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A Retrospective Comparison of Daptomycin Thrice-Weekly versus Q48H Dosing in Hemodialysis Patients with Vancomycin-Resistant Enterococcus (VRE) or Methicillin-Resistant *Staphylococcus aureus* (MRSA) Bacteremia

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Abstract Background. Multi-drug resistant bacteria are a growing concern in healthcare. Daptomycin is being used with increasing frequency in the treatment of vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremias in hemodialysis (HD) patients. Thrice-weekly dosing of daptomycin in this population would allow for coordination of dosing with common outpatient HD schedules. The aim of this study is to determine if thrice-weekly dosing of daptomycin is equivalent to dosing every 48 hours in patients receiving chronic intermittent hemodialysis. Equivalence will be assessed with regard to microbiological cure, clinical cure, hospital length of stay, and mortality. Methods. All patients with positive blood cultures who received at least one dose of daptomycin between January 1st 2009 and December 31st 2010 at Indiana University Health Methodist and University Hospitals were identified. Adult patients with end-stage renal disease on a stable thrice-weekly hemodialysis regimen, confirmed VRE or MRSA bacteremia, and at least three doses of inpatient daptomycin therapy were enrolled in the study. Results. Twelve patients met criteria for inclusion in this study. Nine received daptomycin every 48 hours for the treatment of bacteremia, and three received daptomycin thrice-weekly after dialysis. There was no difference in time to clearance of blood cultures between the Q48H and thrice-weekly groups (2.11±2.15 days vs. 4.33±4.16 days; p=0.241). Length of hospital stay was not statistically significantly different between the two groups (22.8 days vs. 14.9 days; p=0.065). Conclusions. Thrice-weekly dosing of daptomycin may be effective for the treatment of bacteremia in hemodialysis patients.

Keywords Bacteremia, Daptomycin, Hemodialysis, MRSA, VRE

1. Introduction

Multi-drug resistant bacteria are a growing concern in healthcare. Two increasingly problematic gram-positive pathogens are methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE).

Greater than 50% of *S. aureus* isolates are considered methicillin-resistant, and vancomycin remains the first-line treatment for MRSA infections.[1-3] The Clinical Laboratory and Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) define strains with a minimum inhibitory concentration (MIC) of $\leq 2\text{mCg/mL}$ as susceptible to vancomycin, meaning there is a high likelihood of therapeutic success if this agent is used. However, available literature indicates that higher MICs (*i.e.* $\geq 1.5\text{mCg/mL}$) are associated with increased risk of treatment failure in bacteremia.[2,3] Thus, patients with infections due to MRSA with elevated vancomycin MICs may be candidates for treatment with alternative antibiotics, such as daptomycin.

Approximately 95% of VRE strains identified in the United States are *Enterococcus faecium*. Isolates of *Enterococcus* with MICs of $> 4\text{mCg/mL}$ have a high likelihood of treatment failure and are thus considered resistant to vancomycin. These organisms also possess intrinsic resistance to many other antibiotic classes, and treatment options are limited to linezolid, quinupristin/dalfopristin, and daptomycin.[4]

General risk factors for MRSA and VRE bacteremia include previous exposure to broad-spectrum antibiotics, prolonged hospitalization (>5 days), admission to the intensive care unit, and the presence of invasive devices.[5,6]

In addition to frequently possessing these risk factors, hemodialysis (HD) patients are often immunocompromised and repeated exposure to healthcare settings increases their likelihood of developing MRSA or VRE bacteremia requiring treatment.

According to the package insert, the recommended dosing of daptomycin for the treatment of bacteremia in patients receiving HD is 6mg/kg IV every 48 hours.[7] In contrast, the Infectious Disease Society of America recommends administering 6mg/kg IV after each dialysis session.[8] A growing body of pharmacokinetic data exists to support post-dialysis dosing, but clinical evidence is limited. If effective, thrice-weekly post-dialysis dosing could provide significant benefits including completion of therapy in the outpatient setting, improved convenience for both the patient and the healthcare provider, and significant cost savings.

The objective of this study was to assess clinical outcomes in chronic hemodialysis patients with MRSA or VRE bacteremia treated with thrice-weekly compared to Q48H daptomycin and to determine if these two dosing schedules may be equivalent in this population.

2. Subjects and Methods

2.1. Selection Criteria

All patients who received at least one dose of daptomycin between January 1st 2009 and December 31st 2010 at Methodist and Indiana University Hospitals were identified. Subjects were included if they were at least 18 years old, had end-stage renal disease on a stable thrice-weekly HD regimen, had an MRSA or VRE bacteremia confirmed by at least one positive blood culture, received three or more doses of daptomycin on one of the study schedules, and had at least three recorded white blood cell (WBC) counts. Subjects who had a polymicrobial (gram-positive and gram-negative) bacteremia or clearly identifiable concomitant MRSA pneumonia were excluded from the study. Subjects were also excluded if they had received daptomycin within 30 days prior to admission or had any deviation from the study regimen. The study was reviewed and approved by the Indiana University-Purdue University Indianapolis/Clarian Institutional Review Board.

2.2. Data Collection

Data were obtained through a retrospective review of electronic medical records. Demographic information included age, gender, height, weight, and comorbidities. Length of hospital stay, in-hospital mortality, identity of the isolate (MRSA or VRE) and its susceptibility (MIC) to vancomycin and daptomycin were also recorded. Clinical indicators of infection, including daily maximum temperature (T_{max}) and WBC count, were tracked. Date of first positive blood culture and first completely negative

blood culture were used to assess microbiologic cure.

2.3. Outcome Measures

The primary outcome of this study was occurrence of microbiological cure (clearance of blood cultures) prior to discharge. Secondary outcomes included occurrence of clinical cure (T_{max} < 38.3°C, WBC < 11.5 cells/mm³) prior to discharge, length of hospital stay, and in-hospital mortality.

2.4. Statistical Analysis.

A Kolmogorov-Smirnov test was used to determine the normality of distribution of the data. Fisher's exact and chi-square tests were used to compare demographic characteristics between cohorts, and Student's t-test was used to compare continuous data. A p-value of less than or equal to 0.05 was considered to indicate a statistically significant difference.

3. Results

Twelve patients met inclusion criteria for this study. Nine subjects received daptomycin every 48 hours for treatment of bacteremia and three received daptomycin thrice-weekly after dialysis. Patient demographic characteristics are shown in Table 1. Of the twelve subjects, nine had VRE, two had MRSA, and one had concomitant VRE and MRSA. The MICs of the isolates to vancomycin and daptomycin are shown in Figures 1 and 2, respectively. Of note, two MRSA isolates had MIC ≤ 1 mg/dL to vancomycin and thus may have been treated effectively with vancomycin. However, one isolate was identified in an individual with a documented vancomycin allergy, and the other was identified concomitantly with VRE. The maximum MIC to daptomycin in the identified organisms was 3 mg/dL.

The mean dose of daptomycin received was 7.8 ± 1.4 mg/kg (based on actual body weight) for the Q48H group, compared to 7.2 ± 1.2 mg/kg for the thrice-weekly group (p=0.517). Doses ranged from 5.8 to 10.6 mg/kg in the Q48H group and from 5.9 to 8.3 mg/kg in the thrice-weekly group.

All patients achieved microbiological cure, defined as the clearance of blood cultures prior to hospital discharge. There was no difference in time from initiation of daptomycin therapy to clearance of blood cultures between the Q48H and thrice-weekly groups (2.11±2.15 days vs. 4.33±4.16 days; p=0.241). All study subjects demonstrated clearance of cultures within five days of initiating daptomycin therapy, with the exception of the single subject infected with both MRSA and VRE who was treated for 9 days before cultures were completely negative (Figure 3). There was no relationship between time to culture clearance and daptomycin dose.

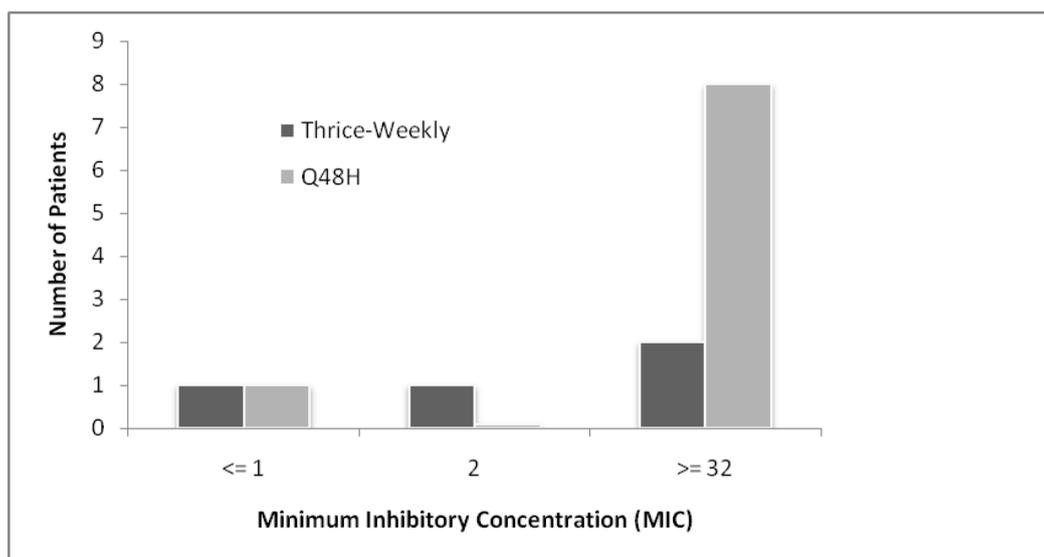
No patients were febrile (T_{max} ≥ 38.3°C) upon initiation of daptomycin, and only three patients in the Q48H group

had a clinically significant WBC count (defined as > 11.5 cells/ mm^3 at the study institutions) on initiation of daptomycin. Length of hospital stay was not significantly different between the two groups, however a trend toward shorter length of stay was noted in the thrice-weekly group (22.8 days vs. 14.9 days; $p=0.065$).

Table 1. Subject Demographic Characteristics

Characteristic	Value	
	Thrice-Weekly	Q48H
Age (years)*	55 (32 – 57)	58 (27 – 64)
Female	0 (0)	5 (55.6)
Male	3 (100)	4 (44.4)
Actual Body Weight (kg)*	81 (60 – 135)	64 (55 – 88)
Dose (mg/kg ABW)*	7.4 (5.9 – 8.3)	7.9 (5.8 – 10.6)
Length of Stay*	14.9 (7.8 – 17.9)	22.8 (5.9 – 75)
In-hospital mortality [#]	0 (0)	0 (0)

*Median (Range), [#]Number (%)

**Figure 1.** Minimum Inhibitory Concentrations (MICs) of Study Isolates to Vancomycin.

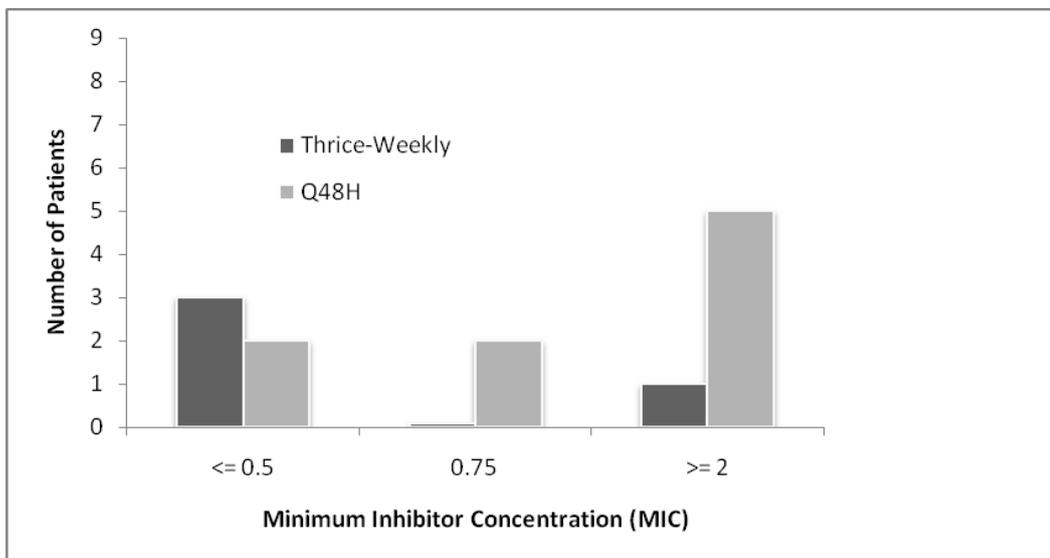


Figure 2. Minimum Inhibitory Concentrations (MICs) of Study Isolates to Daptomycin.

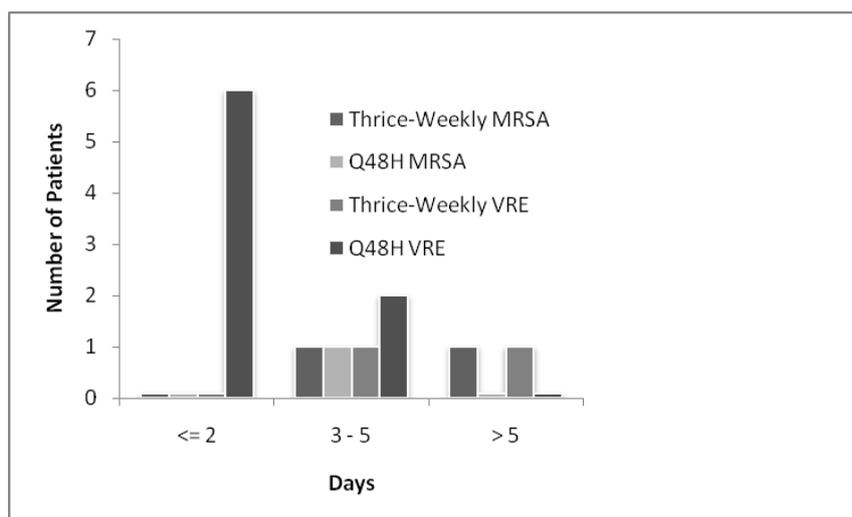


Figure 3. Time to Clearance of Blood Cultures.

4. Discussion

Daptomycin is being used with increasing frequency in the treatment of MRSA and VRE bacteremia in HD patients. Thrice-weekly dosing would provide significant cost savings to the healthcare system. Perhaps more importantly, thrice-weekly dosing of daptomycin would be more convenient for both patients and healthcare providers when treatment can be completed on an outpatient basis. The combination of these benefits has the potential to drastically increase adherence to prescribed antibiotic regimens. However, these potential benefits are of no value if thrice-weekly dosing of daptomycin proves ineffective. Further studies to confirm that thrice-weekly dosing is non-inferior to Q48H dosing for the treatment of bacteremia are thus justified.

Salama and colleagues published a pharmacokinetic study

in which six non-bacteremic HD patients were given a single 6mg/kg IV dose of daptomycin following an HD session.[9] Serial blood samples were collected for 44 hours after the dose and throughout the subsequent session. This data was then used to model trough serum concentrations at 44 and 68 hours after 6mg/kg, 8mg/kg, and 10mg/kg post-HD doses. Based on their results, the authors predicted that HD patients would maintain daptomycin concentrations sufficiently above the MIC of *S. aureus* ($\leq 1\text{mCg/mL}$) and *E. faecium* ($\leq 4\text{mCg/mL}$) at 68 hours after a 6, 8, or 10 mg/kg dose. This suggests that HD patients should be able to receive thrice-weekly post-dialysis doses of daptomycin rather than Q48H, allowing for coordination of dosing with common outpatient HD schedules (e.g., every Monday/Wednesday/Friday).

Patel and colleagues used pharmacokinetic modeling and Monte Carlo simulations in effort to characterize daptomycin

pharmacokinetics in HD patients and identify an ideal dosing regimen for HD patients receiving daptomycin therapy.[10] Blood samples were collected from twelve non-bacteremic HD patients over three consecutive days during the patient's regular dialysis routine. A single dose of daptomycin 6mg/kg IV was administered to each patient on study day 1 after hemodialysis. The mathematic models employed in this study demonstrated that administering daptomycin during or immediately following HD results in pharmacokinetic values similar to those seen in studies of non-dialysis patients. Based on their results, the authors suggest that it may be appropriate to administer a 50% larger daptomycin dose prior to a two day dialysis holiday (i.e. with Friday dialysis in patients receiving HD every Monday/Wednesday/Friday or with Saturday dialysis in patients receiving HD every Tuesday/Thursday/Saturday).

In effort to develop a single, pharmacokinetically-optimized daptomycin dosing regimen for the dialysis population, data from Salama and Patel was pooled along with data from a multiple-dose kinetic study conducted by Benziger et al.[11,12] Results of the combined analysis support the recommendation that administration of standard daptomycin doses during or post-HD on dialysis days, with a 50% dose increase prior to the 72-hour interdialytic period will achieve daptomycin concentrations that most closely resemble exposure to Q24H dosing in non-dialysis patients.

While results of these pharmacokinetic studies suggest a high likelihood of success when daptomycin is administered thrice-weekly with dialysis, clinical evidence is still lacking. The current study found no statistically significant difference in microbiological cure between patients who received daptomycin thrice-weekly after dialysis and those who received the antibiotic on a Q48H regimen. It should be noted that the average daptomycin doses used in these patients were higher than currently recommended (7.7 mg/kg vs. 6mg/kg).

In designing this study, the intent was to assess the time to clinical cure using common indicators of infection: temperature and WBC counts. Despite having documented bacteremia, none of the subjects observed were febrile upon initiation of daptomycin. One possible explanation for this is that hemodialysis alters body temperature regulation, and HD patients may have an altered fever response in the setting of infection.[13] Similarly, only 3 patients in the Q48H group had elevated WBC counts above 11.5 cells/mm^3 at the initiation of daptomycin, possibly due to an overall immunocompromised state and inability to mount an appropriate response to infection. This interesting observation suggests that we may not be able to rely on generally accepted clinical indicators to identify infection or to assess clinical status and cure.

This study has several limitations which must be noted. First of all, the practice of administering daptomycin thrice-weekly after dialysis was a somewhat novel concept at the beginning of the study period. This is believed to be a large contributing factor to the small study population

identified. The retrospective nature of the study inherently eliminates the opportunity to establish a study protocol. Thus, blood cultures were checked and re-checked at the discretion of the provider, and there were no guidelines for standardized dosing of daptomycin. Finally, as discussed previously, the effects of hemodialysis and overall immunocompromised status of patients in this study population make it challenging to assess the impact of treatment on indicators of clinical cure.

The treatment of multi-drug resistant bacteremia in the end-stage renal disease population is often multifactorial and complicated by comorbid conditions and unconventional clinical responses to therapy. While the results of this study cannot establish noninferiority of thrice-weekly daptomycin compared to Q48H dosing, they do provide evidence to support further research.

5. Conclusion

Other studies have aimed to better characterize the pharmacokinetics of daptomycin in hemodialysis patients and determine the most appropriate dosing regimen in this population. To the best of our knowledge, this is the first attempt to compare clinical outcomes in patients treated with thrice-weekly, post-dialysis daptomycin to those of patients treated with every 48 hour dosing. Although our study population was small, the results suggest that the use of more convenient and less costly thrice-weekly dosing may be an appropriate approach for the treatment of bacteremia in patients on hemodialysis.

Conflict of Interest Statement

The authors have had no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated. The results of this study were presented at the 2011 Great Lakes Pharmacy Resident Conference (continuing education presentation) and the 2011 American College of Clinical Pharmacy Annual Meeting (poster).

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