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Association of daptomycin dosing regimen and mortality in patients with VRE bacteraemia: a review

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VRE are associated with ∼1300 deaths per year in the USA. Recent literature suggests that daptomycin, a cyclic lipopeptide antibiotic with concentration-dependent bactericidal activity, is the preferred treatment option for VRE bacteraemia, yet the optimal dosing strategy for this indication has not been established. *In vitro* evidence suggests that higher-than-labelled doses of daptomycin are required to optimally treat VRE bacteraemia and to inhibit the development of resistance. However, concern of dose-dependent toxicities, notably increases in creatine phosphokinase and the development of rhabdomyolysis, are a barrier to initiating high-dose schemes in clinical practice. Thus, the effectiveness and safety of high-dose daptomycin regimens in clinical practice have remained unclear. While early studies failed to identify differences in mortality, newer, larger investigations suggest high-dose (≥9 mg/kg) daptomycin is associated with reduced mortality in patients with VRE bacteraemia compared with standard (6 mg/kg) dosing regimens. Additionally, the high-dose regimens appear to be safe and may be associated with improved microbiological outcomes. The purpose of this review is to examine the published evidence on the effectiveness and safety of high-dose daptomycin compared with standard dosing regimens for VRE bacteraemia.

Background

VRE is an increasingly common pathogen in the USA, causing an estimated 20000 infections and 1300 deaths annually in the USA.[1] The incidence of infections caused by VRE has remained relatively stable, although significant increases over time have been observed in Atlanta and Detroit.[2] *Enterococcus faecium*, the enterococcal species most commonly associated with vancomycin resistance, is the fifth most common cause of central-line-associated bloodstream infections in the general hospital population and the third most common cause in cancer patients, who are often at high risk of morbidity and mortality due to VRE infections.[3] The challenge of VRE is not limited to North America, however. In Europe, the overall prevalence of vancomycin-resistant *E. faecium* is gradually increasing; the ECDC reported the population-weighted mean percentage for vancomycin-resistant *E. faecium* across the European Union/European Economic Area (EU/EEA) at 11.8% in 2016, indicating a slightly increasing rate over the previous years. Within the EU/EEA, however, there is significant regional variation in the prevalence of VRE. For example, Iceland, France and the Netherlands report VRE rates <1%, which is in stark contrast to the rates of other nations including the UK (17%), Greece (27.9%) and Ireland (44.1%).[4]

VRE is most commonly treated with either linezolid or daptomycin, with no randomized clinical trials existing to support one treatment option over the other. Recent studies with robust sample sizes and strict statistical methods suggest daptomycin might be superior to linezolid for treatment of VRE bacteraemia.[5–8] Other VRE-active antimicrobial agents include tigecycline and quinupristin/dalfopristin, but issues with adverse effects and drug availability have led to limited use of these agents in practice.

Comparison of daptomycin and linezolid for VRE bacteraemia

Daptomycin is approved by the US FDA for the treatment of complicated skin and skin structure infections (SSTIs) and *Staphylococcus aureus* bacteraemia (including MRSA), although it is frequently used off-label to treat bacteraemia caused by VRE.[9,10] Unlike daptomycin, linezolid carries an FDA-approved indication for VRE infections, including bacteraemia. This approval was based on a randomized, multicentre, double-blind trial comparing two linezolid dosing regimens in patients with documented VRE infections (including bacteraemia) as well as an open-label compassionate-use programme for patients with VRE infections.[11] The randomized trial demonstrated an overall cure rate of 67% in

patients receiving 600 mg intravenously or orally twice daily, with a cure rate of 59% in those with secondary bacteraemia. Given the lack of alternative treatment options available at the time, comparative data were not felt to be necessary for the inclusion of VRE infections (including bacteraemia) in the product labelling. As the clinical use of daptomycin for VRE infections expanded, interest grew in determining which, if either, agent was superior. Three early meta-analyses suggested a potential survival benefit of linezolid when compared with daptomycin for VRE bacteraemia; however, the significant limitations of these initial pooled analyses are acknowledged by the authors, including substantial study heterogeneity, significant confounders between treatment groups, inclusion of low-quality conference abstracts and a large number of patients treated with low-dose daptomycin (<6 mg/kg), as discussed below.[5,6,12]

Indeed, these initial three meta-analyses were conducted at roughly the same time and included many of the same studies. The first analysis, performed by Whang *et al.*,[12] identified nine studies comparing outcomes when using daptomycin and linezolid for VRE bacteraemia. All studies were retrospective and observational in nature, with small sample sizes ranging from 54 to 235 subjects. The analysis noted a trend towards increased survival in linezolid-treated patients [OR 1.3 (95% CI 0.996–1.8), $P = 0.053$] with no differences in microbiological cure [OR 1.0 (95% CI 0.4–1.7), $P = 0.95$] or clinical cure [OR 1.2 (95% CI 0.5–2.1), $P = 0.68$]. This analysis did not adjust for confounders and the authors cite observed selection bias in four studies favouring daptomycin for patients with haematological abnormalities. The meta-analysis by Balli *et al.*[6] involved 10 retrospective studies, including 967 patients in total, and reported higher overall mortality [OR 1.41 (95% CI 1.06–1.89)] in those treated with daptomycin, with similar findings in a pooled analysis of only studies with adjusted OR for potential confounders. In the third meta-analysis, Chuang *et al.*[5] included 13 studies, including 4 conference abstracts, none of which was classified as high quality. Again, all studies were retrospective and small in sample size, ranging from 31 to a maximum of 201 subjects and they found higher mortality in patients receiving daptomycin [OR 1.43 (95% CI 1.09–1.86), $P = 0.009$].

While each of these three meta-analyses favoured linezolid therapy, several caveats must be applied in their interpretation. The studies included in these analyses were small and retrospective observational assessments, with many failing to adjust for potential confounders. Furthermore, some of the studies included in the meta-analysis included patients without bacteraemia or infections besides VRE, further limiting the applicability of these studies. As suggested by the authors of each analysis, the inclusion of healthier patients in the linezolid-treated cohort may have also influenced these results. Moreover, there was significant heterogeneity in the definition of mortality utilized by the included studies, with various endpoints considered, such as 14 day mortality, mortality at the end of therapy and all-cause mortality at 7 days after the end of therapy, making assessment of the impact of therapy on mortality difficult to compare. Perhaps most importantly to the remainder of this review, the majority of the studies assessed daptomycin at an average dose of 6 mg/kg, with very few patients receiving higher doses.

In 2015, a national Veterans Affairs (VA) study published by Britt *et al.*[7] presented the largest and most methodologically robust VRE bloodstream infection study to date. All patients with at least one blood culture positive for VRE were included. Patients were excluded if treated with linezolid and daptomycin combination therapy (including sequential therapy) or treated with either agent for <48 h. Only the first case of VRE bacteraemia per patient was included. This large, retrospective cohort study of 644 patients found linezolid to be associated with significantly higher treatment failure [risk ratio (RR) 1.15 (95% CI 1.02–1.30), $P = 0.026$], microbiological failure [RR 1.10 (95% CI 1.02–1.18), $P = 0.011$] and 30 day mortality [RR 1.17 (95% CI 1.04–1.32), $P = 0.014$], compared with daptomycin. With these new data, Zhao *et al.*[13] conducted a new meta-analysis that aimed to address the methodological issues with the prior meta-analyses. Their analysis used validating scoring indices (including APACHE II and the Charlson Comorbidity Index) to account for differences in patient baseline characteristics and excluded studies with insufficient daptomycin dosing (<6 mg/kg) and low-quality conference abstracts. The final analysis included 10 full studies and 1 conference abstract and found no difference in crude overall mortality between linezolid and daptomycin [RR 1.07 (95% CI 0.83–1.37), $P = 0.61$]. No differences in rates of clinical cure, microbiological cure and VRE bacteraemia relapse were identified. Importantly, the authors commented on the limited use of high-dose daptomycin in the included studies, limiting the ability to make inferences about daptomycin dose optimization.

In a follow-up VA study (again authored by Britt *et al.*[8]), the safety and effectiveness of continuous versus sequential therapy with daptomycin or linezolid for vancomycin-resistant *E. faecium* bacteraemia was assessed, as sequential therapy patients had been excluded in the initial study. With 2630 patients in the study, the authors again found linezolid to be associated with increased 30 day mortality [RR 1.13 (95% CI 1.02–1.26), $P = 0.015$] in a propensity-matched analysis. Patients who were switched from linezolid to daptomycin had a lower mortality than those who remained on linezolid [RR 1.29 (95% CI 1.03–1.63), $P = 0.021$] and a longer median time to switching was associated with increased 30 day mortality (3 days versus 6 days, $P < 0.001$).

Although the data comparing linezolid and daptomycin are conflicted, the results of more recent, larger studies, as well as an updated meta-analysis by Zhao *et al.*,[13] indicate that daptomycin may be a preferred option for VRE bacteraemia, a view endorsed by many clinicians.[14] More recent data suggest that the specific daptomycin dose is of critical importance in patient outcome, perhaps explaining the lack of benefit offered by daptomycin relative to linezolid observed in the earlier meta-analyses. In this review, we evaluate published primary literature on the use of standard-dose (6 mg/kg) versus high-dose daptomycin (>6 mg/kg) for treatment of VRE bacteraemia to identify whether high-dose strategies are associated with reduced mortality in patients with bloodstream infections caused by VRE. Additionally, we examine if high-dose daptomycin is associated with an unacceptable increased risk of toxicity in these studies and assess the rates of microbiological success associated with high- and standard-dose daptomycin regimens.

Methods

A comprehensive literature search was conducted using the PubMed, Embase and Scopus databases with the following search term: [Daptomycin AND Enterococcus AND ('bloodstream infection' or bacteremia)]. Only

original research articles and meta-analyses were eligible for inclusion. The titles and abstracts of each paper were manually reviewed to identify potentially relevant articles. In addition, the references of identified studies were reviewed for additional publications not identified by the search terminology. Papers reporting exclusively on *in vitro* or animal studies, organisms other than *Enterococcus* spp. and/or drugs other than daptomycin were excluded. Studies that did not compare outcomes between patients receiving high- and low-dose daptomycin were also excluded. Results were limited to original research articles with full-text availability in the English language; all papers between January 2003 (the year of initial approval for daptomycin) and March 2017 were included. The primary exposure of interest was high-dose daptomycin (doses >6 mg/kg) in comparison with standard-dose daptomycin (doses ≤6 mg/kg). The primary outcome of interest was mortality; safety and microbiological success were included as secondary outcomes.

Optimizing daptomycin dosing for VRE bacteraemia

Daptomycin exhibits concentration-dependent bactericidal activity, best characterized by the AUC to MIC ratio (AUC/MIC): increasing exposures of the drug lead to enhanced bacterial killing *in vitro* and *in vivo*.[15] In contrast to *S. aureus*, daptomycin MICs are 2- to 4-fold higher for VRE and the required AUC/MIC thresholds may be higher in VRE;[16,17] thus there is reason to believe that the standard, FDA-approved doses (4–6 mg/kg) for SSTIs and *S. aureus* bloodstream infections may be suboptimal for the treatment of infections caused by VRE. Furthermore, it has been demonstrated *in vitro* that higher daptomycin doses (10–12 mg/kg) are needed to prevent the development of resistance in enterococcal isolates.[18] While several studies performed early after daptomycin was initially marketed addressed daptomycin dosing considerations for VRE infections, they considered 6 mg/kg to be a high dose.[19–21] In one of the first clinical evaluations of high-dose daptomycin by current practice definitions (>6 mg/kg) for enterococcal infections, Casapao *et al.*[22] showed an in-hospital mortality rate of 27% amongst the subset of 148 patients with VRE bloodstream infection. Although this study was descriptive in nature and did not compare outcomes of high-dose regimens with standard dosing (6 mg/kg), it suggested that high-dose daptomycin may be a viable option for VRE bacteraemia.[22] However, given that daptomycin is associated with dose-dependent increases in creatine phosphokinase (CPK) and rare cases of rhabdomyolysis,[23,24] there is concern over increasing daptomycin doses in clinical practice and increased risk of adverse events. Therefore, the optimal dose of daptomycin that best balances effectiveness with toxicity for VRE bacteraemia remains to be defined.

Association of daptomycin dose and mortality

A total of six studies to date have evaluated standard-dose (6 mg/kg) versus high-dose (>6 mg/kg) daptomycin for the treatment of VRE bacteraemia, although only two were designed to specifically assess the question of the effectiveness of daptomycin in the treatment of VRE bacteraemia. Key information extracted from the studies reporting on mortality are presented in Table 1. The earliest study, performed by Hayakawa *et al.*,[25] was a retrospective analysis of patients with VRE bacteraemia between 2008 and 2010 at the eight-hospital Detroit Medical Center (DMC) and was primarily designed to determine clinical and economic outcomes associated with different treatment strategies (i.e. linezolid, β-lactam antibiotics or daptomycin) for VRE bacteraemia. A total of 56 patients of 225 in the overall cohort (24.9%) were treated with daptomycin. In this small subgroup, 21 patients received >6 mg/kg daptomycin, of whom 9 (42.9%) died in hospital, which was not clinically or statistically different from the group receiving 6 mg/kg (16/35, 46%; $P = 1.00$). No further adjusted analyses of mortality related to daptomycin dose were reported in this study.

Chong *et al.*[26] performed a single-centre, retrospective review of patients with haematological malignancy or prior HSCT and VRE bacteraemia at the University of North Carolina, primarily designed to determine the impact of elevated daptomycin MICs (3 or 4 mg/L versus ≤2 mg/L) on mortality. In the overall cohort of 42 episodes of VRE bacteraemia, 33 (78.6%) had information available on daptomycin dosing. Of these 33 patients, 13 (39.4%) were treated with high-dose (>6 mg/kg) daptomycin. In a univariate Cox proportional hazard analysis for 30 day overall mortality, the use of high-dose daptomycin as compared with standard-dose daptomycin was not associated with decreased mortality [HR 0.62 (95% CI 0.12–3.06), $P = 0.55$]. No adjusted analyses of daptomycin dose were performed in this study. Shukla *et al.*[27] conducted a similar analysis in 62 patients at four institutions across the USA to assess the influence of elevated daptomycin MICs on all-cause mortality. Initial daptomycin dose (stratified by ≥8 mg/kg versus lower dose) was not found to be significantly associated with in-hospital mortality (37.1% versus 44.4%, $P = 0.56$).

As part of an analysis of the comparative effectiveness of linezolid versus daptomycin for the treatment of VRE bacteraemia, Chuang *et al.*[28] performed a retrospective review of patients with VRE bacteraemia at two hospitals affiliated with the National Taiwan University Hospital between 2010 and 2015. A total of 141 patients who received daptomycin were included in this analysis, although it is worth noting that patients may have been switched from linezolid to daptomycin, potentially confounding the association between daptomycin dose and mortality. When assessed as a continuous variable with the use of a generalized additive model, each 1 mg/kg increase in daptomycin dose was associated with a 24% decrease in 14 day mortality [adjusted odds ratio (aOR) 0.76 (95% CI 0.59–0.98), $P = 0.03$]. Based on visual analysis of the fitted probabilities, a daptomycin dose cut-off of ≥9 mg/kg was chosen as the optimal dose associated with reduced patient mortality. When compared with doses of 6–9 mg/kg and adjusted for potential confounding variables (including corticosteroid use, platelet count and severity of illness), daptomycin doses ≥9 mg/kg were associated with a 74% reduction in 14 day mortality [aOR 0.26 (95% CI 0.09–0.74), $P = 0.01$].

In the largest study on the topic performed to date, and the first designed specifically to address the role of high-dose daptomycin in patients with VRE bacteraemia, Britt *et al.*[29] retrospectively reviewed the records of patients admitted to any Veterans Affairs Medical Center (VAMC) between 2004 and 2014 with VRE bacteraemia. This study notably excluded any patients receiving <48 h of daptomycin, those receiving <5.5 mg/kg and those receiving other VRE-active antimicrobial agents. A total of 911 patients were included although quantitative MIC data were available in only a small minority of cases ($n = 43$, 4.7%), of which 27 (62.8%) were 3 or 4 mg/L. Patients were categorized according to the daptomycin dose received [6 mg/kg (standard), 8 mg/kg (medium) or

Table 1. Studies reporting on daptomycin dosing and mortality for VRE bacteraemia

Study	Study design	No. of patients	Mortality endpoint	Mortality (%)	Mortality HR[a]	Mortality aOR[a]
Hayakawa *et al.* (2014)[25]	retrospective, multicentre	6 mg/kg: 35 >6 mg/kg: 21	in-hospital mortality	6 mg/kg: 46% >6 mg/kg: 43%	NR	NR
Chong *et al.* (2016)[26]	retrospective, single centre	6 mg/kg: 20 >6 mg/kg: 13	30 day mortality	NR	6 mg/kg versus >6 mg/kg: HR 0.62 (95% CI 0.12–3.06), P=0.55	NR
Shukla *et al.* (2016)[27]	retrospective, multicentre	<8 mg/kg: 27 ≥8 mg/kg: 35	in-hospital mortality	<8 mg/kg: 44.4% ≥8 mg/kg: 37.1%	NR	NR
Chuang *et al.* (2016)[28]	prospective, multicentre	6–9 mg/kg: 107 ≥9 mg/kg: 34	14 day mortality	6–9 mg/kg: 41.1% ≥9 mg/kg: 23.5%	NR	≥9 mg/kg versus 6–9 mg/kg: aOR 0.26 (95% CI 0.09–0.74), P = 0.01
Britt *et al.* (2017)[29]	retrospective, multicentre	6 mg/kg: 709 8 mg/kg: 142 10 mg/kg: 60	all-cause mortality	6 mg/kg: 30.3% 8 mg/kg: 33.1% 10 mg/kg: 16.7%	6 mg/kg versus ≥10 mg/kg: HR 2.58 (95% CI 1.27–4.88), P < 0.01 8 mg/kg versus ≥10 mg/kg: HR 2.52 (95% CI 1.27–5.00), P < 0.01	NR
Chuang *et al.* (2017)[30]	retrospective, multicentre	<7 mg/kg: 36 7–9 mg/kg: 51 ≥9 mg/kg: 25	14 day mortality	<7 mg/kg: 50.0% 7–9 mg/kg: 33.3% ≥9 mg/kg: 20.0%	NR	7–9 mg/kg versus <7 mg/kg: aOR 0.47 (95% CI 0.16–1.40), P = 0.18 ≥9 mg/kg versus <7 mg/kg: aOR 0.09 (95% CI 0.02–0.44), P < 0.01

NR, not reported.
[a]HRs or aORs of mortality of first indicated dose in comparison with the second indicated dose.

≥10 mg/kg (high)]. The majority of patients received a standard dose (709, 77.8%), while 142 received a medium dose (15.6%) and 60 (6.6%) received a high dose. A number of significant differences existed in characteristics between the three groups, most notably that a significantly higher number of patients received infectious diseases consultation in the medium- and high-dose daptomycin groups. A significant time bias may have also been present, as the proportion of patients receiving high-dose daptomycin increased dramatically from <10% before 2011 to ∼25% from 2011 onward. Cox proportional hazard models were constructed and a clear dose-dependent effect was observed for daptomycin dosing and overall mortality. In comparison with high-dose daptomycin (≥10 mg/kg), patients receiving lower doses of daptomycin were significantly more likely to die, with an adjusted HR in the low-dose group of 2.58 (95% CI 1.27–4.88, P = 0.004) and in the medium-dose group of 2.52 (95% CI 1.27–5.00, P = 0.008). A secondary analysis of 30 day mortality also identified a significant reduction in mortality with high-dose daptomycin compared with standard- and medium-dose daptomycin [RR 0.83 (95% CI 0.74–0.94), P = 0.015].

As a follow-up to their previous study,[28] a subsequent retrospective review performed by Chuang *et al.*[30] confirmed and expanded upon these findings. Given the overlapping cohorts and authors, it is highly likely that patients included in this study represent a more refined subset of those included in the prior study by the same group. Patients were excluded if they received <6 mg/kg of daptomycin or were treated with any other VRE-active agent prior to daptomycin. The primary mortality outcome was all-cause 14 day mortality. A total of 112 patients were included and a clear dose-dependent effect was observed. Multivariable logistic regression models were constructed for two dose-specific analyses. When daptomycin dose was considered as a continuous variable, the observed aOR for mortality for each mg/kg increase in daptomycin dose was 0.60 (95% CI 0.42–0.87, P = 0.01). In addition, in comparison with doses <7 mg/kg, doses of 7–9 mg/kg were associated with a non-significant decrease in 14 day mortality [aOR 0.47 (95% CI 0.16–1.40), P = 0.18], while doses ≥9 mg/kg were associated with a statistically significant decrease in 14 day mortality [aOR 0.09 (95% CI 0.02–0.44), P = 0.003].

Daptomycin dose and microbiological outcomes

Among the previously mentioned studies, those performed by Hayakawa *et al.*,[25] Chong *et al.*[26] and the initial Chuang *et al.*[28] study did not report on microbiological success as a function of daptomycin dose. The study performed by Shukla *et al.*[27] reported that microbiological failure, defined as persistent bacteraemia on

day 4 or later or death with persistent positive blood cultures, was similar among groups treated with high- and low-dose daptomycin (51.4% versus 59.3%, $P = 0.54$). Chuang *et al.*[30] used an identical definition of microbiological failure to that of Shukla *et al.*[27] in their second study; however, only 56 of the 112 patients (50%) were evaluable for this outcome. Of these, 31 (55.4%) experienced microbiological failure.[30] The median dose of daptomycin was similar in groups with and without failure [7.8 mg/kg (IQR 6.5–8.7 mg/kg) versus 7.6 mg/kg (IQR 6.9–8.4 mg/kg), $P = 0.78$]. The specific details of the adjusted analysis are not available, although the authors note that daptomycin dose was not a significant predictor of microbiological failure.

King *et al.*[31] performed a retrospective analysis of 46 patients with VRE bacteraemia at a single centre in New Jersey between 2008 and 2010 specifically designed to assess the influence of high-dose (>6 mg/kg) versus low-dose (≤6 mg/kg) daptomycin on time to microbiological eradication (defined as the first negative blood culture). In this study, there was no difference in microbiological eradication between the high- and low-dose daptomycin groups [median 2 days (IQR 1–2.25 days) versus 2 days (IQR 1–3 days), P = not significant]. Kaplan–Meier analysis for time to microbiological cure stratified by both high- versus low-dose and high versus low MIC (3 or 4 mg/L versus ≤2 mg/L, respectively) identified no significant differences in time to clearance (log-rank $P = 0.66$). No adjusted analyses were performed and, based on the authors' sample size calculations, the study was significantly underpowered to detect a difference in time to microbiological cure. Britt *et al.*[29] performed a similar analysis, with time to microbiological clearance again defined as time to the first negative blood culture. In Kaplan–Meier analysis stratified into standard, medium or high dose as previously defined, a clear dose-dependent decrease in time to microbiological clearance was observed (log-rank $P < 0.001$). In unadjusted Cox proportional hazard models, both medium-dose [HR 0.78 (95% CI 0.55–0.90), $P = 0.012$] and high-dose [HR 0.70 (95% CI 0.41–0.84), $P = 0.006$] daptomycin were associated with decreased time to microbiological clearance as compared with standard-dose daptomycin. Interestingly, time to microbiological clearance was not significantly different when comparing the medium- and high-dose groups with one another [HR 0.89 (95% CI 0.60–1.22), $P = 0.459$].

Safety of high-dose daptomycin

Only two of the previously reviewed studies reported on elevations of CPK or rhabdomyolysis. Britt *et al.*[29] defined CPK elevations using two different methods. In the first, CPK was considered as a dichotomous variable—for patients without pre-existing elevations in CPK, an elevation was defined as an increase to ≥3 times the upper limit of normal (ULN), while for those with a pre-existing elevation in CPK, an increase to ≥5 times the ULN was needed. CPK was also considered as a continuous variable. In order to link CPK elevations to rhabdomyolysis and resulting acute kidney injury (AKI), the standard RIFLE (risk, injury, failure, loss, end-stage kidney failure) classification was used. Among the 595 patients with multiple CPK measurements, elevations occurred in only 7 (1.2%). The majority of elevations occurred in patients in the standard-dose group (6/441, 1.4%) compared with 1/103 (1.0%) in the medium-dose group and 0/51 in the high-dose group ($P = 0.504$). The median CPK was similar in all three groups. No association was observed between CPK elevations and AKI ($P > 0.999$) and, importantly, no increased risk of CPK elevations was observed among users of statins, a medication that may synergistically act with daptomycin to raise CPK levels ($P = 0.556$). Of note, the study was not designed or powered to assess this outcome. Chuang *et al.*[30] noted that 7/112 patients (6.3%) experienced an elevated CPK, defined as ≥10 times the ULN, with no statistically significant difference observed among standard-, medium- and high-dose treatment groups ($P = 0.99$).

Discussion of the available human data

In vitro data strongly support the association between increased daptomycin doses and improved antibacterial efficacy, including the prevention of development of resistance in enterococcal isolates.[18,32,33] However, improved antibacterial efficacy *in vitro* does not necessarily translate into improved patient-level outcomes. Among the studies reviewed, three of six were unable to identify decreased mortality with high-dose daptomycin in patients with VRE bacteraemia.[25–27] Notably, these studies were all primarily designed to address questions other than the role of high-dose daptomycin, included a small number of patients and did not clearly differentiate the clinical characteristics of the patients receiving high- or low-dose daptomycin. Therefore, the ability of these studies to address the role of high-dose daptomycin is somewhat limited. Chuang *et al.*[28] identified a significant difference in mortality between daptomycin doses ≥9 mg/kg and those receiving 6–9 mg/kg, favouring high-dose regimens.

Subsequently, two studies specifically sought to compare daptomycin doses. Both of these studies, although retrospective in nature, identified statistically and clinically significant differences in mortality across dosing levels.[29,30] These studies provided possible answers to two clinically relevant questions. First, daptomycin doses >6 mg/kg were associated with significantly reduced mortality in patients with VRE bacteraemia as opposed to standard 6 mg/kg dosing. Second, both studies identified that a medium-dose strategy (8 mg/kg in the case of Britt *et al.*[29] or 7–9 mg/kg in the case of Chuang *et al.*[30]) was associated with similar outcomes as the standard dose, and therefore the most aggressive, high-dose regimens are likely necessary to maximize patient outcomes. In the case of Britt *et al.*,[29] the cohort consisted solely of VAMC patients, while the study performed by Chuang *et al.*[30] included only patients hospitalized in Taiwan. Although retrospective in nature, the consistent findings in these non-overlapping, disparate populations provide some degree of confidence in the results. However, one cannot rule out the possibility that use of high-dose daptomycin is a marker for more aggressive interventions, such as obtaining infectious diseases consultation, in patients with longer life expectancy, particularly given that VRE bacteraemia primarily affects patients with multiple medical comorbidities. Of clinical importance, neither of these studies identified a signal for increased toxicity with the use of higher daptomycin doses, mitigating concerns that have been raised over using more aggressive dosing in seriously ill, hospitalized patients.[23,29,30,34] These findings are in general agreement with other analyses addressing the safety of high-dose daptomycin.[35–37]

It is worth noting, however, that improved microbiological outcomes in relation to high-dose daptomycin were only observed in one of these studies.[29] Given that rapid microbiological clearance is the presumed causal pathway for reduced mortality in patients

who receive high-dose daptomycin, the lack of association does call into question whether reduced mortality is truly a result of high-dose daptomycin or is the product of another unidentified, unmeasured factor. Although possible, strong *in vitro* evidence makes the above observation unlikely and issues with study design are possibly behind the lack of consistent microbiological findings. With only 42 patients, the study by King *et al.*[31] was underpowered to detect such an association and, in the case of Chuang *et al.*,[30] microbiological success was assessed at only a single timepoint (at day 4 of bacteraemia).

Conclusions

Although previous studies were conflicting, more recent literature with larger sample sizes and improved statistical methodologies support daptomycin as the agent of choice for the treatment of VRE bacteraemia.[5,7,14] Despite strong *in vitro* and *in vivo* data that have demonstrated the benefits of high-dose daptomycin, there remain relatively few studies that have addressed this topic in relation to patient outcomes.

A prospective randomized controlled trial comparing standard- and high-dose daptomycin would be beneficial to provide additional insights into this important clinical conundrum, although with the evidence available, such a study may be perceived as lacking clinical equipoise. An ideal study should compare various high-dose daptomycin regimens (i.e. 10 versus 12 mg/kg) to determine if an optimal high-dose regimen exists. Such a study should also aim to identify if a minimum dosing strategy is needed to limit the development of daptomycin-resistant isolates, which are of increasing concern globally.[38,39] A randomized study would also allow for a more thorough evaluation of adverse events, including skeletal muscle toxicity. While the evidence is not conclusive, available data suggest that high-dose daptomycin is preferred for the treatment of VRE bacteraemia in comparison with lower doses and is not associated with increased risk of toxicity. At our institution, a National Cancer Institute-designated comprehensive cancer centre, daptomycin (at a dose of 10 mg/kg intravenously daily) is generally the preferred agent for VRE bacteraemia, with weekly monitoring of CPK.

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