2017

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Citation/Publisher Attribution

Timbrook, T. T., Caffrey, A. R., Luther, M. K., Lopes, V. and LaPlante, K. L. (2018), Association of Higher Daptomycin Dose (7 mg/kg or Greater) with Improved Survival in Patients with Methicillin-Resistant *Staphylococcus aureus*Bacteremia. Pharmacotherapy, 38: 189-196. doi:10.1002/phar.2070
Available at: http://dx.doi.org/10.1002/phar.2070

Higher Daptomycin Dose Associated with Improved Survival in Methicillin-Resistant Staphylococcus aureus Bacteremia

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Keywords: daptomycin, bacteremia, mortality, *Staphylococcus aureus*

Acknowledgements of External Support: This research received no external funding.

This work was presented, in part, at the 27th Annual European Congress of Clinical Microbiology and Infectious Diseases.

Abbreviated title (53 characters): Effect of daptomycin dose in MRSA bacteremia

Text word count: 2,365

Abstract

Study Objective Current guidelines recommend higher daptomycin doses than the label dose of 6 mg/kg for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia; however, the evidence supporting this is from *in vitro* and cases series studies. The objective of this study was to evaluate the comparative effectiveness of daptomycin dose in MRSA bacteremia.

Design Retrospective national cohort study

Setting Veterans Affairs Medical Centers

Patients A total of 371 patients with MRSA bacteremia between 2002 and 2015 treated initially with vancomycin within 24 hours of initial culture collection and switched to daptomycin therapy within 7 days were included in the study, with 138 patients (37.2%) receiving higher than label daptomycin dose.

Measurements and Main Results Clinical outcomes were compared among those with daptomycin label dose (6 mg/kg) and those with higher dose (≥7mg/kg), using propensity score matched Cox proportional hazards regression models. To identify dose partitioning associated with optimal survival, categorization and regression tree (CART) analysis was used among patients controlling for confounding with a 30-day mortality disease risk score. Propensity score matched 30-day mortality was 8.6% (6/70) among higher dose vs 18.6% (13/70) among label dose (hazard ratio [HR] 0.31, 95% confidence interval [CI] 0.10-0.94). No differences were observed in inpatient mortality, length of stay, 30-day readmission, or 30-day *S. aureus* reinfection. CART analysis resulted in doses of ≥7mg/kg providing benefit only among patients with higher (>51%) predicted probabilities of 30-day mortality ($p<0.001$).

Conclusion This is the first comparative effectiveness study of daptomycin dose in MRSA bacteremia. Survival benefits were observed with higher than label daptomycin dose (≥7mg/kg) for the treatment of MRSA bacteremia. These data suggest higher than label doses of daptomycin may be preferred over label dose for improving clinical outcomes in MRSA bacteremia.

Introduction

Staphylococcus aureus bloodstream infections (BSIs) contribute to significant mortality rates, approximately 20%.[1] Label dose of daptomycin for *Staphylococcus aureus* BSI with or without infective endocarditis was established in a randomized study at 6 mg/kg based on daptomycin's non-inferiority to the standard of care, vancomycin, with or without an aminoglycoside.[2] More recent data has suggested improved outcomes with daptomycin over vancomycin in MRSA BSI.[3, 4] However, the optimal dose of daptomycin for MRSA-BSI remains unclear.

Current national guidelines yield varying recommendations on daptomycin dose for MRSA-BSIs, generally recommending ≥8 mg/kg.[5-8] These recommendations are based predominantly on *in vitro* data and a case series of 61 patients receiving a mean daptomycin dose of 8 mg/kg with any type of infection, at any site, caused by any gram-positive organism.[9-13] To date, no studies have examined the comparative effectiveness of daptomycin label dose to higher dose in MRSA BSI. Therefore, the objective of this study was to evaluate clinical outcomes among higher than label daptomycin dose in MRSA BSI.

Methods

Study Population

Our study population included patients age ≥ 18 years who were admitted to any Veterans Affairs medical center between January 1, 2002 to October 14, 2015 with MRSA bacteremia based blood cultures positive for MRSA. Patients initiated on vancomycin within 24 hours of initial culture collection and then switched to daptomycin within 7 days were included as guidelines recommend consideration of therapy switch if persistently bacteremic for almost a week or sooner if patients condition is worsening despite source control measures.[6] Patients on dialysis during the current admission or previous year and patients with a staphylococcal BSI in the 30 days prior to admission were excluded.

Data Sources

Clinical data was obtained from the national VA electronic health data which includes International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), diagnostic and procedure codes, chemistry and microbiology data, vitals, and pharmacy data, including bar code medication administration records.[14] This study was approved by the Institutional Review Board and Research and Development Committee of the Providence Veterans Affairs Medical Center.

Variable Definitions

Daptomycin mg/kg dose was calculated based on actual body weight and initial daptomycin dose, and rounded to the nearest integer. Patients were excluded if they received an initial daptomycin dose of <5.5 mg/kg, as this is below labeled dose. Patients were then categorized as daptomycin label dose (6 mg/kg) and higher than label dose (≥7mg/kg). All doses higher than label dose were included as optimal off-label dose remains undefined and has often include any dose higher than label dose.[13, 15-18]

ICD-9-CM codes were utilized to identify historical and current admission comorbidities. Severity of illness was assessed using a modified Acute Physiology and Chronic Health Evaluation (APACHE) III score as previously described within the VA system.[19, 20] Age and APACHE III score were both dichotomized on their medians. Time to initial daptomycin dose and infectious diseases consult were evaluated from index blood culture.

The primary outcome assessed was 30-day mortality from index culture. Secondary outcomes included time to inpatient mortality, hospital discharge, intensive care discharge, creatine

phosphokinase (CPK) elevations, as well as 30-day readmission and *S. aureus* reinfection. Inpatient mortality, hospital discharge, intensive care discharge were measured from index culture, and 30-day readmission and S. aureus reinfection were assessed from the discharge date. Baseline creatine phosphokinase (CPK) levels were evaluated for the lowest value during the 7 days before index blood culture through the 2 days after blood culture. An elevated baseline CPK was defined as greater than the upper limit of normal (ULN). Elevated CPK levels from baseline were defined as ≥3 times the ULN if normal baseline CPK and ≥5 times the ULN if elevated baseline CPK.[21] CPK elevations were evaluated for 6 weeks past baseline.

Statistical analysis

Group differences were evaluated using chi-square or Fisher's exact tests for categorical variables and t-test or Wilcoxon rank sum for continuous variables. Propensity scores were developed based on variables including age, severity of illness, ICU admission, comorbid conditions, medical history, presence of infectious diseases consult, year of treatment, hospital-onset infection, time to initial daptomycin dose, and source of infection (Supplemental Table S1). This logistic model was developed using unconditional logistic regression, with backwards, step-wise elimination.[22, 23] Assessments were made for multicollinearity and goodness of fit.[24] Caliper matching was performed using a caliper of 0.005, and replacements were not performed.[24] Cox proportional hazard models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for the outcomes. Sensitivity analyses were performed with propensity score quintile adjusted Cox models.

To determine an optimal daptomycin dose associated with survival, disease risk scores (DRS) were used to control for confounding variables and subsequently analyzed via a classification and regression tree (CART) analysis.[25, 26] The DRS model was based on all-cause 30-day mortality and developed among "unexposed" patients (6mg/kg) with the model then being

applied to higher dose patients to determine their predicted probabilities of the outcome (Supplemental Table S1). The initial CART analysis included DRS and mg/kg dose. In sensitivity analyses, weight and creatinine clearance (CrCl) were included in the CART, with dose being included as mg dose. Mg dose was evaluated as limited PK/PD data suggest "fixed" mg dose as a possible alternative to mg/kg dose.[27] The DRS was also developed using unconditional logistic regression with backwards, step-wise elimination. CART optimal tree selection was evaluated using cross-validation to determine pruning by complexity parameter with the least misclassification error. CART analysis was performed using the *rpart* package in R version 3.3.3 (R Foundation for Statistical Computing) while all other analyses were performed in SAS version 9.2 (SAS Institute, Cary, NC).

Results

We identified 371 patients with MRSA bacteremia meeting our inclusion and exclusion criteria (Figure 1) with 138 patients (37.2%) receiving higher than label daptomycin dose (Table 1). Among patients with higher daptomycin dose (≥7 mg/kg), there were 42.8% (n=59), 50.0% (n=69), and 7.2% (n=10) patients on 7 mg/kg, 8-9 mg/kg, and ≥10 mg/kg regimens, respectively. In the overall cohort, patient baseline characteristics and clinical presentation were similar between dose groups (Table 1). Average body mass index was higher among those receiving the label dose compared with those treated at higher doses (28.8 vs 27.0; p=0.02). Likewise, more patients with label dose were obese compared with higher dose (39.9% vs 29.0%; P=0.03). Finally, treatment with label dose vs higher dose varied by treatment period (2009-2015 74.3% vs 87.7%; P=0.002).

Propensity score matched 30-day mortality was 18.6% (13/70) in the label dose group and 8.6% (6/70) in the higher dose group (hazard ratio [HR] 0.31, 95% confidence interval [CI] 0.10-0.94; Figure 2). No differences were observed in propensity score matched time to inpatient mortality

(HR 0.13, 95% CI 0.02-1.00), length of stay (HR 1.37, 95% CI 0.83-2.25), 30-day readmission (HR 0.62, 95% CI 0.31-1.24), or 30-day *S. aureus* reinfection (HR 1.00, 95% CI 0.25-4.00). In sensitivity analyses with propensity score quintile adjusted Cox models, none of the outcomes differed significantly between the label dose and high dose groups.

Evaluations for an optimal daptomycin dose determined by CART analysis are shown in Figure 3. The DRS partitioned at a predicted probability of 0.51 for 30-day mortality. Further CART partitioning established a daptomycin dose breakpoint at ≥7mg/kg yielding a 30-day mortality benefit (P<0.001) among patients with higher DRS (≥51.0%). A significant daptomycin dose breakpoint was not found among patients with lower DRS (<51.0%). Consistent with this absence of partitioning, dose stratification in the low DRS group by 6mg/kg versus ≥7mg/kg reflected no difference in 30-day mortality (6.1% vs 9.2%; P=0.31). Sensitivity analyses using mg/kg doses rounded to 0.1 mg had similar results, indicating higher survival with daptomycin dose at ≥6.6 mg/kg among DRS ≥51.0%. Additional sensitivity analyses adding weight and CrCl by mg dose did not partition on weight, CrCl, or mg dose.

In an unmatched safety evaluation of the overall cohort, 73% (273) of patients had CPK levels and 31.3% (116) had a baseline level. Among patients with a baseline CPK level, a total of 5.2% had elevations. When stratified by daptomycin dose, CPK elevations were observed in 7.0% (5/71) of 6 mg/kg, 0% (0/22) of 7 mg/kg, 7.1% (1/14) of 8-9 mg/kg, and 0% (0/3) of ≥10 mg/kg daptomycin dose regimens. Crude CPK elevations among label vs higher daptomycin dose were not significantly different (7.0% vs 3.0%; P=0.66).

Discussion

Our study sought to evaluate clinical outcomes (30-day mortality, inpatient mortality, length of stay, 30-day readmission, 30-day *S. aureus* reinfection, and CPK elevations) among those with

higher than label daptomycin dose (≥7mg/kg vs label dose of 6mg/kg) in MRSA BSI and identify an optimal daptomycin dose regimen. Consistent with *in vitro* studies suggesting increased effectiveness with higher doses[9-11], our comparative effectiveness study demonstrated higher doses were associated with improved survival. These results support current guidelines in recommending higher than label daptomycin dose in patients with MRSA BSI.[5-8]

While two recent studies have concluded higher than labeled daptomycin dose (≥9 and ≥10 mg/kg) translates to improved clinical outcomes in vancomycin-resistant enterococcal (VRE) BSIs[28, 29], our study is the first to establish this evidence in MRSA BSIs. A few studies have evaluated higher daptomycin dose, however their results have been limited in interpretation for MRSA BSIs since they included any infection site by any gram-positive organism and most of these studies lacked a comparison group.[13, 16, 30, 31] Studies focusing specifically on BSI with or without infective endocarditis have also been limited in interpretation due to lack of dose comparisons and inclusion of all gram-positive organisms.[17, 18, 32]

Several *in vitro* and *in vivo* studies have suggested advantages of higher daptomycin dose with increased log reduction of bacterial burden[12, 33], more rapid bactericidal activity[9, 11, 34-36], and suppression of non-susceptible isolates.[10, 33] Several studies have demonstrated increased activity with higher daptomycin doses using daptomycin non-susceptible MRSA, hVISA, and VISA isolates[33, 34], though daptomycin non-susceptible isolates are likely rare as a trend analysis of 12,181 MRSA isolates from medical centers in the United States only found 0.11% that were daptomycin non-susceptible.[37]

Prior to the present study, the most relevant work in determining the impact of higher daptomycin dose on clinical outcomes in MRSA BSI has been from simulation modeling performed using data from a randomized, non-inferiority study comparing daptomycin to the

standard of care for right-sided infective endocarditis.[2, 38] In the multivariable analysis of the simulation study, 24 h AUC/MIC, creatinine clearance, albumin, and disease category (left-sided endocarditis, right-sided endocarditis or complicated bacteremia, or uncomplicated bacteremia) were found to be predictors of clinical response.[38] Using these data, Monte Carlo simulations suggested improved clinical success (clinical cure or partial improvement in clinical signs and symptoms not requiring further treatment) with increased daptomycin exposure among certain patient populations stratified by outcome probability of response.[38] We observed survival benefits with increased daptomycin exposure which builds on the results of the simulation study, as our CART analysis identified clinical benefit with higher than label daptomycin dose regimens among patients with worse survival probabilities.

Two studies have suggested fixed daptomycin dose may be an alternative to a mg/kg dose.[27, 39] One study evaluated fixed dose and clinical outcomes among 50 critically ill patients receiving 6-8 mg/kg/day of daptomycin for *Staphylococcus* species-related infections. Using those data, Monte Carlo simulations (MCS) were performed to determine the cumulative fraction of response (CFR) and risk for muscle toxicity achieved by various fixed dose regimens. Fixed dose regimens (500 mg and 750 mg for non-septic and septic patients, respectively) achieved higher CFR than mg/kg dose strategies while simultaneously decreasing probabilities of muscle toxicities. In our sensitivity analyses, fixed dose was not found to be predictive of 30-day mortality. Moreover, the small, fixed dose study calculated probabilities of daptomycin trough levels associated with risk for muscle toxicity to be 4.88-11.0% among non-septic patients. In contrast, using our more direct surrogate measure of muscle toxicity, CPK, we found elevations to be infrequent in our cohort, and lower in higher dose group than in the label dose group. Our results of infrequent CPK elevations are consistent with a recent larger cohort of 911 patients among whom CPK elevations were rare (<1%) among those receiving higher than label daptomycin dose.[28]

Several considerations should be made when interpreting our results. As a retrospective observational study, unmeasured residual confounding may be present. Although all patients were initiated on vancomycin, vancomycin minimum inhibitory concentrations (MICs) were not analyzed, however the effect of these on outcomes remains unclear.[40] Similarly, daptomycin MIC was not analyzed, yet MRSA isolates with daptomycin non-susceptibility remains rare.[37] We did not evaluate the impact of concomitant or prior MRSA active agents that some patients may have received. Some data has suggested combination therapy with daptomycin and another antibiotic may increase effectiveness for MRSA.[41, 42] Future studies should consider the impact of these factors on clinical outcomes. Identification of source control was not available from our data. Our safety evaluation for CPK elevation was among a limited sample due to lack of baseline testing for many patients. However, two recent studies evaluating higher daptomycin dose regimens in VRE have suggested similar rates of elevations compared to label dose.[28, 29] Finally, while our CART analysis suggests a benefit with doses of ≥7mg/kg among patients with higher (>51%) predicted probabilities of 30-day mortality, CART analyses may be sensitive in determining cutoffs based on the number of observations occurring at a splitting node (N=54 for the high risk patients).[43] As a larger node of patients could have resulted in an alternative cutoff, we recommend, and believe our data supports, the use of guideline recommended dosing of 8-10 mg/kg for MRSA bacteremia with or without infective endocarditis.[6]

Conclusion

This is the first comparative effectiveness study of daptomycin doses in MRSA bacteremia. Treatment of MRSA bacteremia with higher than label daptomycin doses was associated with lower rates of 30-day mortality. These data suggest higher doses of daptomycin may be preferred over label dose to improve survival in MRSA bacteremia, particularly among patients at high risk of poor outcomes.

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Acknowledgments

We thank Thomas P. Lodise for his constructive review of this manuscript.

The views expressed are those of the authors and do not necessarily reflect the position or policy of the United States Department of Veterans Affairs. This work was presented, in part, at the 27th Annual European Congress of Clinical Microbiology and Infectious Diseases. This material is based upon work supported, in part, by the Office of Research and Development, Department of Veterans Affairs. Tristan Timbrook and Aisling Caffrey had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding.

This work was unfunded.

Conflicts of interest.

T.T.T. has received honorarium as a speaker and/or advisor for BioFire Diagnostics, GenMark Diagnostics, and Roche Diagnostics. A.R.C. has received research funding from Pfizer, Cubist (Merck), The Medicines Company. K.L.L. has received research funding or honorarium as an advisor for Cubist (Merck), BARD/Davol, Biomerieux, Forest (Allergan), Ocean Spray, The Medicines Company, Cempra, and Pfizer.

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Table 1. Characteristics of patients receiving daptomycin label dose and higher dose

Characteristic	Daptomycin Dose					
	Overall Cohort			Propensity Matched		
	6 mg/kg (n=233)	≥7 mg/kg (n=138)	P-value	6 mg/kg (n=70)	≥7 mg/kg (n=70)	P-value
Age (years)	64.0 ± 12.7	64.8 ± 9.8	0.55	66.1±9.3	64.5±12.9	0.40
Male gender	230 (98.7)	132 (95.7)	0.06	69 (98.6)	69 (98.6)	1.00
Body mass index	28.8 ± 7.0	27.0 ± 6.5	0.02	29.6±7.3	30.6±8.3	0.45
Obese	93 (39.9)	40 (29.0)	0.03	31 (44.3)	33 (47.1)	0.73
Year						
2002-2009	60 (25.8)	17 (12.3)	0.002	18 (25.7)	16 (22.9)	0.69
2010-2015	173 (74.3)	121 (87.7)		52 (74.3)	54 (77.1)	
Charlson score	1.8 ± 1.8	1.9 ± 1.7	0.62	2.1±1.9	2.1±1.9	0.86

Commorbidities						
Alcoholism	23 (9.9)	13 (9.4)	0.89	6 (8.6)	5 (7.1)	0.75
Diabetes	136 (58.4)	74 (53.6)	0.37	44 (62.9)	45 (64.3)	0.86
Chronic kidney disease	67 (28.8)	34 (24.6)	0.39	16 (22.9)	24 (34.3)	0.13
Liver Disease	34 (14.6)	19 (13.7)	0.83	10 (14.3)	13 (18.6)	0.49
Malignancy	58 (25.0)	37 (26.8)	0.68	14 (20.0)	18 (25.7)	0.42
Community-onset infection[a]	173 (74.3)	106 (76.8)	0.58	51 (72.9)	55 (78.6)	0.43
Intensive care	47 (20.2)	18 (13.0)	0.08	8 (11.4)	9 (12.9)	0.80
Severity of illness[b]	45.0 ± 18.1	45.4±18.0	0.84	44.8±17.1	44.2±17.8	0.83
Sources of infection[c]						
Endocarditis[d]	14 (6.0)	11 (8.0)	0.46	7 (10.0)	3 (4.3)	0.19
Skin and soft tissue culture site	32 (13.7)	13 (9.4)	0.22	8 (11.4)	8 (11.4)	1.00
Urine	22 (9.4)	13 (9.4)	0.99	9 (12.9)	8 (11.4)	0.80
Other or unknown	165 (70.9)	101 (73.2)	0.62	46 (65.7)	51 (72.9)	0.36
Infectious disease consult	172 (73.8)	112 (81.2)	0.11	54 (77.1)	55 (78.6)	0.84
Time to consult (days)	3.2±4.1	3.6±4.8	0.38	3.4±4.1	2.8±2.4	0.32

Time of vancomycin to daptomycin switch (days)	3.9±1.8	4.0±1.7	0.62	4.0±1.9	4.0±1.7	0.78
Inpatient daptomycin therapy duration (days)	13.8±17.5	12.4±12.0	0.40	16.3±19.7	13.7±15.7	0.38

Data are no. (%) and means ± standard deviations; Data are from overall cohort before matching.
[a]Within 72 h of index culture; [b]Modified APACHE III score; [c]Culture-confirmed source of infection; [d]Source of infection defined by ICD-9-CM code; ICU, intensive care unit; MRSA, methicillin-resistant Staphylococcus aureus

Figure 1. Flow diagram for inclusion and exclusion

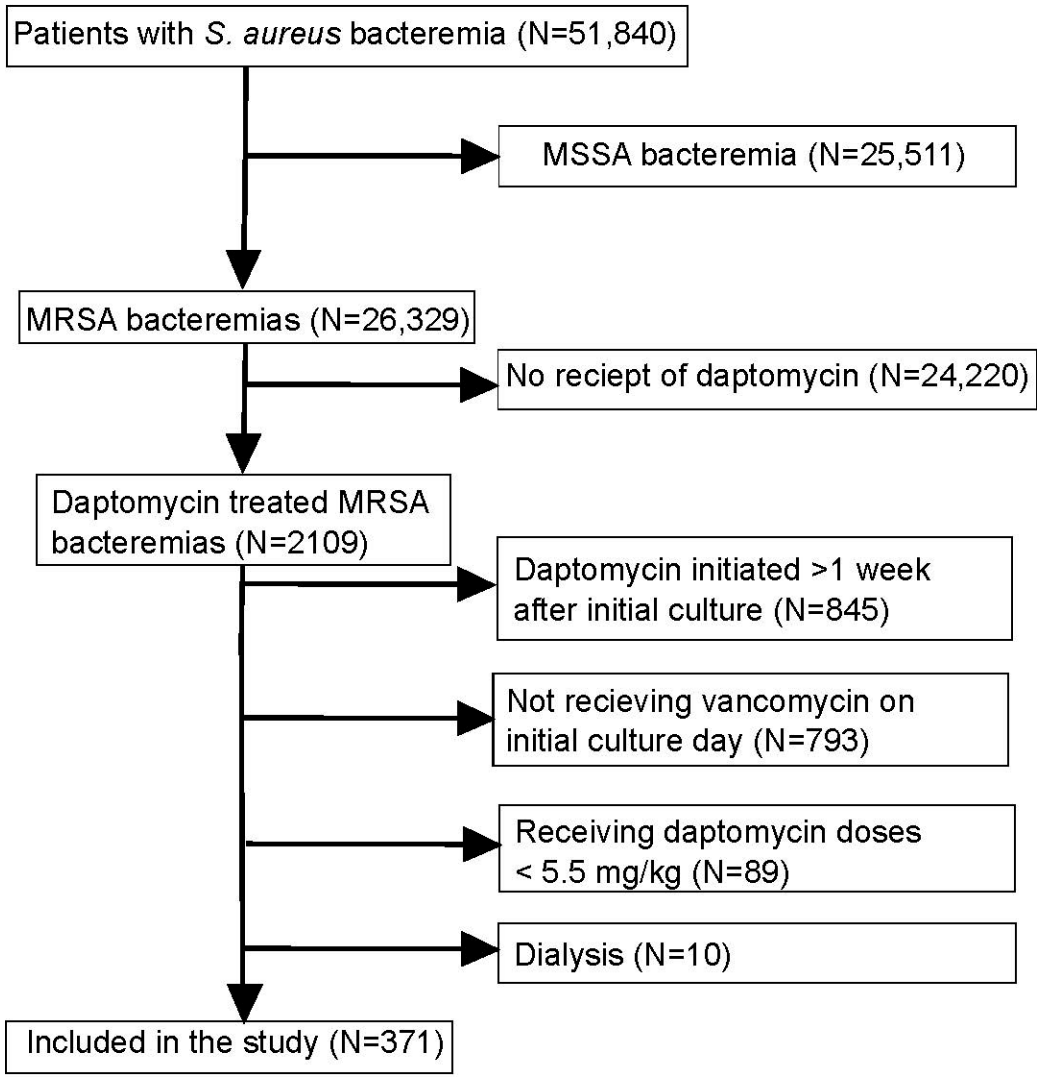


Figure 2. Survival probability among patients receiving daptomycin label dose and higher dose

Legend: Propensity score model C-statistic 0.828, Hosmer and Lemeshow Goodness of Fit p=0.1525, Probability distributions by exposure (Supplemental Figure S1).

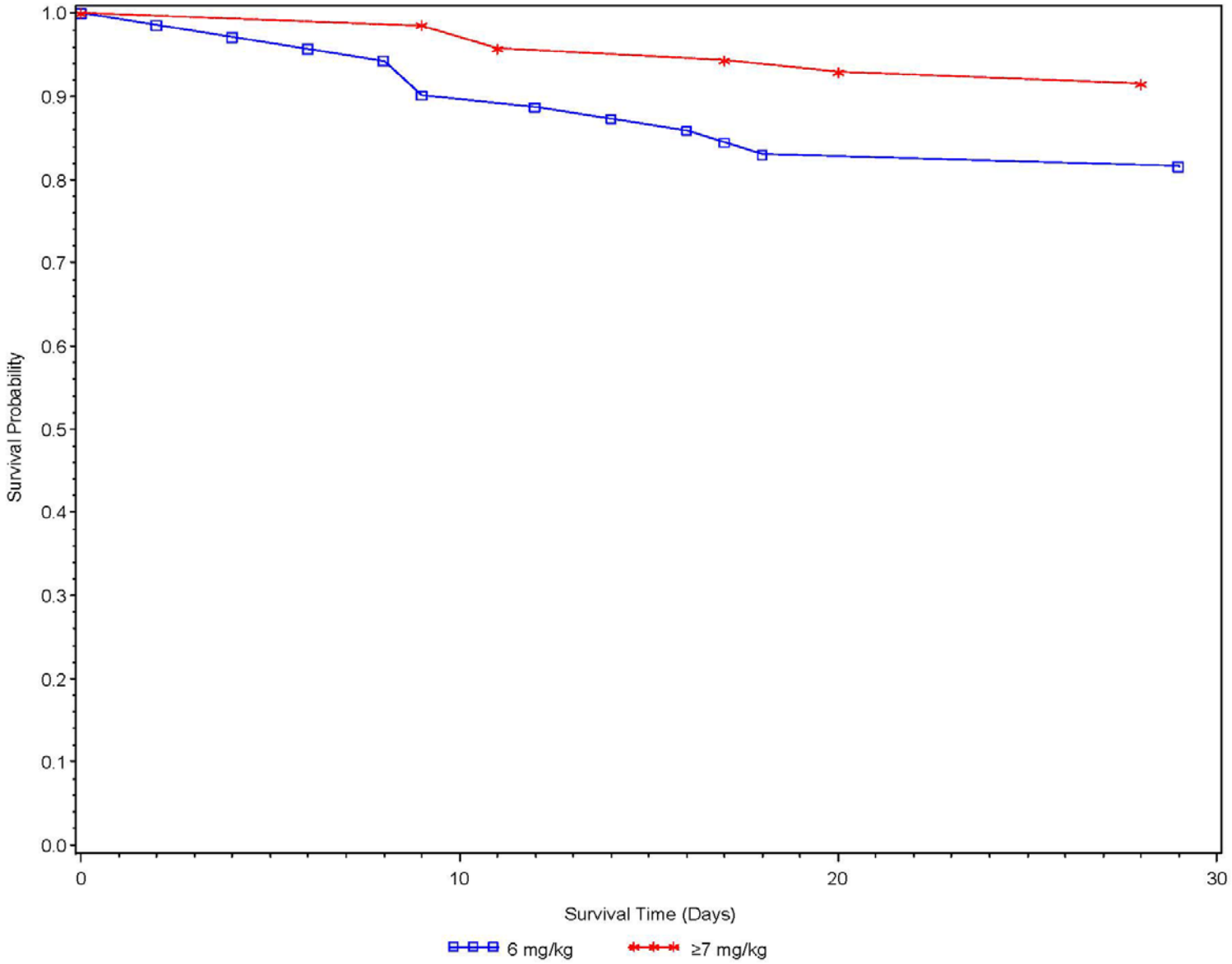
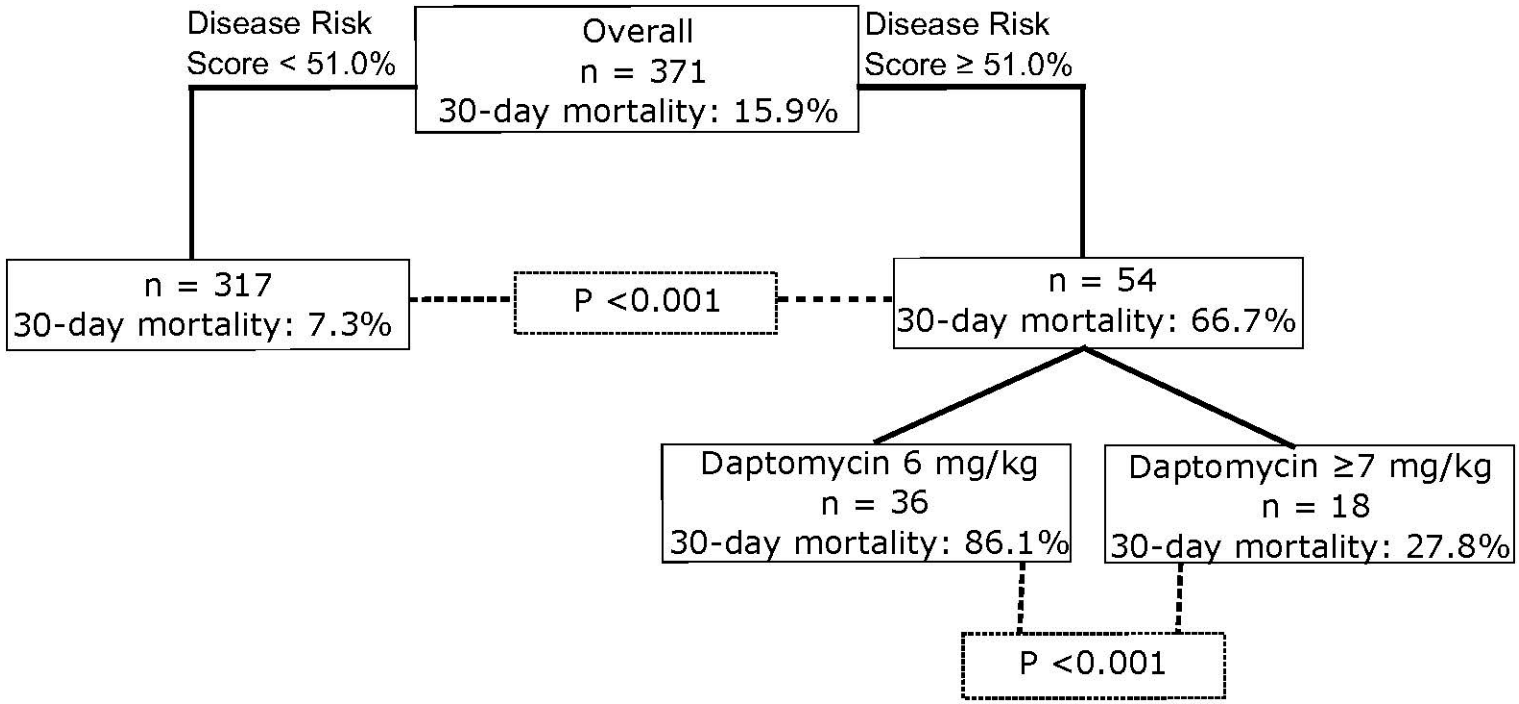

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Survival Probability
0
10
20
30
Survival Time (Days)
6 mg/kg
≥7 mg/kg

Figure 3. Comparison of 30-day all-cause mortality by classification and regression tree (CART)-derived breakpoints on disease risk score (DRS) and daptomycin mg/kg dose

Legend: Disease risk score model C-statistic 0.959, Hosmer and Lemeshow Goodness of Fit p=0.9493



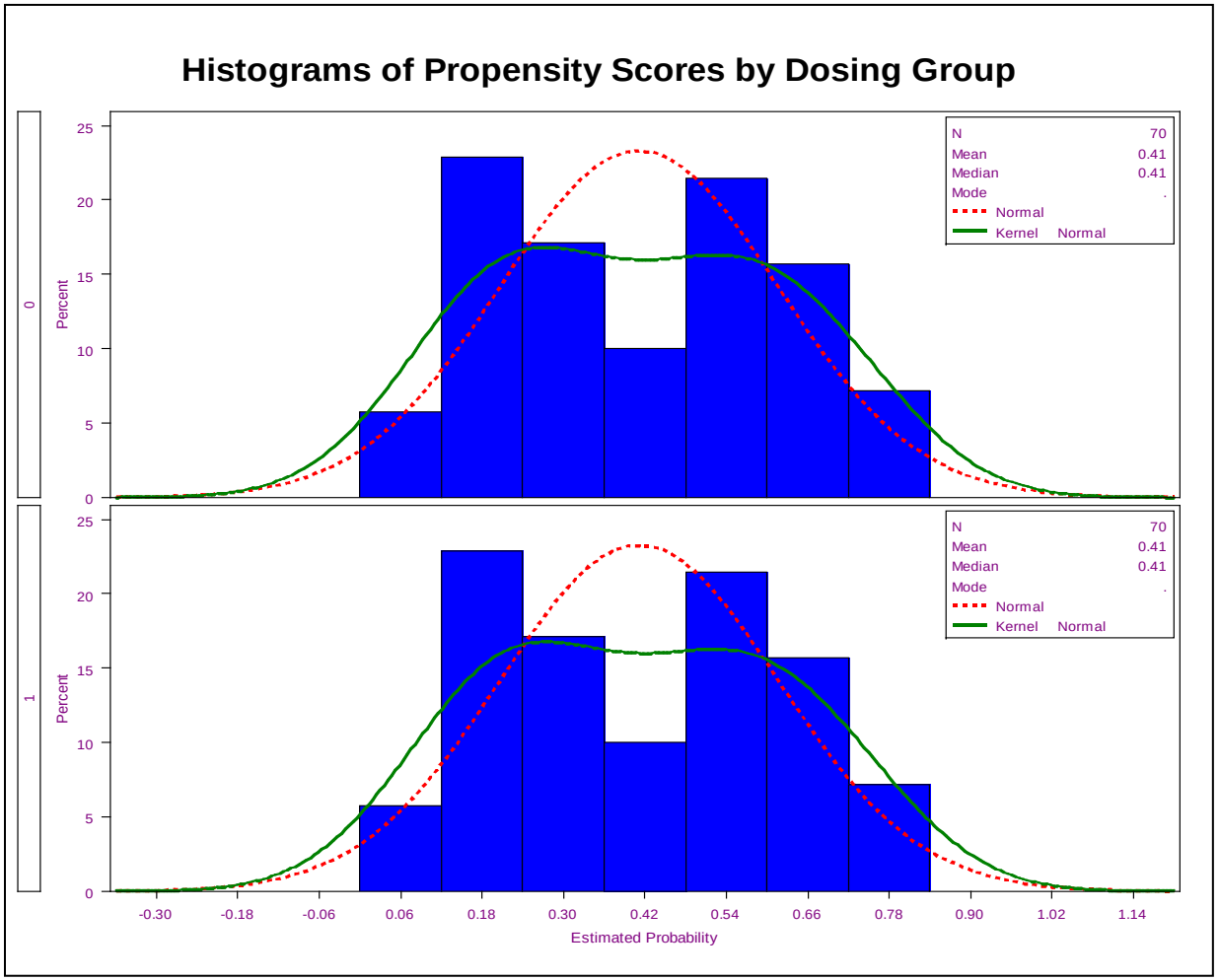
Supplemental Tables

Table S1: Variables included in final model

Propensity model	Disease risk score model

• Year, ≥65, ICU admission, sex, hospital (center effects), APACHE III, community onset, hepatic failure, ID consult
• Current diagnosis
  • Diabetes without complications, fluid or electrolyte disorder, abscess, administrative/social admission, anxiety, diverticulosis/diverticulitis, adverse care, gram negative infection, MRSA, nutritional disease, peritonitis, lymphoma, valve disease
• Historical diagnosis (within 1 year)
  • Arrhythmia, renal disease, depression, drug abuse, gangrene, abscess, bacterial infection, cataracts, cognitive disorder, industrial accident, ear or other sensory organ disorder, fever, GI disorder, headache, medical, occlusion, osteoarthritis, peritonitis, phlebitis, respiratory failure, retinal, septicemia, sprain/strain, surgical site infection, streptococcus infection, osteoporosis, peptic ulcer disease
• Source
  • Skin (culture)
	• Year, ≥65, ICU admission, hospital (center effects), severe sepsis, ID consult, albumin level, operation during current admission
	• Current diagnosis
	  • Respiratory failure, residual
	• Historical
	  • Depression, bacterial infection, lower respiratory, osteoporosis
	• Source
	  • Endocarditis (ICD-9)

Figure S1: Probability distributions by exposure



Note. Dosing group "0" for 6 mg/kg, "1" for ≥7mg/kg