6 mg/kg and 12 mg/kg and prevented the appearance of DAP-resistant isolates (which were only observed when using DAP 6 mg/kg alone) [67]. Furthermore, the combination of DAP plus ceftaroline was able to restore DAP susceptibility when tested against a DAP-resistant *E. faecium* strain in vitro [72]. From the clinical perspective, there are five cases in which the addition of ampicillin (in four cases) [62,64,65,73] or ceftaroline (one case) [72] to daptomycin was successfully used as rescue therapy in patients who were failing DAP treatment. Of note, in two of these cases, a third agent was also added (tigecycline in one and gentamicin in the other) [62,64]. Interestingly, in three of the four cases in which ampicillin was used, the enterococcal isolate was resistant to this antibiotic. The mechanisms underlying the synergism between DAP and β-lactams are obscure, but in vitro data have shown that exposure to ampicillin (even in isolates with high-level resistance) or ceftaroline enhances the binding avidity of DAP for the bacterial cell membrane, an observation that is paralleled with synergistic activity observed in time–kill assays [65,72]. Unfortunately, this synergism may not be universal and is probably dependent on specific genetic changes that are yet to be fully understood. Indeed, the combination of DAP plus ampicillin was synergistic when used against an *E. faecium* isolate (DAP MIC = 3 μg/mL) harbouring changes in the LiaFSR system, but no additional killing effect was seen after adding ampicillin to DAP against an *E. faecium* isolate that harboured mutations in the *yycFG* system, another regulatory system associated with DAP-R in *E. faecium* [56].

Combinations of DAP with other compounds have also been tested, but data supporting these regimens are less compelling. Use of DAP combined with aminoglycosides has been reported in five cases; however, in only one of these cases was an aminoglycoside the only additional antimicrobial used [49]. In the other reports, gentamicin was added to DAP plus ampicillin (vancomycin-resistant *E. faecium* IE), to DAP plus doxycycline (vancomycin-resistant *E. faecium* bacteraemia in a newborn), to DAP plus rifampicin (vancomycin-resistant *E. faecium* mitral IE) and to DAP plus rifampicin and tigecycline (see below) [60,62,74,75]. Of interest, in one of these reports, it was also demonstrated that the combinations of DAP plus gentamicin and DAP plus rifampicin were synergistic in vitro [75]. In addition, the combination of DAP with gentamicin was shown to be synergistic against vancomycin-resistant *E. faecium* in a rabbit model of IE [23].

Lastly, the combination of DAP plus tigecycline has been successfully reported in four cases. In two of these, no other antimicrobial was added and the regimen was able to sterilise the bloodstream of patients diagnosed with IE due to vancomycin-resistant *E. faecium* [61,76]. In one of the remaining cases, ampicillin was used along with DAP and tigecycline to treat a neutropenic patient with persistent bacteraemia due to a vancomycin-resistant *E. faecium* that developed resistance to linezolid and daptomycin during therapy [64]. Finally, a patient with IE due to a linezolid-resistant vancomycin-resistant *E. faecium* that failed therapy with DAP 6 mg/kg was successfully treated with a regimen consisting of DAP 8 mg/kg, tigecycline, rifampicin and gentamicin [60].

In summary, and considering the limited evidence available to date, DAP monotherapy at the currently approved doses is likely to be unreliable to treat severe enterococcal infections. The issue is even more relevant when dealing with enterococci exhibiting DAP MICs in the higher range of susceptibility as many of these isolates already harbour mutations that abolish the bactericidal activity of DAP. The mechanisms underlying clinical and microbiological failures with DAP are the subject of active research by several groups and it is likely that, in the short term, new information will provide additional clues to identify patients at high risk of DAP failure and to improve clinical outcomes.

8. Concluding remarks

Treatment of severe MDR enterococcal infections is an important clinical challenge for clinicians worldwide. As one of the few compounds with in vitro bactericidal activity, DAP has risen as an interesting alternative in the management of these infections. Unfortunately, the amount of good quality clinical data supporting its use is scarce and prospective clinical trials evaluating its efficacy would be of considerable benefit. A better understanding of the molecular mechanisms of DAP-R and tolerance in enterococci should contribute to the development of new tools to predict therapeutic failures in high-risk patients. In the interim, pharmacological strategies such as the use of higher DAP doses and DAP combination regimens (particularly with β-lactams) may serve as valuable approaches to increase and/or preserve DAP's activity against MDR enterococci.

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Highlights

- VRE infection is an important clinical challenge due to the lack of reliable options against these organisms.
- DAP retains *in vitro* bactericidal activity against VRE, although this compound is not approved for infections caused by these organisms.
- The use of DAP was shortly followed by the development of DAP-resistance leading to therapeutic failures.
- DAP susceptible isolates with MICs close to the current breakpoint frequently harbor mutations associated with DAP-resistance.
- Alternatives for the treatment of DAP-resistant VRE are limited but the combination of DAP plus B-lactams is promising.

Table 1

Summary of clinical studies comparing the efficacy of daptomycin and linezolid for the management of vancomycin-resistant enterococci (VRE) bacteraemia

Reference	Patients per group		Mean DAP dose (range) (mg/kg)	Microbiological success (%)		*P*-value	Clinical success (%)		*P*-value	Relapse (%)		*P*-value	Mortality (%)		*P*-value	Comments
	DAP	LNZ		DAP	LNZ		DAP	LNZ		DAP	LNZ		DAP	LNZ		
Mave et al. [40]	30	68	6	90	88	0.8	NR	NR	NR	7	3	0.41	26.7	20	0.51	An aminoglycoside was used in 47% of cases with DAP and in 59% of cases with LNZ. Reported inpatient all-cause mortality
McKinnell et al. [41]	86	104	NR	71	83	NR	NR	NR	NR	NR	NR	NR	37	27	NR	Trend towards increased mortality with DAP, but not significant in multivariate analysis. DAP group had more neutropenia (29% vs. 7.7%; $P < 0.001$) and less consultations to ID specialists (24.0% vs. 8.1%; $P = 0.003$). No data on combination therapy. 30-Day all-cause mortality
Crank et al. [42]	67	34	5.5 (4– 8)	NR	NR	NR	NR	NR	NR	NR	NR	NR	46	29	0.1	DAP group had more shock (31% vs. 11%; $P = 0.049$) and previous treatment with VAN (84% vs. 52%; $P = 0.002$) or LNZ (31% vs. 0%; $P < 0.001$). Twelve patients in the DAP group received a second agent. Inpatient all-cause mortality
Twilla et al. [43]	63	138	6.1 (3.4– 10.4)	94	94	1	75	74	1	12	3	0.03	24	18	0.348	DAP group had more haematological malignancies (33% vs. 14%; $P = 0.002$) and liver transplants

Reference	Patients per group		Mean DAP dose (range) (mg/kg)	Microbiological success (%)		*P*-value	Clinical success (%)		*P*-value	Relapse (%)		*P*-value	Mortality (%)		*P*-value	Comments
	DAP	LNZ		DAP	LNZ		DAP	LNZ		DAP	LNZ		DAP	LNZ		
																(13% vs. 4%; P = 0.02). No d = 0.02). No data on combinat = 0.02). No data on combinat = 0.02). No data on combinat = 0.02). No data on combinat
Kraft et al. [44]	43	29	5.5 (4.5– 6)	NR	NR	NR	81 *a*	82 *a*	0.57	NR	NR	NR	23	24	0.93	Performed in haematology and SCT unit. The DAP group had more SCTs (51% vs. 17%; *P* = 0.006)
Hayakawa, et al. [45] *b*	56	112	6 (6– 12)	NR	NR	NR	NR	NR	NR	NR	NR	NR	45	25	0.01 *c*	Immunosuppression, haematological malignancies and indwelling devices were more frequent in the group given DAP. Combination therapy used in 6 patients in the DAP group and 9 in the LNZ group. Inpatient all-cause mortality

DAP, daptomycin; LNZ, linezolid; NR, not reported; ID, infectious diseases; VAN, vancomycin; SCT, stem cell transplant.

*a*Outcome was a composite analysis that included persistence of bacteraemia, recurrence, addition of a second agent, change of therapy to another agent, and mortality. No data on combination therapy provided. Reported 30-day, all-cause mortality.

*b*Also compared a group of therapy with β-lactams.

*c*The difference was abolished after controlling for time to effective therapy, VRE species and length of stay prior to VRE isolation.