The Efficacy of Daptomycin versus Vancomycin for MRSA Bloodstream Infection in Patients with Impaired Renal Function

A thesis submitted by

Adam Weston, MD

In partial fulfillment of the requirements for the degree of

Master of Science

in

Clinical and Translational Research

TUFTS UNIVERSITY
Sackler School of Graduate Biomedical Sciences

May, 2013

Advisers:

David Snydman, MD

Yoav Golan, MD

Christina Holcroft, ScD

John Griffith, PhD

Abstract

Background: There is an increasing use of daptomycin for Methicillin-resistant *Staphylococcus Aureus* (MRSA) bloodstream infections. However, there has been concern regarding its efficacy in patients with impaired renal function, reflected in a recent package insert change by the FDA. However, this decision was based on a small, post-hoc subgroup analysis and it is unclear whether this is a true association.

Methods: We performed a single center, retrospective cohort study of patients with MRSA bloodstream infection who received at least 3 consecutive days of either vancomycin or daptomycin. Vancomycin treated patients were matched 2:1 with daptomycin patients using a propensity score built to estimate their propensity to receive daptomycin, n=150 total. After matching, additional conditional logistic regression was used to evaluate for outcome of treatment failure (a composite of in hospital mortality, persistent bacteremia, or recurrence) in vancomycin vs. daptomycin treated subjects across various renal functions.

Results: In our multivariable model, neither the usage of daptomycin (OR 0.45, 95% CI 0.11-1.79) nor a GFR of <50 ml/min/1.73m^2 (OR 1.06, 95%CI 0.4-2.86) were significantly associated with treatment failure (Table 3). Additionally, there was no significant interaction between them (p=0.6) indicating that the effect of daptomycin, compared to vancomycin, did not differ significantly in patients with either a GFR greater than or less than 50 ml/min/1.73m^2. Similar non-significant results were seen for the individual outcomes of mortality, persistent bacteremia, and recurrence. In addition, there

was no significant variation of the treatment effect of the use of daptomycin across the stages of chronic kidney disease.

Conclusions: In our study we did not find a significant interaction of renal function with antibiotic choice. However, our sample size was small and smaller effects may be significant in a larger prospective trial.

Acknowledgements

I wish to thank Dr. Jennifer Chow and Dr. Cheleste Thorpe for their assistance in outcome adjudication.

Dr. Weston is supported by the National Institute of Health [2T32AI055412-06]

The project described was supported by the National Center for Research Resources Grant Number UL1 RR025752 and the National Center for Advancing Translational Sciences, National Institutes of Health, Grant Number UL1 TR000073. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Table of Contents

List of tables

Table 6. An analysis of the days of positive blood cultures in all patients and those who did and did not have the outcome of persistent bacteremia. All data are in days +/- SD.

List of Figures

List of abbreviations

MRSA= Methicillin-resistant *Staphylococcus Aureus*

BSI=Bloodstream Infection

MIC=Minimal Inhibitory Concentration

FDA=Food and Drug Administration

CrCl=Creatinine Clearance

MDRD= Modification of Diet in Renal Disease

GFR= Glomerular Filtration Rate

Introduction

1.1 Background

Methicillin-resistant *Staphylococcus Aureus* (MRSA) infections remain a major clinical issue in the United States and worldwide. MRSA caused approximately 90,000 invasive infections per year as of 2005 and MRSA bloodstream infections (BSI) carry a mortality of 25-30% even in the current antibiotic era.[1, 2] For many years vancomycin has been the mainstay of MRSA bloodstream infection treatment. However, recent studies have suggested that daptomycin may be a preferred alternative to vancomycin, particularly in cases of vancomycin clinical failure with elevated vancomycin minimal inhibitory concentrations (MICs). [3]Daptomycin usage in patients with MRSA bacteremia has increased over time, potentially due to this concern with the efficacy of vancomycin. [4] There are some concerns with the use of daptomycin however. In November, 2010 the Food and Drug Administration (FDA) made changes to the package insert of daptomycin warning physicians of a possible decrease in efficacy of daptomycin in patients with moderate renal impairment. [5]This was based on a subgroup analysis of the original phase III MRSA bloodstream infection trial data showing a marked difference in clinical success, as determined by a blinded adjudication committee at the test-of-cure visit 6 weeks after the last dose of antibiotics, in patients with a creatinine clearance (CrCl) of <50 ml/min. The daptomycin treated patients had 14% (2/14) success rate compared to a 41% (7/17) success rate in vancomycin treated patients. [6]

However, this subgroup analysis had only a small number patients in total with a CrCl<50 ml/min. Furthermore, this post hoc analysis excluded patients with a CrCl<30. This has

raised concerns among physicians as to whether there is truly a difference in efficacy in these patients or if this is the result of multiple subgroup analyses and random chance, particularly as the physiologic mechanism of daptomycin's poor performance in patients with impaired renal function is unclear. As the usage of daptomycin increases, especially in patients with an elevated MIC of S. aureus to vancomycin, this clinical question becomes increasingly relevant, particularly as the rate of chronic kidney disease continues to rise among American adults.[7]

We performed a retrospective analysis of patients with a broad range of renal functions receiving either daptomycin or vancomycin to determine the effect of the interaction between the usage of daptomycin and impaired renal function on the outcome of treatment failure (i.e. does the effect of daptomycin vary with renal function compared to vancomycin). Our hypothesis was that the effect of daptomycin as compared to vancomycin was similar regardless of renal function. This was done in a real world setting, more accurately reflecting the current usage of these drugs and a complexity of patients not enrolled in the original randomized trial. We studied a larger number of patients and used propensity score matching to account for potential bias by indication for treatment.

Materials and Methods

2.1 Patient Selection

This was a retrospective cohort study using a previously established database of all patients who developed MRSA bacteremia at a single tertiary care hospital between January 2001 and August 2011. This database contained some outcome, comorbidity, antibiotic use, and microbiologic data but additional chart review needed to be conducted, after propensity score matching, to collect supplementary comorbidity data and outcome data. No patients were excluded due to missing comorbidity or outcome data. To be included in the study patients must have been greater than 18 years old and have had at least one positive blood culture for MRSA. Only first episodes of MRSA BSI were evaluated. Patients must have received either vancomycin or daptomycin for at least 3 consecutive days to be included in the current analysis. Most patients in our clinical setting were switched to daptomycin from vancomycin for a variety of clinical reasons, which were recorded. To be included in our study, patients in the daptomycin group may have received vancomycin for up to 10 days prior to this switch, or longer as long as the ratio of total daptomycin treated days:days of prior antibiotics remained ≥2, indicating that the majority of their treatment was done with daptomycin. Patients were excluded if there was any intravascular foreign material not removed within 4 days of the first positive blood culture, the patient had a polymicrobial bloodstream infection, or if a pneumonia was likely the source of the bloodstream infection. (Fig. 1) Renal function was assessed on the first day of bacteremia, using the Modification of Diet in Renal Disease (MDRD) method for calculating a glomerular filtration rate (GFR). Daptomycin was always dosed at 6 mg/kg or greater. The decision to use doses greater than 6 mg/kg was up to the treating physician. Vancomycin was dosed for

a goal trough level of 15-20 mcg/mL. All patients at our institution with *S. aureus* BSI receive a mandatory infectious disease consult done by a rotation of approximately 25 physicians.

2.2 Statistical Analysis

Daptomycin treated patients were matched with vancomycin treated patients in a 1:2 ratio using a propensity score and an optimal matching algorithm. After excluding subsequent episodes of BSI and patients who did not meet inclusion criteria a propensity score was built on a data set of 267 patients to predict the use of daptomycin using baseline variables present prior to the initiation of any antibiotics (Figure 1). However, detailed comorbidity data were not available prior to matching and not able to be included in the propensity score. Variables included in the propensity score were age, sex, race, APACHE II score, Charlson Comorbidity Index, functional status of the patient, and the presence of a vancomycin MIC of 2 mg/L by broth microdilution. In addition, as the total days of bacteremia was a very strong predictor ($p<0.001$) of receiving daptomycin, the days of positive blood cultures prior to a possible switch to daptomycin, in those patients who were switched, was also included. Within the vancomycin group, this was defined as the total days of positive blood cultures as there was no switch in this group. This was done to attempt to equalize the number of days of positive blood cultures prior to a possible switch to daptomycin. As this was done prior to the possible intervention of daptomycin (the clinical decision point to switch or not switch) this may be considered a "baseline" variable. This resulted in 50 patients treated with daptomycin matched to 100 patients treated with vancomycin. Using 10,000 simulations, done by John Griffith, we determined that we would have a power of 83% to detect an interaction difference (i.e. a variation in

the effect of daptomycin compared to vancomycin in patients with a GFR both greater than and less than 50 ml/min/1.73m^2) as large as seen in original trial data.

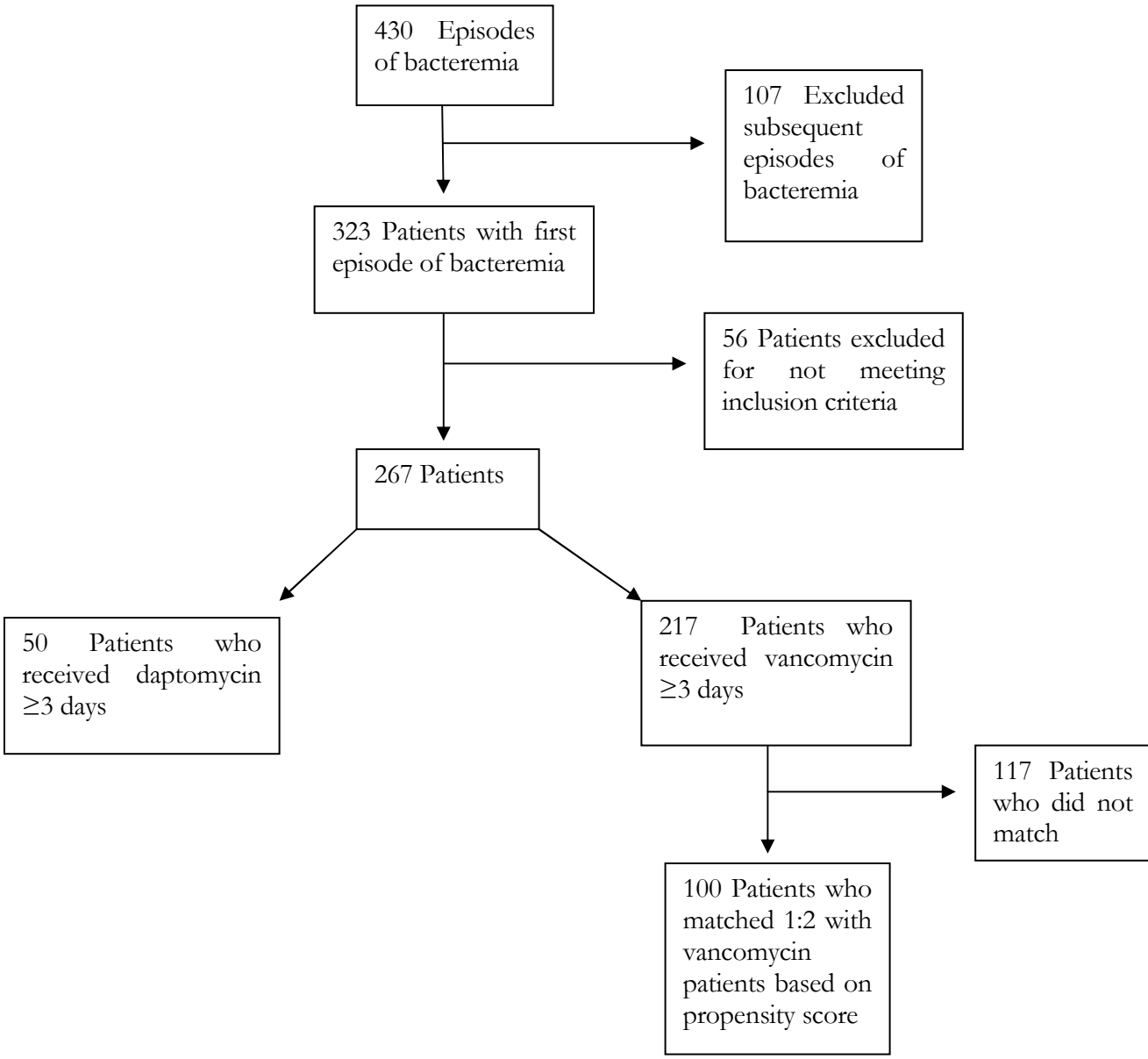

Figure 1. Patient selection flow diagram illustrating the patient selection process.

After matching, additional chart review was performed to gather more detailed comorbidity information. Using this additional information further adjustment was performed using multivariable conditional logistic regression, to account for matching, to evaluate for the main effects of daptomycin and renal impairment with treatment failure as well as the interaction between them. The interaction term was defined as an evaluation of how the treatment effect of daptomycin compared to vancomycin varied in patients with GFRs both above and below 50 ml/min/1.73m^2 and was tested using a likelihood ratio test. Renal impairment was evaluated using a categorical variable dividing the GFR into <50 ml/min/1.73m^2, 51-100 ml/min/1.73m^2, and >100ml/min/1.73m^2. This was done after evaluating the non-linear relationship of GFR to treatment failure with natural inflection points at 50 and 100 ml/min/1.73m^2 (Figure 4).

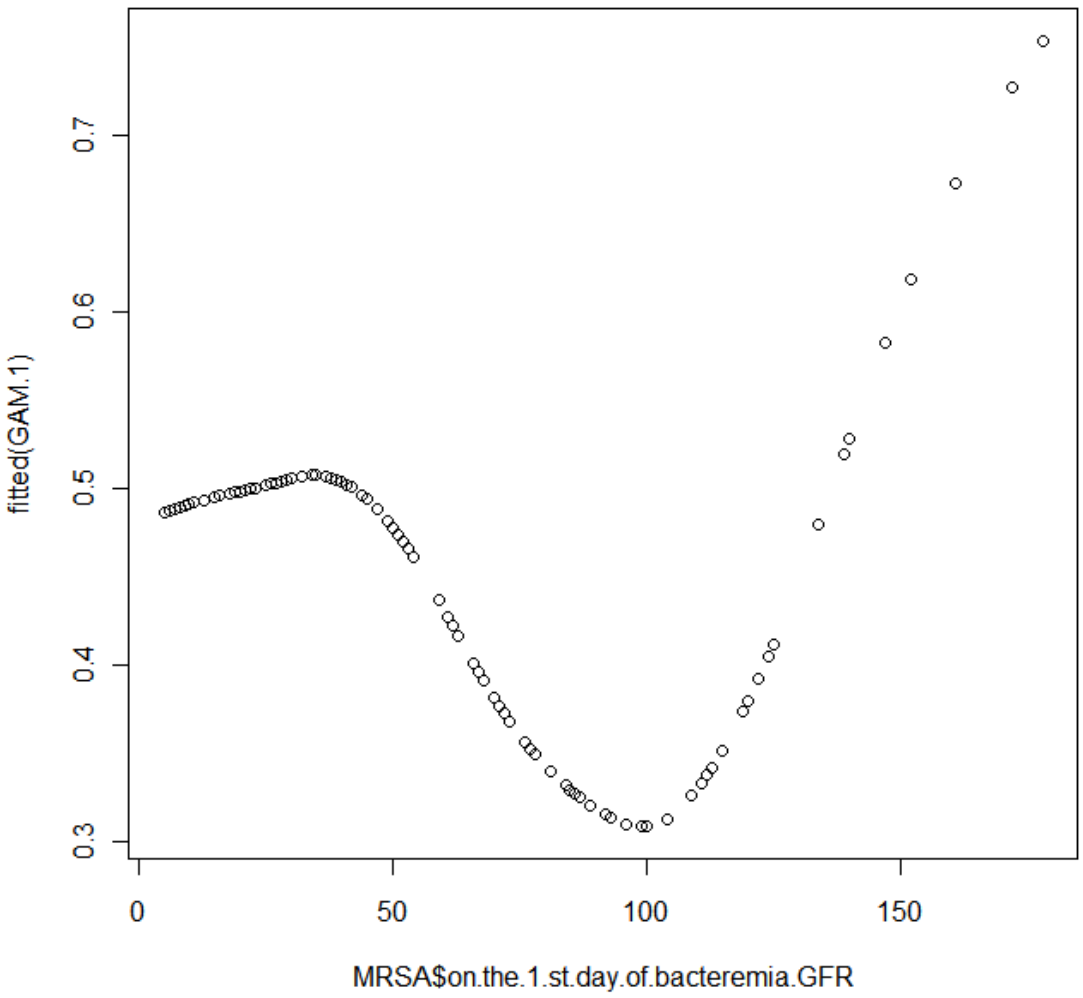

Figure 4. A generalized additive model (GAM) form of the data with failure on the y-axis and GFR on the x-axis, showing a non-linear association between the log odds of treatment failure and GFR with a change around a GFR of 50 and another possible change around 100.

The multivariable model was constructed using significant ($p<0.05$) results from a univariable analysis of multiple factors and their association with treatment failure, limited by the degrees of freedom available in our data set. These variables included: the presence of endocarditis, the presence of liver disease (defined as a Child-Pugh class ≥B), the risk level of the source of infection, and year of treatment to account for variation in clinical treatment over time. In addition, the total days of MRSA-active antibiotics (including vancomycin) prior to a switch to daptomycin was forced into the model with vancomycin treated patients being categorized as 0. This was done as we felt we needed to account for the early effects of vancomycin usage on our outcomes given the relatively long period of vancomycin usage prior to a switch to daptomcyin in our data. In addition, the reason for a switch to daptomycin was excluded from this model as the addition of the factor did not substantially change the estimates of our model but substantially increased the variability. The source of BSI was classified into 3 categories, as previously described: low risk (associated mortality rate <10%), which included urinary tract, ear-nose-larynx, gynecologic, and several manipulation-related sources; intermediate risk (associated mortality rate 10%–20%), which included central line associated, osteoarticular, soft-tissue, and unknown sources; and high risk (associated mortality rate >20%), which included endovascular, abdominal, and central nervous system sources. [3]. Sensitivity analyses of those patients in whom recurrence data was not available were performed assuming both a similar rate of failure in this group as the remaining patients in their group (daptomycin vs. vancomycin) and assuming that all non-evaluable patients were a failure were also performed. All statistical analysis performed with R v.2.13.1.

2.3 Outcome Assessment

Treatment failure was a composite endpoint consisting of in hospital mortality, recurrence of MRSA BSI within 30 days of cessation of antibiotic therapy, or persistent bacteremia ≥ 5 days after the start of drug of interest (vancomycin or daptomycin respectively). This form of composite outcome was chosen after extensive literature review. A majority of retrospective trials on BSI use this type of outcome with similar components, including mortality, persistent bacteremia, and recurrence. This outcome was independently assessed by two blinded adjudicators with disagreements settled by consensus. Each component of the composite endpoint was assessed individually as well. Tufts University IRB approval was obtained for this study.

Results

3.1 Study Population Characteristics

The average age of study patients was 61 years and 60% of the subjects were men. There were no statistically significant differences between comparison groups on variables that were included in the propensity score indicating a good match (Table 1). All patients in the daptomycin group matched with 2 patients in the vancomycin group. Additional results of the propensity score matching process can been seen in Figures 2 and 3. In addition, many of the variables that were not included in the propensity score matching were also similar between the two groups. On the other hand, there was a significantly greater proportion of patients with a hematologic malignancy and recent prior surgery in the vancomycin group whereas patients in the daptomycin group had a larger proportion of low and high risk sources of infection. There was no significant difference in renal function between the two groups with 29 patients (58%) in the daptomycin group having a GFR of <50 ml/min/1.73m^2 vs. 51 patients (51%) in the vancomycin group. In those patients with a GFR of <50 ml/min/1.73m^2 the average GFR was 24.5 with a standard deviation of 14. There was also little variation in renal function throughout admission with an average change in creatinine from the first day of bacteremia to discharge of -0.37.

	Daptomycin (% or SD) n=50	Vancomycin (% or SD) n=100	p-value
Variables Used in the Propensity Score			
Mean Age	58.34	61.64	0.27
Male	28(56)	62(62)	0.48
Race			
White	36(72)	78(78)	0.42
Black	8(16)	10(10)	0.29
Asian	4(8)	10(10)	0.69
Hispanic	2(4)	2(2)	0.47
Mean APACHE II score	13.22	13.98	0.55
Mean Charlson Comorbidity Index	5.76	6.13	0.48
Vancomycin MIC ≥2	10(20)	22(22)	0.78
Functional Status			
Independent	17(34)	30(30)	0.62
Partly Dependent	20(40)	40(40)	1
Fully Dependent	13(26)	30(30)	0.61
Total days of Positive Blood Cultures Prior to Switch	5(+/-5.23)	3.68(+/-4.95)	0.14
Variables Collected Via Chart Review After Matching			
Liver Disease	10(20)	20(20)	1
Diabetes	23(46)	36(36)	0.24
CHF	16(32)	25(25)	0.37
CAD	16(32)	25(39)	0.4
Solid Malignancy	2(4)	13(13)	0.083
Hematologic Malignancy	2(4)	15(15)	0.045
COPD	8(16)	17(17)	0.88
Prior Surgery within 30 days	1(2)	21(21)	0.002
History of Stroke	6(12)	9(9)	0.56
Endocarditis	13(26)	11(11)	0.018
Risk Level of source			
Low	13(26)	6(6)	<0.001
Intermediate	17(34)	72(72)	<0.001
High	20(40)	22(22)	0.021
Immunosuppression	10(20)	20(20)	1
HIV	3(6)	3(3)	0.38
Hemodialysis	11(22)	19(19)	0.67
Prior History of MRSA Infection (not bloodstream)	26(52)	42(42)	0.25
Average GFR	53.8 (+/- 37.4)	60.5 (+/- 44.6)	0.31
GFR<50 ml/min/1.73m^2	27(58)	51(51)	0.42
Outcomes			
Failure Composite Outcome	17(34)	51(51)	0.048
In Hospital Mortality	8 (16)	35 (35)	0.015
Persistent Bacteremia	7(14)	21(21)	0.3
Recurrence	6(12)	5(5)	0.12

Table 1. Clinical characteristics of the comparison groups after matching. The upper variables represent those variables available and used in the construction of the propensity score. The lower variables were collected after matching via additional chart review. In those patients in the vancomycin group, the total days of positive blood cultures was used.

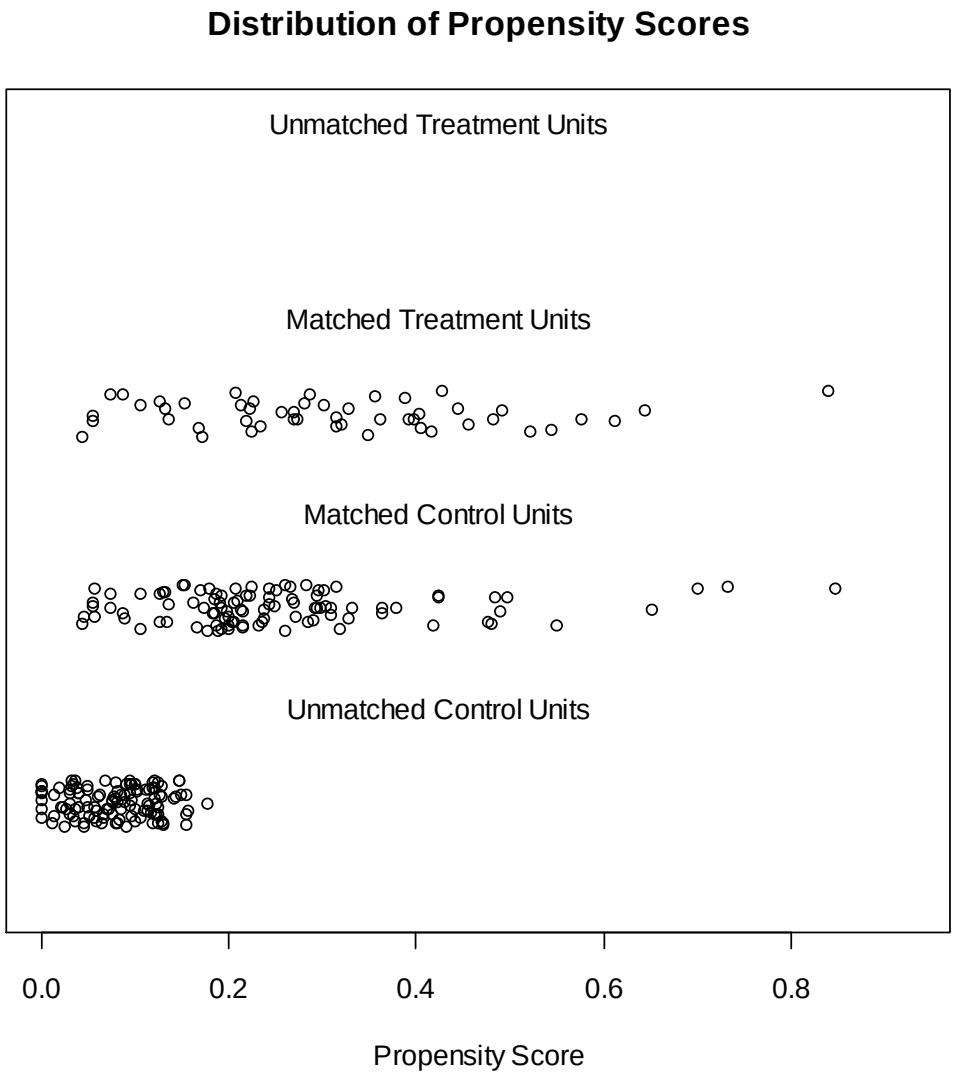

Figure 2. The distribution of propensity scores after matching. Treatment units represent those patients treated with daptomycin while controls represent those patients treated with vancomycin.

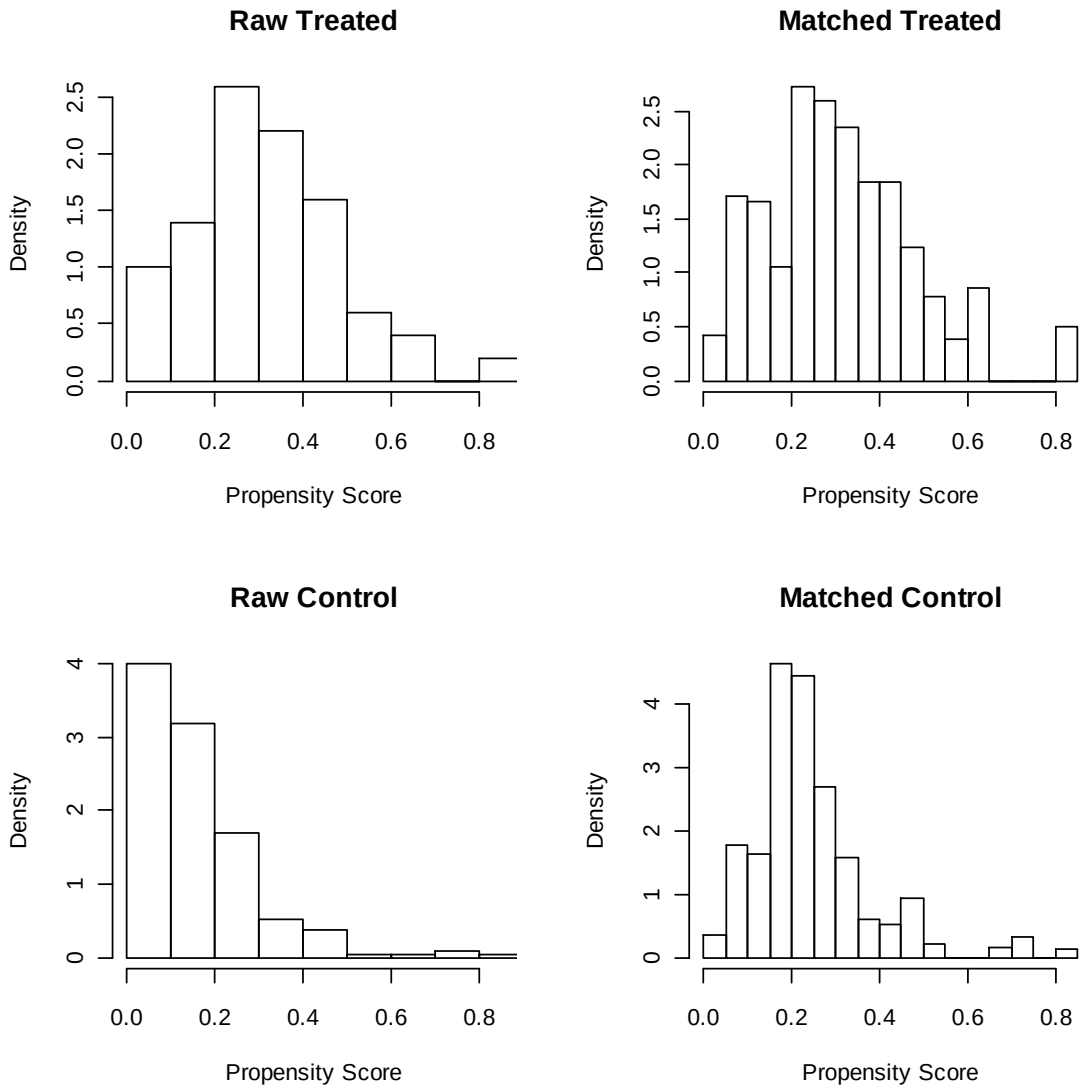

Figure 3. A comparison of the distribution of propensity scores before and after matching.

3.2 Antibiotic Usage and Safety

Patients in the vancomycin group received vancomycin for an average of 21 days with a first

vancomycin level of 16.7 on average drawn after a mean of 2 days. Patients in the daptomycin group received an average of 28 days of daptomycin therapy after a mean of 7 days of prior therapy. The average dose of daptomycin was 6.8mg/kg (range 5.1-10.8 mg/kg). All daptomycin patients with a CrCl of <30 ml/min. received the drug at least every 48 hours as recommended while some patients on hemodialysis received it at every dialysis session . Only 2(4%) of the patients received daptomycin as primary initial therapy. Most of the patients previously received vancomycin (82%) while 12% received linezolid and 4% received clindamycin. The most common reasons for switching to daptomycin were persistently positive blood cultures (13/50, 26%), a decision made by the infectious disease consultants (11/50, 22%), clinical failure in the opinion of the treating physician (7/50, 14%), and unknown (6/50, 12%). In the daptomycin group, only 2 patients (4%) had creatinine phosphokinase (CPK) elevations greater than 5 times the upper limit of normal (>1000 IU/L) while on daptomycin, necessitating cessation of the drug. These two patients were receiving doses of 5.7 mg/kg and 8mg/kg.

3.3 Outcome Descriptions

All patients had complete outcome data for the outcomes of in hospital mortality and persistent bacteremia. For the outcome of recurrence, 19% of the patients in vancomycin group and 14% of the patients in the daptomycin group were lost to follow up at discharge and could not be evaluated for recurrence of MRSA BSI. The unadjusted data show a significantly higher rate of failure and mortality in the vancomycin group and a suggestion of increased recurrence in the daptomycin group, though this result was not statistically significant (Table 1). Additional analyses of the patterns of failure and persistent bacteremia can been seen in Tables 5 and 6.

	Total	GFR<50	GFR>50
Failure Composite Outcome	68/150 (45%)	39/80 (49%)	29/70 (41%)
Mortality	31/150 (21%)	15/80 (19%)	16/70 (23%)
Persistent Bacteremia	14/150 (9%)	10/80 (12%)	4/70 (6%)
Recurrence	9/150 (6%)	5/80 (6%)	4/70 (6%)
Bacteremia and Mortality	12/150 (8%)	10/80 (12%)	2/70 (3%)
Bacteremia and Recurrence	2/150 (1%)	0/80 (0%)	2/70 (3%)

Table 5. An analysis of failure stratified by renal function.

	Total patients (n=150)	Persistent Bacteremia (n=28)	No Persistence
Count from therapy of interest start	2.7+/- 4.24 (1-25)	9.6+/-5.8 (5-25)	1.1+/-1.1 (1-4)
Count total days	4.12+/-5.1 (1-30)	11.5+/-6.9 (5-30)	2.4+/-2.3 (1-6)

Table 6. An analysis of the days of positive blood cultures in all patients and those who did and did not have the outcome of persistent bacteremia. All data are in days +/- SD.

3.4 Associations with Failure

Univariable analysis showed several factors associated with treatment failure that were then used in the multivariable model (Table 2). These included: the presence of endocarditis, the presence of liver disease, the risk level of the source of infection, total days of vancomycin given prior to a switch to daptomycin, and year of treatment. In our multivariable model, neither the usage of daptomycin (OR 0.45, 95% CI 0.11-1.79) nor a GFR of <50 ml/min/1.73m^2 (OR 1.06, 95%CI 0.4-2.86) were significantly associated with treatment failure (Table 3). Additionally, there was no significant interaction between them (p=0.6) indicating that the effect of daptomycin, compared to vancomycin, did not differ significantly in patients with either a GFR greater than or less than 50 ml/min/1.73m^2. Similar non-significant results were seen for the individual outcomes of mortality, persistent bacteremia, and recurrence (Table 3). Additionally, no significant interaction between a GFR of <50 ml/min/1.73m^2 and daptomycin usage was seen for these outcomes as well (Table 3). Within this same multivariable model significant liver disease (OR 4.14, p=0.005) and the highest risk source of infection (OR 5.11, p=0.028) remained significant predictors of failure and the presence of endocarditis was nearly a significant predictor of failure(OR 3.45, p=0.08).

Factor	OR	p-value
Daptomcyin Usage	0.49	0.05
GFR<50 ml/min/1.73m^2	1.34	0.37
Coronary Artery Disease	1.35	0.38
Central Line or Devices present	1.73	0.1
Congestive Heart Failure	1.06	0.88
Chronic Obstructive Pulmonary Disease	1.67	0.24
Days of Antibiotics Given Prior to Daptomycin	1.04	0.37
Days Prior to any MRSA Active Antibiotic Given	0.93	0.64
Diabetes	0.78	0.46
Endocarditis	4.56	0.003
Hemodialysis	0.84	0.67
Hematologic Malignancy	1.85	0.24
HIV	0.59	0.55
History of Stroke	1.43	0.51
History of any MRSA Infection	1.34	0.37
History of MRSA Bacteremia	1.12	0.77
Immunosuppression	1.37	0.44
Liver Disease	3.00	0.011
Prior MRSA active antibiotic (overall)		0.34
Vancomycin	0.41	0.54
Clindamcyin	1.57	0.99
Linezolid	0.20	0.37
Prior Surgery	0.81	0.65
Reason for Switch to Daptomycin (Overall)		0.065
Risk Level of Source (Overall)		<0.001
Solid Malignancy	0.30	0.07
Time to Vancomycin level	0.99	0.94
Vancomycin Level	1.01	0.77
Year treated	1.27	0.002

Table 2. Univariate analysis of factors associated with treatment failure.

	Daptomycin (95% CI)	GFR<50 ml/min/1.73m² (95% CI)	Test of interaction
Failure	0.45 (0.11-1.79)	1.06 (0.4-2.86)	p=0.6
Mortality	0.61 (0.11-3.25)	1.79 (0.58-6.30)	p=0.33
Persistent Bacteremia	0.25 (0.03-2.04)	1.09 (0.3-4.39)	p=0.15
Recurrence	3.21 (0.38-28.59)	0.61 (0.13-3.41)	p=0.88

Table 3. Results of the multivariable analysis showing the independent association with treatment failure, mortality, persistent bacteremia, and recurrence of daptomycin usage and a GFR <50 ml/min/1.73m^2. The non-significant test of interaction ($p>0.05$) indicates that the effect of daptomycin on a particular outcome did not significantly between patients with a GFR greater than or less than 50 ml/min/1.73m^2. Additional variables adjusted for as described in results.

An alternative way to evaluate the relationship between daptomycin, vancomycin, and renal function is to compare the effects on different sub-groups divided by renal function (a

GFR greater than or less than 50 ml/min/1.73m^2. Using those patients who received vancomycin with a GFR>50 ml/min/1.73m^2 as the reference group, there was no significant association with the usage of vancomycin or daptomycin with failure in patients with a GFR<50 ml/min/1.73m^2 (Table 4). There was also no association with failure in those patients who received daptomycin with a GFR>50 ml/min/1.73m^2 (Table 4). Similar non-significant results were seen for the individual outcomes of mortality, persistent bacteremia, and recurrence (Table 4).

	Failure(95% CI, p-value)	Mortality (95% CI, p-value)	Persistent Bacteremia (95% CI, p-value)	Recurrence (95% CI, p-value)
Daptomcyin in GFR <50 ml/min/1.73m2	0.6 (0.11-3.24, 0.56)	1.18 (0.14-9.84, 0.88)	0.75 (0.06-9.1, 0.82)	2.71 (0.23-35.4, 0.43)
Vancomycin in GFR <50 ml/min/1.73m2	1.15 (0.47-2.77, 0.76)	0.96 (0.37-2.42, 0.92)	1.61 (0.49-5.49, 0.43)	0.56 (0.07-3.69, 0.55)
Daptomycin in GFR >50 ml/min/1.73m2	0.4 (0.08-1.91, 0.26)	0.37 (0.04-2.52, 0.34)	0.14 (0.01-1.63, 0.15)	2.14 (0.18-22.4, 0.52)
Vancomycin in GFR >50 ml/min/1.73m2	1 (ref)	1 (ref)	1 (ref)	1 (ref)

Table 4. Results of the multivariable analysis showing the how daptomycin or vancomycin usage in patients with a GFR<50 ml/min/1.73m^2 and those treated with daptomcyin with a GFR >50 ml/min/1.73m^2 predicts treatment failure and each of the components of the composite outcome (mortality, persistent bacteremia, and recurrence) compared to patients treated with vancomycin with a GFR >50 ml/min/1.73m^2. Additional variables adjusted for as described in results.

3.5 Additional Analyses

In examining the rate of recurrence, 19% of the patients in vancomycin group and 14% of the patients in the daptomycin group were lost to follow up at discharge and could not be evaluated for recurrence of MRSA BSI. Sensitivity analyses assuming both a similar rate of failure in this group as the remaining patients in that group and assuming that every non-evaluable patient was a failure did not significantly change our results. Our current definition of persistent bacteremia may have a bias in favor of daptomycin as patients on daptomycin may have had several days of positive blood cultures on vancomycin prior to the switch to daptomycin. These days are not counted towards the outcome of persistent bacteremia. Furthermore, a patient later in their course of therapy, regardless of the type of therapy are more likely to clear their blood cultures as this is the natural course of the disease. In order to account for this possible bias an analysis was performed defining persistent bacteremia as ≥5 days of positive blood cultures from the start of any therapy. This analysis was not significantly different from our primary results, in that there was no significant association of either daptomycin (OR 0.53, 95% CI 0.1-2.28) or a GFR of <50 ml/min/1.73m^2 (OR 1.33, 95% CI 0.51-3.57) with treatment failure nor was there a

significant interaction between the two (p=0.78). Finally, as some measure of the number of positive blood cultures, while a strong predictor of daptomycin usage, was used in the building of the propensity score this may minimize the outcome of persistent bacteremia as it makes the groups more similar. After propensity score matching, the outcomes show a 14% rate of persistent bacteremia in the daptomycin group and a 21% rate of persistent bacteremia in the vancomycin group. While it appears that the propensity score matching was unable to equalize this outcome, the difference might have been larger without the effect of the propensity score. In order to account for this effect, we performed an additional analysis using an alternative definition of failure that did not include the outcome of persistent bacteremia. This analysis was also not significantly different from our primary results. There was no significant association of either daptomycin (OR 0.88, 95% CI 0.22-3.45) or a GFR of <50 ml/min/1.73m^2 (OR 1.31, 95% CI 0.48-3.79) with treatment failure nor was there a significant interaction between the two (p=0.64).

Further evaluation of the effect of renal function was undertaken by stratifying renal function by the Kidney Disease Outcome Quality Initiative (KDOQI) stages of chronic kidney disease. In this model, neither Daptomycin usage (p=.84) nor any stage of chronic kidney disease (p>0.33 for all) was significantly associated with failure. Furthermore, there was no significant interaction between any stage of kidney disease and daptomycin usage (p>0.28 for all).

Discussion

In this study we evaluated if there was a significant variation in the effect of daptomycin with renal function. We were unable to detect a significant interaction. This is in contrast to the original phase III data which showed significantly worse outcomes for those patients treated with daptomycin and a CrCl of <50 ml/min. Despite the limited data and a lack of a physiologic mechanism, the FDA was concerned enough to warn physicians of a possible decrease in efficacy of daptomycin used in patients with moderate renal impairment. We feel that our data should somewhat reassure clinicians if they choose to use daptomycin to treat MRSA BSI in these patients.

We used the MDRD equation to calculate renal function as opposed to the Cockcroft-Gault creatinine clearance more commonly used for drug dosage calculations. We chose to use GFR as this may be a more accurate representation of their renal function compared to a Cockcroft-Gault creatinine clearance. [8]This method is also likely more readily available to clinicians, often being automatically calculated in many electronic medical records. Furthermore, there was no association or interaction with the usage of daptomycin across a range of renal function, suggesting a lack of a relationship with renal impairment regardless of how it was calculated.

Our results may differ from the trial data for a number of reasons. We had a greater number of patients in our evaluation, including more than double the number of patients with a GFR of <50 ml/min/1.73m^2, granting decreased statistical variation and increased power. The original data was a post-hoc subgroup analysis, with a small number of patients, and possible significant differences between the subgroups. We accounted for differences in

our population in multiple ways including propensity score matching and further multivariable regression. Our patient population also more likely reflects the current usage patterns of daptomycin and vancomycin in a real world setting. Additional advantages of our study include a blinded assessment of outcome and the evaluation across a wide array of renal functions.

However, there are some limitations to this study. Due to the retrospective nature of our study, we may not have been able to control for all measured and unmeasured confounders that may affect this association. Residual confounding that differentially affects strata defined by renal function could mask true effect modification. Arguing against this is that our model identifies liver disease, a high risk source of infection, and endocarditis as predictors of failure, similar to prior literature. [9, 10] This indicates that our model is at least similarly complete as others that have been used. We also attempted to account for a possible bias in favor of daptomycin using an alternative definition of persistent bacteremia that "counted" days of positive blood cultures prior to a switch to daptomycin as well. There may be further bias in the outcome of persistent bacteremia as a component of the number of positive blood cultures was used in the propensity score. This was done as the number of positive blood cultures was the strongest indicator for the usage of daptomycin in our analysis and we also felt clinically that it was a strong predictor of use. However, this may have minimized the differences seen in the outcome of persistent bacteremia. However, even the propensity score was unable to account fully for this difference with the daptomycin group still having a higher number of positive blood cultures on average after matching, with the daptomycin group having 5 on average before and after matching and

the vancomycin group increasing from 2.6 to 3.7. However, this difference may have been greater without the effect of the propensity score. In order to account for this, we performed an additional analysis removing persistent bacteremia from our composite failure outcome. While statistically not significant, this analysis did suggest a possible increase in the odds of treatment failure with the usage of daptomycin in patients with impaired renal function. We do not feel that this potential confounding affected the other aspects of our composite variable as an analysis showed there was no significant (clinically or statistically) association of the total days of positive blood cultures with mortality, recurrence, or the combination of the two in the total data and stratified by GFR group or stratified by the usage of daptomycin or vancomycin (OR around 1.02-1.07 for all, $p>0.21$ for all).

This brings to bear the issue of power. Despite having a greater number of patients than in the original study, the power of this study to detect a small difference in the interaction between daptomycin and renal impairment is limited.We were unable to find a significant effect modification of renal function on the impact of daptomycin. However, this study includes every patient treated with daptomycin for a substantial period of at least 8 years at a large tertiary hospital. If a treatment difference exists between daptomycin and vancomycin in patients with impaired renal function, it is likely small and certainly smaller than the large difference seen in the original data that caused the FDA's change in the package insert.

As the usage of daptomycin for MRSA BSI and the prevalence of kidney disease continue to increase, physicians may be reassured by this data. While data from a randomized,

controlled comparative efficacy trial would be ideal to definitively answer this question, a proposed trial by Cubist (clinicaltrials.gov identifier NCT01104662) was terminated, possibly due to difficulties with recruitment, early in June, 2012 after recruiting only 92 subjects. With our data, we were unable to detect that renal impairment of any kind has a significant impact on the efficacy of daptomycin in the treatment of MRSA bacteremia. While this is the first study to evaluate this question, further non-randomized prospective or larger retrospective studies may be needed to provide additional reassurance to clinicians.

References

1. Klevens RM, Morrison MA, Nadle J, et al. Invasive methicillin-resistant Staphylococcus aureus infections in the United States. Invasive methicillin-resistant Staphylococcus aureus infections in the United States **2007**;298(15):1763.

2. Shurland S, Zhan M, Bradham DD, Roghmann MC. Comparison of mortality risk associated with bacteremia due to methicillin-resistant and methicillin-susceptible Staphylococcus aureus. Infect Control Hosp Epidemiol **2007**;28(3):273.

3. Moore CL, Osaki-Kiyan P, Haque NZ, Perri MB, Donabedian S, Zervos MJ. Daptomycin versus vancomycin for bloodstream infections due to methicillin-resistant Staphylococcus aureus with a high vancomycin minimum inhibitory concentration: a case-control study. Clin Infect Dis **2012**;Jan;54(1):51.

4. TreatmentTrends: MRSA and Serious Gram-Positive Infections (US) 2012. Available at: http://bio-trends.com/News-and-Events/Press-Releases/MRSA-Serious-Gram-Positive-Infections-071112. Accessed 11/21, 2012.

5. Cubicin (Daptomycin) Package Insert 11/30/2010. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021572s022s023s024s027s030s032lbl.pdf. Accessed 08/15, 2011.

6. FDA Label and Approval History 11/30/2010. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/021572s022,s023,s024,s027,s030,s032ltr.pdf. Accessed 08/15, 2011.

7. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis **2003**;41:1.

8. Teruel Briones JL, Gomis Couto A, Sabater J, et al. Validation of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation in advanced chronic renal failure. Nefrologia **2011**;31:677.

9. Pastagia M, Kleinman LC, Lacerda de la Cruz, E.G., Jenkins SG. Predicting Risk for Death from MRSA Bacteremia. Emerg Infect Dis **2012**;18:1072.

10. Walraven CJ, North MS, Marr-Lyon L, Deming P, Sakoulas G, Mercier RC. Site of infection rather than vancomycin MIC predicts vancomycin treatment failure in methicillin-resistant Staphylococcus aureusbacteraemia. J Antimicrob Chemother **2011**;66:2386.