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Outcomes with daptomycin in the treatment of *Staphylococcus aureus* infections with a range of vancomycin MICs

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Objectives: Recent recommendations by the Infectious Diseases Society of America for the treatment of *Staphylococcus aureus* suggest the use of alternative agents when vancomycin MIC values are ≥2 mg/L. This study examines the outcome of patients treated with daptomycin for *S. aureus* infections with documented vancomycin MICs.

Patients and methods: All patients with skin, bacteraemia and endocarditis infections due to *S. aureus* with vancomycin MIC values in CORE 2005–08, a retrospective, multicentre, observational registry, were studied. The outcome (cure, improved, failure or non-evaluable) was the investigator assessment at the end of daptomycin therapy. Success was defined as cure or improved.

Results: Five hundred and forty-seven clinically evaluable patients were identified with discrete vancomycin MIC values [MIC <2 mg/L: 451 (82%); MIC ≥2 mg/L: 96 (18%)]. The vancomycin MIC groups were well matched for patient characteristics, types of infections, first-line daptomycin use (19%) and prior vancomycin use (58%). Clinical success was reported in 94% of patients. No differences were detected in the daptomycin success rate by the vancomycin MIC group overall or by the infection type. A multivariate logistic regression also failed to identify vancomycin MIC as a predictor of daptomycin failure. Adverse event (AE) rates were not different when analysed by MIC group; both groups had ∼17% of patients with one AE.

Conclusions: In this diverse population, daptomycin was associated with similar outcomes for patients, regardless of whether the vancomycin MIC was categorized as <2 or ≥2 mg/L. Further studies are warranted.

Keywords: lipopeptides, *S. aureus*, CORE

Introduction

Increasing data suggest that vancomycin is losing its clinical and microbiological potency against *Staphylococcus aureus*. Vancomycin efficacy is complicated by several findings. Multiple published reports have noted a shift to higher vancomycin MIC values within the accepted susceptibility range for *S. aureus* and intermethod variability has been noted.[1–3] The susceptibility breakpoint for vancomycin is defined as ≤2 mg/L by the CLSI and the FDA. However, this still results in a nearly 100% susceptibility rate and does not allow for the microbiological identification of patients at a greater risk of failure.[4] Additionally, there have been a number of reports of vancomycin treatment failures for methicillin-resistant *S. aureus* (MRSA) isolates with vancomycin MIC values of ≥2 mg/L compared with ≤1 mg/L.[5–8]

A common response to these findings has been to utilize higher vancomycin doses and trough serum concentrations, to increase the likelihood of achieving antibiotic exposures necessary for treatment. However, there are limited data to support the safety of sustained trough serum vancomycin concentrations of 15–20 mg/L, and several additional studies have suggested that outcomes observed in patients with higher vancomycin trough levels were no better than those seen in patients with lower trough values.[9–12] Vancomycin activity is best predicted by the AUC/MIC ratio and pharmacodynamic modelling suggests that microbiological success or clearance is optimized when the vancomycin AUC/MIC ratio exceeds 400.[13–15] Despite

vancomycin trough levels of 15–20 mg/L, the achievement of an AUC/MIC ratio of >400 is unlikely for isolates with a vancomycin MIC of ≥2 mg/L. Therefore, it has been recommended that alternative therapies should be considered.[13]

Daptomycin is a cyclic lipopeptide antimicrobial agent with extensive Gram-positive activity, including activity against many vancomycin-resistant organisms. It is indicated for complicated skin and skin structure infections (cSSSIs), as well as bacteraemia and right-sided endocarditis caused by MRSA and methicillin-susceptible *S. aureus* (MSSA). Data exist that higher vancomycin MIC values may correlate with similar shifts in the distribution of MIC values of daptomycin.[16–20] Although the mechanism is unclear, vancomycin-intermediate *S. aureus* (VISA) isolates have variable susceptibility to daptomycin, but these isolates remain relatively uncommon.[4,21,22] Recent data suggest that daptomycin maintains bactericidal activity against *S. aureus* with reduced susceptibility to vancomycin, including heterogeneous VISA (hVISA) strains.[23] The clinical relevance of these alterations in susceptibility has yet to be investigated.

The purpose of this analysis is to examine the clinical outcomes in daptomycin-treated patients with *S. aureus* skin, bacteraemia and endocarditis infections with vancomycin MIC values of <2 mg/L versus those with MIC values of ≥2 mg/L.

Patients and methods

CORE® (Cubicin® Outcomes Registry and Experience) is a multicentre, retrospective, observational study that collects the post-marketing experience with daptomycin in the USA. Data collection began in November 2003 and is ongoing. This study collects patient information, including demographics, infections, treatments and outcomes at the end of daptomycin therapy. This study was conducted in compliance with Institutional Review Board (IRB) requirements at each site. After IRB approval, clinical information was collected from medical records by trained study investigators, most commonly an infectious disease physician along with a research nurse or clinical pharmacist. A standardized case report form was used to collect patient information.

Each year, sites either randomly selected (CORE 2005–06) or reported on sequentially treated (CORE 2007–08) patients receiving daptomycin at any dose or duration from those treated at each study site. The sites were monetarily compensated for participation. The type of infection was determined by the principal investigator according to clinical signs and symptoms, and microbiology culture reports. Patients were not excluded for any underlying disease, such as severe renal or hepatic impairment, or immunosuppression. In the subset assessed in the current analysis, we included patients with a positive culture from any site for *S. aureus* with a reported vancomycin MIC value that could be categorized as <2 or ≥2 mg/L. Additionally, the analysis was restricted to those patients evaluable for efficacy for skin, bacteraemia or endocarditis, classified as cure, improved or failure over the time frame from January 2005 to December 2008.

The CORE methods from the first year of the study have previously been published.[24] From 2005 to present, multiple changes have been implemented, including the collection of more detailed patient and infection details, susceptibility data, and adverse events (AEs).

Data collection for the CORE database

Both clinical and microbiological data were collected. Demographic data collected included: age ranges (e.g. 18–30 years etc.); gender; weight; renal function [creatinine clearance (CL_{CR}) range] at daptomycin initiation and at the end therapy (e.g. <30 or ≥30 mL/min); type of dialysis, if applicable; underlying diseases; patient location 48 h prior to daptomycin initiation; prior antibiotic therapy; infection details; outcomes; discharge information; efficacy; and safety assessments. Culture results from before or shortly after initiation of daptomycin were reported. Susceptibility data for multiple antibiotics, including vancomycin, were collected, if available, based on each institution's individual local methods. Isolates were not tested in a central laboratory. Details of daptomycin and other antibiotic therapy collected include: daptomycin initial and final dose; dosing interval; and length of therapy. Other antibiotic therapy details included prior, concomitant and follow-up antibiotics, and discontinuation reason. Time to clinical response (investigators documented the number of days that passed before there was a clinical improvement based on signs and symptoms), as well as safety and efficacy assessments were documented, as described below.

Efficacy assessment

Treatment responses were assessed by the investigator at the completion of daptomycin therapy. Patients were considered evaluable for efficacy analysis (clinically evaluable) if the clinical response to daptomycin was classified as cured, improved or failed. The clinically evaluable population excluded those classified as non-evaluable. Cured was defined as 'clinical signs and symptoms are resolved and/or no additional antibiotic therapy necessary or infection cleared with a negative culture result reported at end of therapy'. The infection was classified as improved if there was 'partial resolution of clinical signs and symptoms and/or additional antibiotic therapy necessary at end of therapy'. Failed was defined as 'inadequate response to therapy; resistant, worsening or new/recurrent signs and symptoms; a need for a change in antibiotic therapy; or positive culture result reported at the end of therapy'. The infection response was classified as non-evaluable if the investigator was 'unable to determine response at end of therapy because record did not contain adequate information'. Beginning in 2007, when CORE began collecting reasons for non-evaluability, the most frequent reason for a non-evaluable determination was 'lost to follow-up' (transfer to another institution to complete daptomycin therapy). Treatment success was defined as the sum of cured and improved outcomes.

Safety assessment

All patients who received daptomycin were eligible for the safety analysis. Throughout the daptomycin treatment period and up to 30 days following the last dose of daptomycin, changes in physical findings, clinical signs and symptoms, and laboratory values consistent with serious and non-serious AEs were to be documented. The AE was serious if it resulted in any of the following: death; was life-threatening; disability/incapacity; hospitalization; congenital anomaly/birth defect; or an important medical event. The following additional information was collected for all AEs: day of onset relative to daptomycin start; severity (mild, moderate or severe); relationship to daptomycin (not related or possibly related); action taken with daptomycin (none, stopped permanently, dose reduced or stopped temporarily); other action taken (none, concomitant medication, procedure performed or other); outcome (resolved, resolved with residual effects, death, ongoing or unknown); and resolution (day of resolution or day of last contact relative to daptomycin start).

Statistical analysis

Clinical outcome as reported was the outcome of interest. Categorical variables were compared with the χ^2 or Fisher exact test, as appropriate. The multivariate logistic model was conducted using the methodology previously described.[25] In that analysis, all CORE patients from 2005 to 2007 with infections due to *S. aureus* were studied and four variables

were found to be associated with failure: endocarditis; bacteraemia; initial CL_{CR} <30 mL/min; and diabetes. Therefore, these pre-determined risk factors were used in the analysis performed in this study. Statistical significance was defined as $P<0.05$. All statistics were performed using JMP, version 7.0, or SAS v.9.1.3 (SAS Institute, Cary, NC, USA).

Results

Patient demographics and characteristics

Of 4554 patients in CORE 2005–08, there were 1370 patients with skin, bacteraemia or endocarditis infections due to *S. aureus*. Eight hundred and fifty-five patients had a vancomycin MIC reported; 688 patients could be categorized into vancomycin MIC groups of <2 or ≥2 mg/L. Patients with a reported MIC of ≤2 mg/L ($n=167$) could not be placed into these two categories and were excluded. Of the 688 patients with categorizable vancomycin MICs, 547 (80%) patients were evaluable for clinical outcome (cure, improved or failure) and serve as the population for all analyses. The patients excluded for vancomycin MICs of ≤2 mg/L and those non-evaluable for outcome had higher rates of bacteraemia and endocarditis, and factors associated with these diagnoses, such as daptomycin dose ≥6 mg/kg, CL_{CR} <30 mL/min and receipt of daptomycin in an intensive care unit (ICU). The distribution of reported MIC values is shown in Table 1. There were 451 isolates (82%) with a vancomycin MIC of <2 mg/L, of which 72% were MRSA, and the vancomycin MIC ≥2 mg/L group consisted of 96 (18%) isolates, of which 78% were MRSA. Daptomycin MIC values were rarely reported; 64 (12%) patients had a daptomycin *S. aureus* MIC (61 were susceptible to daptomycin and 3 had daptomycin MICs >1 mg/L).

Baseline demographics and characteristics of patients who received daptomycin are shown in Table 2. The characteristics appeared similar between the vancomycin MIC groups. The majority of patients were older than 50 years of age, 51% were male, 17% had an initial CL_{CR} of <30 mL/min and 10% were on dialysis. The median duration of daptomycin therapy was 13 days (minimum 1, maximum 243) overall; 14.5 days (minimum 1, maximum 83) for bacteraemia or endocarditis patients and 13 days (minimum 1, maximum 243) for skin infection patients. The median daptomycin dose was 4 mg/kg for cSSSIs and uncomplicated skin and skin structure infections (uSSSIs), and 6 mg/kg for endocarditis and bacteraemia; no difference in the mean, median or percentage of patients receiving ≥6 mg/kg was seen between the vancomycin MIC groups.

The infection types are summarized in Table 3. The predominant indication was cSSSIs, while bacteraemia and endocarditis comprised 30% of the population.

A majority of patients (442/547, 81%) received antibiotics prior to beginning daptomycin. Of those receiving prior antibiotics, the most common were: vancomycin ($n=255$, 58%); clindamycin ($n=43$, 10%); piperacillin/tazobactam ($n=37$, 8%); trimethoprim/sulfamethoxazole ($n=36$, 8%); linezolid ($n=35$, 8%); and ceftriaxone ($n=32$, 7%). The prior antibiotic therapy was reported as clinically failing in 194/442 (44%) patients. Of those patients receiving prior vancomycin, 86 of 255 patients (34%) switched due to failure. Vancomycin dosing was not collected; however, the use, types and response to prior antibiotics were similar between the vancomycin MIC groups.

Forty-seven percent ($n=256$) of patients received concomitant antibiotics with daptomycin. The most common concomitant antibiotic in both vancomycin MIC groups was rifampicin (<2 mg/L: 50/215, 23%; and ≥2 mg/L: 12/41, 29%), followed overall by cefepime ($n=38$, 15%), vancomycin ($n=37$, 14%) and piperacillin/tazobactam ($n=30$, 12%).

Of the 287 patients categorized as improved, 187 (65%) received antibiotics after daptomycin that had presumed activity against the strain of *S. aureus* cultured. In these patients, the most common reasons for using a follow-up antibiotic were switch to oral antibiotic ($n=112$), switch to less expensive antibiotic ($n=23$) and narrowed spectrum ($n=11$).

Efficacy

Clinical success was reported in 94% of patients (42% cured and 52% improved). No differences were detected in the daptomycin success rate by the vancomycin MIC group overall or by the infection type (Figure 1). It is interesting to note that the proportion of patients identified as cured was higher in the vancomycin ≥2 mg/L group compared with the <2 mg/L group for bacteraemia, cSSSIs and uSSSIs. A lower percentage of endocarditis patients in the ≥2 mg/L group were reported as cured; however, this comparison is based on a small number of patients in this vancomycin MIC group. Daptomycin outcomes for *S. aureus* with vancomycin MICs >2 mg/L ($n=11$) were: >2 mg/L, cSSSIs cured ($n=2$) and uSSSIs cured ($n=5$); 3 mg/L, bacteraemia improved; 4 mg/L, cSSSIs cured ($n=2$); and >256 mg/L, bacteraemia cured.

Daptomycin was used as first-line therapy with a 96% success rate overall (45% cured, 51% improved), and the efficacy was similar in the <2 mg/L group (84/86, 98%) and ≥2 mg/L group (15/17, 88%) ($P=0.13$, Fisher's exact test). The concomitant use of rifampicin and gentamicin predominantly occurred in patients with bacteraemia or endocarditis. Combination treatment with rifampicin success rates were: (i) in bacteraemia,

Table 1. Distribution of MIC values

Vancomycin MIC group [*n* (%)]																
<2 mg/L ($n=451$)											≥2 mg/L ($n=96$)					
≤0.2	≤0.5	<0.5	=0.5	=0.75	≤1	<1	=1	=1.5	<2	>1[a]	=2	≥2	>2	=3	=4	>256
1 (<1)	64 (14)	41 (9)	1 (<1)	1 (<1)	208 (46)	32 (7)	24 (5)	3 (<1)	76 (17)	2 (2)	82 (85)	1 (1)	7 (7)	1 (1)	2 (2)	1 (1)

MICs are the test results as reported in the patient records.
[a]Included in the ≥2 mg/L group given that the next higher 2-fold dilution would be 2 mg/L.

Table 2. Demographics

Characteristic	Vancomycin MIC group		
	MIC <2 mg/L (n=451), n (%)	MIC ≥2 mg/L (n=96), n (%)	all (n=547), n (%)
Male	226 (50)	52 (54)	278 (51)
Age group (years)			
≤50	193 (43)	41 (43)	234 (43)
51–65	147 (33)	27 (28)	174 (32)
≥66	111 (25)	28 (29)	139 (25)
Location 2 days before daptomycin administration			
community	233 (52)	42 (44)	275 (50)
hospital	202 (45)	50 (52)	252 (46)
nursing home/extended care	14 (3)	4 (4)	18 (3)
unknown	2 (0.4)	—	2 (0.4)
Daptomycin administration settings[a]			
inpatient	329 (73)	63 (66)	392 (72)
outpatient	241 (53)	59 (61)	300 (55)
Underlying diseases[b]			
hypertension	185 (41)	38 (40)	223 (41)
diabetes mellitus	142 (31)	31 (32)	173 (32)
other cardiovascular disease[c]	103 (23)	19 (20)	122 (22)
cancer or transplant	51 (11)	14 (15)	65 (12)
chronic renal failure	47 (10)	10 (10)	57 (10)
peripheral vascular disease	33 (7)	10 (10)	43 (8)
anaemia/all haematological disease	33 (7)	8 (8)	41 (7)
chronic obstructive lung disease	33 (7)	8 (8)	41 (7)
ICU stay during daptomycin	52 (12)	10 (10)	62 (11)
CL_{CR} <30 mL/min at start of daptomycin	81 (18)	14 (15)	95 (17)
Dialysis at start of daptomycin	41 (9)	11 (11)	52 (10)

ICU, intensive care unit; CL_{CR}, creatinine clearance.
[a]Patients may have both inpatient and outpatient daptomycin therapy.
[b]Patients may have more than one underlying disease; only underlying diseases ≥7% overall are shown.
[c]Includes acute coronary syndromes, cardiac arrhythmias, valvular heart disease, congestive heart failure and unspecified cardiovascular disease.

Table 3. Infection types

Infection	Vancomycin MIC group		
	MIC <2 mg/L (n=451)	MIC ≥2 mg/L (n=96)	all (n=547)
cSSSIs	222 (49)	41 (43)	263 (48)
uSSSIs	103 (23)	21 (22)	124 (23)
Bacteraemia	107 (24)	28 (29)	135 (25)
Endocarditis	19 (4)	6 (6)	25 (5)

For patients with more than one reported infection type caused by *S. aureus*, they were assigned to a single category by the following hierarchy: endocarditis>bacteraemia>complicated skin and skin structure infections (cSSSIs)>uncomplicated skin and skin structure infections (uSSSIs).

19/22 (86%) with rifampicin versus 104/113 (92%) with no rifampicin (P=0.4); and (ii) in endocarditis, 8/11 (73%) with rifampicin versus 11/14 (79%) with no rifampicin (P=1.0). Patients receiving rifampicin for bacteraemia or endocarditis were older with greater renal dysfunction than those not receiving rifampicin. Gentamicin success rates in bacteraemia were 5/6 (83%) with gentamicin versus 118/129 (91%) with no gentamicin (P=0.4) and in endocarditis were 5/8 (63%) with gentamicin versus 14/17 (82%) with no gentamicin (P=0.3). Gentamicin patients were older and received daptomycin in an ICU more often, but had a lower incidence of reduced initial renal function than those not given gentamicin.

Both MIC groups received vancomycin prior to daptomycin at similar rates and prior use of vancomycin did not have an effect on the daptomycin success rates (238/255, 93%; 41% cured and 52% improved) compared with those receiving a

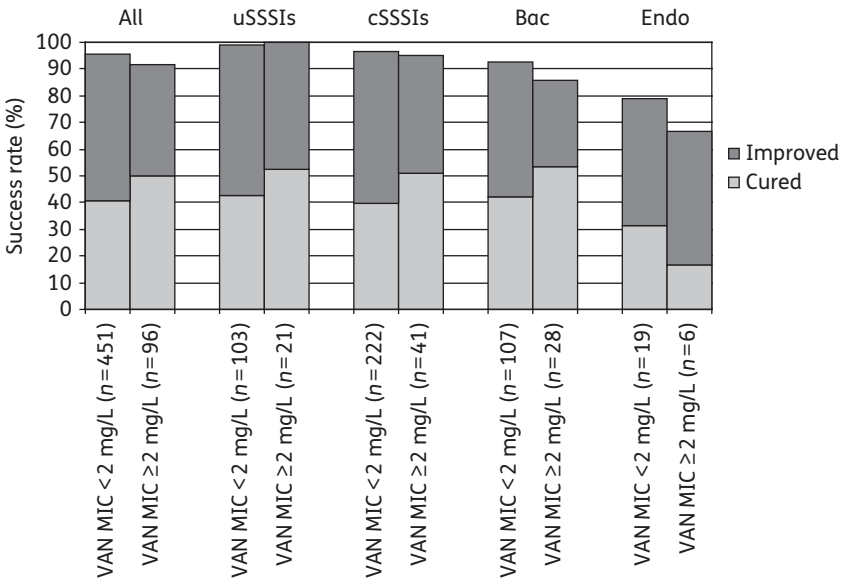

Figure 1. Clinical outcomes with daptomycin. For patients with more than one reported infection type caused by *S. aureus*, they were assigned to a single category by the following hierarchy: endocarditis (Endo) > bacteraemia (Bac) > complicated skin and skin structure infections (cSSSIs) > uncomplicated skin and skin structure infections (uSSSIs).

prior non-vancomycin regimen (179/187, 96%; 43% cured and 53% improved) ($P=0.3$, χ^2 test). In addition, in patients receiving prior vancomycin, clinical success rates were similar by MIC group: <2 mg/L, 198/211 (94%) and ≥2 mg/L, 40/44 (91%) ($P=0.5$, Fisher's exact test). The percentage of patients failing prior vancomycin therapy was similar in the two vancomycin MIC groups. However, in the group of patients receiving prior vancomycin, the daptomycin success rate was greater in patients who had not failed vancomycin therapy [164/169 (97%) non-failures versus 74/86 (86%) failures; $P=0.0009$, χ^2 test] and was seen in both MIC groups. However, the vancomycin failure group had higher incidences of several underlying diseases (immunosuppression, acute renal failure and cardiac arrhythmias) and a higher rate of initial CL_{CR} <30 mL/min (29% versus 15%; $P=0.01$, Fisher's exact test), which has been identified as an independent predictor of failure in CORE patients with *S. aureus*.[25]

The crude analysis of failure for the vancomycin MIC group ≥2 mg/L compared with <2 mg/L resulted in: odds ratio (OR)=1.86; 95% confidence interval (CI), 0.8–4.3; $P=0.15$. A previous analysis identified four variables (endocarditis, bacteraemia, initial CL_{CR} <30 mL/min and diabetes) that were independently associated with daptomycin failures.[25] After controlling for these factors, the results for MIC group were essentially unchanged: OR=1.62; 95% CI, 0.6–4.2; $P=0.32$. Only endocarditis (OR=8.24; 95% CI, 2.4–27.8; $P=0.0007$) and initial CL_{CR} <30 mL/min (OR=2.66; 95% CI, 1.1–6.4; $P=0.03$) remained predictive of daptomycin failure. The clinical outcomes did not differ among the vancomycin MIC group of ≥2 mg/L compared with the <2 mg/L group.

Safety

Safety was assessed primarily as an indicator of the comparability of the vancomycin MIC groups. AEs were reported in 80 (15%) patients overall. AE rates were not different when analysed by MIC group: <2 mg/L group (65/451, 14.4%) and ≥2 mg/L group (15/96, 15.6%) ($P=0.8$, Fisher's exact test). Forty-two AEs were reported in 35 (6%) patients and were classified by the sponsor as possibly related to daptomycin. Two of these AEs (asthenia and rhabdomyolysis) in two (0.4%) patients were assessed as meeting regulatory criteria for seriousness; all resolved. There was no difference in mortality by MIC group: <2 mg/L group (10/451, 2.2%) and ≥2 mg/L group (2/96, 2.1%) ($P=1.0$, Fisher's exact test). The mortality in the bacteraemia subgroup was 4.4%; <2 mg/L group (4/107, 3.7%) and ≥2 mg/L group (2/28, 7.1%). The mortality in the endocarditis subgroup was 12%; <2 mg/L group (3/19, 15.8%) and ≥2 mg/L group (0/6).

Discussion

Vancomycin has been the mainstay in Gram-positive drug therapy for over two decades. More recently, questions have arisen about its limitations and effectiveness. In 2008, the FDA lowered their recommended vancomycin susceptibility breakpoint to match that of the CLSI, based on evidence of limited success in infections due to *S. aureus* isolates with MICs of >2 mg/L. However, these changes did not address the growing data questioning the adequacy of the drug in isolates within the currently defined susceptible category. Sakoulas *et al.*[7] published data on significantly decreased clinical success rates in MRSA bacteraemia patients with vancomycin MIC values of 1–2 mg/L compared with those with MIC values of ≤0.5 mg/L. In that patient population, clinical success with vancomycin therapy was achieved in 55.6% of patients with isolate MICs of ≤0.5 mg/L versus 9.5% of cases with MICs of 1–2 mg/L ($P=0.01$).[7] However, the study involved patients unresponsive to conventional therapy, including vancomycin, and the

authors warned of inappropriately applying the results to predict treatment failure. Despite the limitations of that study, others have correlated vancomycin MICs in MRSA isolates to diminished outcomes. Several publications have shown increased rates of mortality with MICs of 1.5–2 mg/L when compared with infections caused by lower-MIC isolates.[5,7,8,10,11] Soriano *et al.*[8] concluded that a vancomycin MIC value of 2 mg/L was a significant predictor of mortality. Hidayat *et al.*[10] also demonstrated significantly lower end-of-treatment response rates among their high (1.5–2 mg/L) MIC group (62% versus 85% in the low-MIC group, $P=0.02$). These studies used several different methods, including Etest, agar diffusion and automated systems, to reach similar agreement on the limitations of vancomycin in isolates with measured MICs of 1.5–2 mg/L.

Of greater concern is the potential for the decreasing vancomycin susceptibility to have an impact on daptomycin susceptibility and, ultimately, clinical outcomes. Several small studies describing local trends have shown *in vitro* evidence of a shift in vancomycin MIC values (MIC creep).[1,2] In 2006, Wang *et al.*[2] published the largest study to date, which evaluated >6000 isolates collected over 5 years, describing a vancomycin MIC creep from an average vancomycin MIC value of ≤0.5 mg/L to one of 1 mg/L. In a smaller study of 662 isolates, Steinkraus *et al.*[1] evaluated trends in vancomycin MIC values over a 5 year period. All isolates were susceptible to the tested antibiotics; however, significant increases in the geometric mean MIC values for vancomycin were observed.[1] Data derived in these studies could, however, be biased by the antimicrobial testing method used, since it has been described that there is a lack of correlation between antimicrobial testing methods for vancomycin (i.e. broth microdilution, Etest, MicroScan and Vitek).[26,27] Daptomycin has demonstrated almost complete activity against isolates with various vancomycin MIC values, including MICs of 2 mg/L, hVISA and vancomycin-resistant *S. aureus*.[4] Although daptomycin possesses a different mechanism of action compared with vancomycin, there is a relationship for diminished daptomycin activity against the relatively uncommon VISA population. A recent surveillance study showed that 87% (13/15) of VISA isolates tested were susceptible to daptomycin.[28] Additionally, reports of daptomycin susceptibility changing under vancomycin exposure have been described.[16] However, clinical results are of greatest value and these concerns demonstrate a need for further clarification, which served as the impetus for this study.

In our analysis, the vancomycin MIC for *S. aureus* isolates was not a predictor of daptomycin treatment failure. This finding was consistent across different infection types and in a multivariate model accounting for factors previously determined to be associated with daptomycin failure. Of note, no significant difference was detected in the mortality or response rates in patients receiving daptomycin based on vancomycin MIC grouping. Mortality due to *S. aureus* bacteraemia or endocarditis has been reported to be in the range of 20%–30%.[29,30] The relatively low mortality rate in bacteraemia (4%) and endocarditis (12%) patients may have been impacted by the retrospective data collection, as patients or family were not contacted after discharge to document outcomes. Additionally, the lack of efficacy for daptomycin in patients with pulmonary infections probably resulted in an underrepresentation of patients with this significant predictor of death.[30] Lower success rates were seen for endocarditis patients, underscoring the difficulty in treating this population where appropriate adjunctive surgical therapy for source control is important.[31]

Additionally, prior exposure to vancomycin was not associated with diminished daptomycin outcomes. Moise *et al.*[17] demonstrated that there was an increase in the daptomycin MIC values of MRSA isolated from patients on vancomycin therapy and there have been limited published clinical data on the effect of initial vancomycin treatment on daptomycin efficacy. Fowler *et al.*[31] showed that daptomycin was non-inferior to the standard of care in the treatment of *S. aureus* bacteraemia and right-sided endocarditis. In a subanalysis of all patients with MRSA infections, Rehm *et al.*[32] demonstrated that previous vancomycin treatment did not impact daptomycin success rates. Of the patients randomized to daptomycin, 80% had previous treatment with vancomycin and success rates for daptomycin were comparable for patients with prior vancomycin treatment to those who did not have prior vancomycin.

Although patients that failed prior vancomycin therapy showed significantly lower success rates with daptomycin treatment, this occurred regardless of the MIC group, and was probably influenced by the greater severity of illness and potentially higher bacterial load in this subset. Despite this statistical significance, success rates were still >85% for the group failing prior vancomycin therapy and the overall success rate for all patients was in the 90th percentile.

Limitations of our study include its retrospective design and the potential for patient selection bias. Despite positive outcomes with daptomycin, patient outcome was limited to an assessment at the end of daptomycin therapy and the occurrence of relapsing infection should not be discounted. The majority (71%) of patients in this study had skin and skin structure infections, and recurrence rates may be lower than with systemic infections. However, the remaining patients had either bacteraemia or endocarditis and in a prospective evaluation of *S. aureus* bacteraemia, Fowler and colleagues found recurrent *S. aureus* infection in 70 of 724 patients (9.6%) within 3 months of initial positive blood cultures.[33] This is comparable to data from Chang *et al.*[34] that demonstrated a 9.4% recurrence rate within 6 months of initial positive blood cultures in a prospective study of patients with *S. aureus* bacteraemia. The possibility of recurrence must be considered in the evaluation of the success rates in this study. Clinical isolates were not available for follow-up microbiological and molecular analysis. Testing methodologies for MIC values were uncontrolled and based on local practice. However, as previously noted, multiple studies using varied testing methodologies have identified a vancomycin MIC value of 1.5–2 mg/L as a risk factor for vancomycin failure. Confirmatory, standardized MIC values for both daptomycin and vancomycin would provide additional information; however, the shipping, freeze–thaw and passaging of isolates often alters the vancomycin MIC values. Additionally, if the isolates were available for testing, the underlying genotypic and phenotypic determinants could have been determined, which would be beneficial for epidemiological purposes; though these data are not available to physicians when making clinical decisions. Further data on daptomycin MICs would have been valuable in assessing the relationship with vancomycin MICs. Daptomycin MICs were only documented in 12% of patients; this low rate of reporting may be due to the retrospective nature of collecting data and the selective reporting of

susceptibility results on microbiological reports. Additionally, some institutions do not conduct comprehensive daptomycin MIC testing, since resistance to daptomycin in wild-type strains is rare. This patient population represents contemporary daptomycin use with its inherent prescribing variability and for patient types often excluded from prospective study designs.

The proportion of vancomycin MIC values ≥2 mg/L reported in this study was 17.6% (96/547), which is higher than what has been reported in other studies.[35] This could be an advantage of this retrospective study, where a selection bias for daptomycin therapy resulted in a higher proportion of isolates with vancomycin MIC values of ≥2 mg/L. It provides valuable data on these *S. aureus* isolates with higher vancomycin MICs and provides a significant insight into a potential alternative therapy.

Despite the aforementioned limitations, this study summarizes the largest dataset to date on daptomycin use in patients with a broad range of vancomycin MIC measurements for *S. aureus*. These data suggest that daptomycin is an effective and well-tolerated alternative to current treatment options, including vancomycin, in patients with bacteraemia, endocarditis or skin infections for isolates with vancomycin MIC values of ≥2 mg/L.

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