Vancomycin-resistant enterococcal bacteraemia and daptomycin: are higher doses necessary?

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Background: The MIC corresponding to daptomycin susceptibility for vancomycin-resistant enterococci (VRE) is ≤4 mg/L. Based on the concentration-dependent killing properties of daptomycin, there may be concern about achieving adequate concentrations when the MIC approaches the upper end of the susceptible range (3–4 mg/L). Higher doses of daptomycin may be needed to treat VRE isolates with higher MICs.

Methods: We conducted a single-centre retrospective chart review of adult cases with VRE bacteraemia who received daptomycin as initial therapy. The primary outcome was time to microbiological cure (TMC) between standard doses (≤6 mg/kg) and high doses (>6 mg/kg) of daptomycin and whether TMC differed based on MICs. The secondary outcome evaluated the daptomycin MIC distribution and assessed whether recent exposure to vancomycin was associated with higher daptomycin MICs.

Results: Forty-six cases were included in the primary analysis and 60.9% of patients were neutropenic. The two dose groups differed in the baseline characteristics of age, body mass index, blood culture source and catheter removal. Median TMC was 2 days for both dose groups. There was no significant difference in TMC between MIC subgroups of ≤2 mg/L versus >2 and ≤4 mg/L. For the secondary analysis 227 VRE isolates were evaluated and 62% had daptomycin MICs of 3–4 mg/L. Each daptomycin MIC group had a similar incidence of prior vancomycin exposure.

Conclusions: Based on this retrospective review we did not observe a difference in TMC based on daptomycin dose and MIC; however, there were various limitations to this study, and the study was not powered to detect a difference in TMC. Also, prior vancomycin exposure did not appear to influence daptomycin MICs. The frequency of daptomycin MICs of 3–4 mg/L reported in this study is higher than those reported in the literature.

Keywords: high-dose daptomycin, MICs, VRE

Introduction

Daptomycin is an antibiotic that is approved by the FDA for the treatment of bacteraemia and right-sided infective endocarditis caused by Staphylococcus aureus at a dose of 6 mg/kg/day.1 Although it is not approved by the FDA for the treatment of bacteraemia caused by Enterococcus spp., it has in vitro activity against this organism. For all Enterococcus spp., including vancomycin-resistant strains, the CLSI MIC breakpoint for daptomycin susceptibility is ≤4 mg/L.2

Recent studies evaluating clinical strains of Gram-positive organisms in the USA and Canada have revealed that up to 32% of all enterococcal isolates are vancomycin resistant.3,4 Bacteraemia caused by vancomycin-resistant enterococci (VRE) has been associated with higher morbidity and mortality than that caused by vancomycin-susceptible enterococci.5,6 Few antibiotics with activity against VRE have been evaluated clinically in the treatment of bacteraemia due to this organism. Retrospective studies evaluating the use of daptomycin in VRE bacteraemia have reported success rates (microbiological or clinical cure) from 69% to 97.5%, using various doses ranging from 1.1 to 14.8 mg/kg/day.7–13 Only three of these studies have reported VRE susceptibilities to daptomycin.7–9

Most VRE isolates have daptomycin MIC values of ≤2 mg/L; however, several studies have reported anywhere from 5% to 20% of VRE isolates with a daptomycin MIC value of 4 mg/L.3,5

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Daptomycin has concentration-dependent killing\(^1\) and in vivo data have shown that higher doses of daptomycin may be needed to treat VRE isolates with higher MICs.\(^{16,15}\) Results from a neutropenic animal model using an Enterococcus faecium strain with a daptomycin MIC of 2 mg/L demonstrated that peak concentrations between 7 and 25 times the MIC were required to produce a bactericidal effect.\(^{15}\) Peak serum concentrations of daptomycin increase in a linear fashion and for MIC values of \(\leq 2\) mg/L all patients receiving a dose of 6 mg/kg of daptomycin would achieve peak serum concentrations >25 times the MIC.\(^1\) Higher doses of daptomycin (>6 mg/kg) may be needed to achieve higher peak serum concentrations for MIC values >2 and \(\leq 4\) mg/L based on in vivo data from a neutropenic animal model.\(^{1,15}\) Doses of daptomycin up to 12 mg/kg/day have been shown to be well tolerated with generally mild adverse events.\(^{7,8,16–19}\)

To date there have been a limited number of studies evaluating the use of daptomycin in VRE bacteraemia.\(^7–13\) Currently there is no available literature comparing the efficacy of various doses of daptomycin in relation to MIC values. This study retrospectively evaluated the microbiological response to standard doses of daptomycin versus high-dose daptomycin for the treatment of VRE bacteraemia and assessed whether the response differs based on the daptomycin MIC and dose. This study also evaluated the daptomycin MIC distribution in our institution and examined whether prior exposure to vancomycin was associated with VRE isolates with increased daptomycin MICs.

Methods

Study design

This was a retrospective chart review that used the MedMined\(^\text{TM}\) Surveillance System to identify cases of positive VRE blood cultures from January 2008 to March 2010 in patients at Hackensack University Medical Center, a 775 bed teaching hospital in Hackensack, NJ, USA. This time period was chosen due to an observed increase in the use of daptomycin for the treatment of VRE bacteraemia and the use of higher doses of daptomycin at our medical centre. The study protocol was approved by the institutional review board. Cases were included if patients were >18 years of age, had at least one positive blood culture for VRE, had a documented MIC value of daptomycin and received daptomycin as the initial treatment for VRE bacteraemia. Cases were excluded for the following reasons: (i) patients received other antibiotics with activity against VRE (e.g. linezolid or quinupristin/dalfopristin) prior to or concurrently with daptomycin use; (ii) the daptomycin MIC value was >4 mg/L; or (iii) the first negative blood culture was drawn >3 days after a prior positive blood culture.

The following data were collected: baseline characteristics; daptomycin usage; other antibiotic information, including previous vancomycin exposure, concomitant antibiotics and any treatment changes from daptomycin to linezolid or quinupristin/dalfopristin; safety data (creatine phosphokinase [CPK]); and microbiology, including blood culture sites, dates and daptomycin susceptibility. Susceptibility was tested using a daptomycin Etest. Vancomycin exposure was defined as vancomycin use, intravenously and/or orally, for >72 h within the last 30 days prior to the first positive VRE blood culture.

Outcomes

The primary outcome was time to microbiological cure, which was defined as the time from daptomycin initiation to the first negative blood culture (bacterial clearance). Treatment failure was defined as persistence of positive VRE blood cultures at the time of death, or a switch to an alternative antibiotic with activity against VRE. The primary analysis compared time to microbiological cure between two dose groups: patients who received standard-dose versus high-dose daptomycin. Standard doses included doses <6.5 mg/kg and high doses included doses \(\geq 6.5\) mg/kg to allow for variability in daptomycin doses in the context of a retrospective analysis. A subgroup analysis assessed whether frequency and time to microbiological cure differed based on the daptomycin MIC (\(\leq 2\) mg/L or >2 and \(\leq 4\) mg/L) and dose (Figure 1).

The secondary outcome evaluated the daptomycin MIC distribution at our institution. This analysis also assessed whether recent exposure to vancomycin was associated with VRE isolates with higher daptomycin MICs and compared VRE isolates with MIC values of \(\leq 2\), >2 and \(\leq 4\), and >4 mg/L.

Statistical analysis

The normality of the distribution of continuous variables was examined using the Shapiro–Wilks test. The continuous variables were compared using an unpaired two-sided t-test or Mann–Whitney test, as appropriate, and categorical variables were compared using Fisher’s exact test. Time to microbiological cure for all cases was estimated using a Kaplan–Meier method. Time to microbiological cure for treatment failure cases was censored at the time of death or the time the patient was switched to an alternative antibiotic for the treatment of VRE bacteraemia. The univariate analysis comparing time to microbiological cure between the two dose groups was performed using the two-sided log rank test. A multivariate analysis (Cox proportional hazards) was performed to examine whether time to microbiological cure differed based on daptomycin dose and MICs. A sample size calculation was not performed in this exploratory study due to the pre-specified time period. All tests were considered statistically significant at \(P<0.05\). All statistical analyses in this study were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Two hundred and thirty-eight cases of VRE bacteraemia were screened. For the primary analysis 75 cases were initially treated with daptomycin; 15 cases met exclusion criteria and 14 cases were non-evaluable (Figure 1). The most common reason why cases were non-evaluable was that the initial bacteraemia had resolved prior to daptomycin initiation. Forty-six cases observed in 45 patients were evaluated. One patient had a subsequent bacteraemia 1 month after clearance of the initial VRE bacteraemia. There were 24 cases of VRE bacteraemia in the standard-dose group and 22 cases in the high-dose group. Seventy-eight percent of cases had a prior and/or current cancer-related diagnosis and 60.9% were neutropenic. The majority of cases also had catheters in situ at the time of their bacteraemia, but 22.7% of cases in the high-dose group had their catheters removed during treatment compared with 52.4% of cases in the standard-dose group (\(P=0.04\)). Cases in the high-dose group also had significantly more positive blood cultures drawn from a catheter source only (77% in the high-dose group and 38% in the standard-dose group, \(P=0.007\); Table 1).

Continuous variables were not normally distributed and were reported as median and interquartile range (IQR). The median MIC was 3 mg/L in both groups and the median dose was 5.8 mg/kg (IQR 5.35–6 mg/kg) in the standard-dose group and 7.65 mg/kg (IQR 7–8.2 mg/kg) in the high-dose group. Forty-one
patients received daptomycin dosing every 24 h and five patients with renal dysfunction received daptomycin every 48 h. Overall microbiological cure was 78.3% and did not differ significantly between dose groups (Table 2). The median time to

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Standard dose, ≤6 mg/kg (n = 24)</th>
<th>High dose, &gt;6 mg/kg (n = 22)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (IQR)</td>
<td>67 (61.5–70)</td>
<td>59.5 (50.3–62)</td>
<td>0.026</td>
</tr>
<tr>
<td>Sex, male</td>
<td>9 (37.5)</td>
<td>13 (59.1)</td>
<td>0.237</td>
</tr>
<tr>
<td>BMI( a,k ), kg/m(^2), median (IQR)</td>
<td>29.6 (27.1–32.4)</td>
<td>22.7 (19.9–26.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>ICU patients</td>
<td>4 (16.7)</td>
<td>2 (9.1)</td>
<td>0.667</td>
</tr>
<tr>
<td>Oncology patients</td>
<td>18 (75)</td>
<td>18 (81.8)</td>
<td>0.725</td>
</tr>
<tr>
<td>Neutropenic(^ b )</td>
<td>13 (54.2)</td>
<td>15 (68.2)</td>
<td>0.378</td>
</tr>
<tr>
<td>Concomitant BSI(^ c )</td>
<td>4 (16.7)</td>
<td>3 (13.6)</td>
<td>1</td>
</tr>
<tr>
<td>Concomitant antibiotics(^ d )</td>
<td>4 (16.7)</td>
<td>4 (18.2)</td>
<td>1</td>
</tr>
<tr>
<td>Intravascular catheter in place during BSI</td>
<td>21 (87.5)</td>
<td>22 (100)</td>
<td>0.235</td>
</tr>
<tr>
<td>Catheter removed</td>
<td>11 (52.4)</td>
<td>5 (22.7)</td>
<td>0.044</td>
</tr>
<tr>
<td>Positive blood culture source catheter only(^ e )</td>
<td>9 (37.5)</td>
<td>17 (77.3)</td>
<td>0.009</td>
</tr>
<tr>
<td>Intravascular catheter</td>
<td>15 (62.5)</td>
<td>5 (22.7)</td>
<td></td>
</tr>
</tbody>
</table>

\( a \)Height was unavailable in five cases in the standard-dose group and four cases in the high-dose group.

\( b \)Defined as an absolute neutrophil count <500 cells/mm\(^3\).

\( c \)Included Klebsiella spp., E. coli, Candida spp. and coagulase-negative staphylococcal species.

\( d \)Included those with in vitro activity and/or synergy against enterococci (e.g. gentamicin, tobramycin, amikacin or tigecycline).

\( e \)Positive blood cultures from a catheter source only either had no peripheral blood culture drawn or the peripheral blood culture was negative.

Table 2. Microbiological outcomes for the primary analysis\(^ a \)

<table>
<thead>
<tr>
<th>Results</th>
<th>Standard dose, ≤6 mg/kg (n = 24)</th>
<th>High dose, &gt;6 mg/kg (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to microbiological cure(^ b ), days, median (IQR)</td>
<td>2 (1–3)</td>
<td>2 (1–2.25)</td>
</tr>
<tr>
<td>Dose, mg/kg, median (IQR)</td>
<td>5.8 (5.35–6)</td>
<td>7.65 (7–8.2)</td>
</tr>
<tr>
<td>MIC, mg/L, median (IQR)</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
</tr>
<tr>
<td>Microbiological cure, no. (%)</td>
<td>20 (83.3)</td>
<td>16 (72.7)</td>
</tr>
<tr>
<td>Time to microbiological cure due to death, no. (%)</td>
<td>0 (0)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Antibiotic switch, no. (%)</td>
<td>4 (100)</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>Duration of daptomycin treatment prior to death, or antibiotic switch, days, mean (SD)</td>
<td>5 (1.2)</td>
<td>2.5 (1.4)</td>
</tr>
</tbody>
</table>

\(^ a \)Comparisons between the standard-dose group and high-dose group were not statistically significant.

\(^ b \)Time to microbiological cure for patients who cleared their bacteraemia; does not include patients who died or switched to an alternative antibiotic.

\(^ c \)Antibiotic switch to another antibiotic with activity against VRE (e.g. linezolid or quinupristin/dalfopristin).
microbiological cure was 2 days in both the standard- and the high-dose group (P=0.967; Figure 2). The subgroup analysis also found that the rate of and time to microbiological cure was also similar for all MIC subgroups (Figure 3).

For the secondary analysis 238 cases of VRE bacteraemia were evaluated. Eleven cases were excluded because a daptomycin MIC was not available. The majority of isolates evaluated were E. faecium isolates, and 18 (7.9%) of 227 isolates were E. faecalis. There were three isolates that could not be identified to species level, but were known to be VRE organisms. The daptomycin MIC distribution for VRE isolates is shown in Table 3. Of the 227 cases, more than 60% of isolates had a daptomycin MIC of 3 or 4 mg/L. There were 11 VRE isolates with MICs \( \geq 4 \) mg/L, ranging from 6 to 96 mg/L. There was no significant difference among the three MIC groups with regard to prior vancomycin exposure (P=0.189; Figure 4).

For our safety analysis, we evaluated CPK concentrations that were measured during daptomycin treatment. CPK concentrations were measured during daptomycin treatment in 11 cases (4 cases in the standard-dose group and 7 cases in the high-dose group). There were no CPK elevations observed during our study.

### Discussion

To the best of our knowledge this was the first study to compare daptomycin dosing strategies (high dose versus standard dose) in relation to MICs for the treatment of VRE bacteraemia. Based on the pharmacodynamic properties of daptomycin, higher doses may achieve target concentrations of 7–25 times an MIC of 3–4 mg/L.\(^\text{15}\) In our single-centre retrospective study we observed a microbiological cure rate of 78.3% with the use of daptomycin, which was similar to previously reported eradication rates ranging from 80% to 97.5%.\(^\text{8–11}\) In this retrospective evaluation of 46 cases we did not observe any difference in time to microbiological cure between the high-dose and standard-dose groups. After further evaluation no difference was observed between or within MIC subgroups. We also found that 61.7% of isolates at our institution had MICs ranging from 3 to 4 mg/L and there was no difference in prior vancomycin exposure between all MIC groups.

We evaluated time to microbiological cure as the primary outcome under the premise that faster bacterial eradication may lead to better clinical outcomes.\(^\text{20–22}\) This may ultimately affect clinical decision making regarding dosing strategies. There were two baseline characteristics that differed between dose groups that may have affected time to microbiological cure. First, positive blood cultures were drawn more often from a catheter source only in the high-dose group, which may have impaired the ability to differentiate infection from catheter colonization. Catheter source only was defined as having either a negative peripheral blood culture or no peripheral blood culture

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**Table 3. Daptomycin MIC distribution for VRE isolates**

<table>
<thead>
<tr>
<th>Organism (no. tested)</th>
<th>( \leq 1.5 )</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>6</th>
<th>( \geq 8 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. faecalis (18)</td>
<td>5 (27.8)</td>
<td>7 (38.9)</td>
<td>3 (16.7)</td>
<td>2 (11.1)</td>
<td>—</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>E. faecium (206)</td>
<td>15 (7.3)</td>
<td>47 (22.8)</td>
<td>70 (34)</td>
<td>64 (31.1)</td>
<td>3 (1.5)</td>
<td>7 (3.4)</td>
</tr>
<tr>
<td>All isolates(^a) (227)</td>
<td>21 (9.3)</td>
<td>55 (24.2)</td>
<td>74 (32.6)</td>
<td>66 (29.1)</td>
<td>3 (1.3)</td>
<td>8 (3.5)</td>
</tr>
</tbody>
</table>

Data are no. (%) of cases.

\(^a\)Three isolates could not be identified to species level, but were known to be VRE organisms.
Figure 4. Cases with vancomycin exposure prior to the first positive VRE blood culture.

Drawn. Second, fewer patients in the high-dose group had catheters removed during daptomycin treatment. Catheters may not have been removed for various reasons: (i) the requirement of a central line for the administration of chemotherapy and/or transfusions; (ii) clinical suspicion that the source of bacteraemia was through gastrointestinal translocation; or (iii) fast eradication rates (61% of cases had bacterial eradication occur within 3 days of daptomycin initiation). Sources of bacteraemia were not collected in this study, but, based on the neutropenic oncology population, common sources of bacteraemia are gastrointestinal translocation or catheter-related infection.

Baseline characteristics were also unbalanced in regard to age and body mass index (BMI), which may reflect concerns about using high doses of daptomycin in specific populations. The standard-dose group had older patients (median age 67 years) and patients with greater BMIs (median 29.6 kg/m²) compared with the high-dose group (median age 59.5 years and median BMI 22.7 kg/m², \( P \leq 0.026 \)). A recent safety analysis by Figueroa et al. observed that CPK elevations occurred more often in obese patients, but could not determine whether BMI was an independent risk factor. Since patients were not randomized to daptomycin dose groups, physicians may have chosen a more conservative dosing strategy in obese and older patients based on concerns about adverse events. Also, higher doses of daptomycin may have been chosen depending on the patient’s severity of disease. The median doses were 5.8 and 7.65 mg/kg for the standard-dose and high-dose groups, respectively. Due to non-randomized dosing groups, there were patients with similar doses (e.g. 6.6 and 6.4 mg/kg) that were placed in different dose groups, which may have biased our results.

The distribution of daptomycin MICs for VRE isolates in this study was considerably different compared with the literature. Previous data have described up to a 20% incidence of VRE isolates with an MIC of 4 mg/L, while the incidence of MICs ranging from 3 to 4 mg/L in this study was 61.7%. Our institution has a large oncology programme and these patients are generally prone to infections caused by resistant pathogens due to their immunosuppression and exposure to broad-spectrum antibiotics. Whether or not this patient population impacts our daptomycin MIC distribution is unknown. Previously published studies included various North American institutions; however, patient populations were not described.

Recent data have suggested that methicillin-resistant \( S. aureus \) (MRSA) and vancomycin-intermediate \( S. aureus \) (VISA) organisms may have increased daptomycin MICs with prior vancomycin exposure. One of the proposed mechanisms of vancomycin resistance is bacterial cell wall thickening following vancomycin exposure. Given that daptomycin and vancomycin exert their activity on the bacterial cell wall and cell membrane, respectively, and are both relatively large molecules, it has been proposed that daptomycin’s activity may also be decreased due to thickening of the bacterial cell wall. Although mechanisms have been suggested for decreased daptomycin susceptibility for MRSA and VISA, there have not been any published studies evaluating the effect of prior vancomycin use on daptomycin susceptibility for VRE organisms. In studies evaluating clinical and microbiological outcomes in patients with previous vancomycin use, the definition of vancomycin exposure varied from a minimum of a one-time dose of intravenous vancomycin to a minimum of 7 continuous days of intravenous vancomycin within the last 30 days from the first positive blood culture. Since there is no standardized definition for vancomycin exposure, the investigators chose a minimum of 3 days of intravenous and/or oral vancomycin use within the last 30 days from the first VRE blood culture to define vancomycin exposure. We included oral vancomycin in our definition because oncology patients colonized with VRE may have gastrointestinal translocation as a source of bacteraemia. From our results, we were not able to detect any difference in daptomycin susceptibility based on previous vancomycin exposure.

There were several limitations to our single-centre study, primarily due to the retrospective study design. A power analysis performed after data collection revealed that 73 cases would have been needed to achieve 80% power to detect a 1 day difference in time to microbiological cure between the two dose groups and a larger sample size would have been needed to further analyse the MIC subgroups. Also, the frequency with which blood cultures were drawn was not standardized. We excluded cases where repeat blood cultures were drawn >3 days after a prior positive blood culture to decrease the variability between the actual time of bacterial eradication and the time the first negative blood culture was drawn. A maximum of 3 days was chosen by our study team based on guidelines for the treatment of catheter-related bloodstream infections. We also included 22 cases that only had one positive blood culture, which may have been considered contamination, and two cases where bacterial clearance occurred during the same day that daptomycin was initiated, which may have been attributable to a transient bacteraemia or catheter colonization. Lastly, we included intensive care unit admission as the sole assessment of disease severity and did not include any standardized baseline disease severity scores to fully assess the patient population being evaluated.

Conclusions

Based on the results from this retrospective study, we did not observe a difference in time to microbiological cure between patients who received daptomycin doses >6 mg/kg versus doses ≤6 mg/kg for the treatment of VRE bacteraemia. Although no difference was observed, there were various limitations that may have influenced our results, including an underpowered
analysis and differences in baseline characteristics such as catheter removal. Whether infections caused by VRE isolates with daptomycin MICs of 3–4 mg/L are more difficult to treat remains unclear. Prior vancomycin exposure did not appear to influence daptomycin MICs in our sample. Further prospective studies are needed to fully understand the use of various daptomycin dosing schemes in the treatment of VRE bacteraemia and the impact of vancomycin on daptomycin MICs.

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D. M. has received an honorarium for providing an educational lecture for Cubist. The other authors have none to declare.

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