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

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26

27 **Abstract**

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

32 **Design** Retrospective national cohort study

33 **Setting** Veterans Affairs Medical Centers

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

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

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

53 Introduction

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

60
61 Current national guidelines yield varying recommendations on daptomycin dose for MRSA-BSIs,
62 generally recommending ≥ 8 mg/kg.⁵⁻⁸ These recommendations are based predominantly on *in*
63 *vitro* data and a case series of 61 patients receiving a mean daptomycin dose of 8 mg/kg with
64 any type of infection, at any site, caused by any gram-positive organism.⁹⁻¹³ To date, no studies
65 have examined the comparative effectiveness of daptomycin label dose to higher dose in MRSA
66 BSI. Therefore, the objective of this study was to evaluate clinical outcomes among higher than
67 label daptomycin dose in MRSA BSI.

68

69 Methods

70 Study Population

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

79

80

81 Data Sources

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

88

89 Variable Definitions

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

96

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

102

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

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

113

114 Statistical analysis

115 Group differences were evaluated using chi-square or Fisher's exact tests for categorical
116 variables and t-test or Wilcoxon rank sum for continuous variables. Propensity scores were
117 developed based on variables including age, severity of illness, ICU admission, comorbid
118 conditions, medical history, presence of infectious diseases consult, year of treatment, hospital-
119 onset infection, time to initial daptomycin dose, and source of infection (Supplemental Table
120 S1). This logistic model was developed using unconditional logistic regression, with backwards,
121 step-wise elimination.^{22, 23} Assessments were made for multicollinearity and goodness of fit.²⁴
122 Caliper matching was performed using a caliper of 0.005, and replacements were not
123 performed.²⁴ Cox proportional hazard models were used to calculate hazard ratios (HR) and
124 95% confidence intervals (CI) for the outcomes. Sensitivity analyses were performed with
125 propensity score quintile adjusted Cox models.

126

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

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

141

142 **Results**

143 We identified 371 patients with MRSA bacteremia meeting our inclusion and exclusion criteria
144 (Figure 1) with 138 patients (37.2%) receiving higher than label daptomycin dose (Table 1).
145 Among patients with higher daptomycin dose (≥ 7 mg/kg), there were 42.8% (n=59), 50.0%
146 (n=69), and 7.2% (n=10) patients on 7 mg/kg, 8-9 mg/kg, and ≥ 10 mg/kg regimens,
147 respectively. In the overall cohort, patient baseline characteristics and clinical presentation were
148 similar between dose groups (Table 1). Average body mass index was higher among those
149 receiving the label dose compared with those treated at higher doses (28.8 vs 27.0; $p=0.02$).
150 Likewise, more patients with label dose were obese compared with higher dose (39.9% vs
151 29.0%; $P=0.03$). Finally, treatment with label dose vs higher dose varied by treatment period
152 (2009-2015 74.3% vs 87.7%; $P=0.002$).

153

154 Propensity score matched 30-day mortality was 18.6% (13/70) in the label dose group and 8.6%
155 (6/70) in the higher dose group (hazard ratio [HR] 0.31, 95% confidence interval [CI] 0.10-0.94;
156 Figure 2). No differences were observed in propensity score matched time to inpatient mortality

157 (HR 0.13, 95% CI 0.02-1.00), length of stay (HR 1.37, 95% CI 0.83-2.25), 30-day readmission
158 (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
159 sensitivity analyses with propensity score quintile adjusted Cox models, none of the outcomes
160 differed significantly between the label dose and high dose groups.

161

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

172

173 In an unmatched safety evaluation of the overall cohort, 73% (273) of patients had CPK levels
174 and 31.3% (116) had a baseline level. Among patients with a baseline CPK level, a total of 5.2%
175 had elevations. When stratified by daptomycin dose, CPK elevations were observed in 7.0%
176 (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
177 daptomycin dose regimens. Crude CPK elevations among label vs higher daptomycin dose
178 were not significantly different (7.0% vs 3.0%; $P = 0.66$).

179

180 **Discussion**

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

183 higher than label daptomycin dose (≥ 7 mg/kg vs label dose of 6mg/kg) in MRSA BSI and identify
184 an optimal daptomycin dose regimen. Consistent with *in vitro* studies suggesting increased
185 effectiveness with higher doses⁹⁻¹¹, our comparative effectiveness study demonstrated higher
186 doses were associated with improved survival. These results support current guidelines in
187 recommending higher than label daptomycin dose in patients with MRSA BSI.⁵⁻⁸

188
189 While two recent studies have concluded higher than labeled daptomycin dose (≥ 9 and ≥ 10
190 mg/kg) translates to improved clinical outcomes in vancomycin-resistant enterococcal (VRE)
191 BSIs^{28, 29}, our study is the first to establish this evidence in MRSA BSIs. A few studies have
192 evaluated higher daptomycin dose, however their results have been limited in interpretation for
193 MRSA BSIs since they included any infection site by any gram-positive organism and most of
194 these studies lacked a comparison group.^{13, 16, 30, 31} Studies focusing specifically on BSI with or
195 without infective endocarditis have also been limited in interpretation due to lack of dose
196 comparisons and inclusion of all gram-positive organisms.^{17, 18, 32}

197
198 Several *in vitro* and *in vivo* studies have suggested advantages of higher daptomycin dose with
199 increased log reduction of bacterial burden^{12, 33}, more rapid bactericidal activity^{9, 11, 34-36}, and
200 suppression of non-susceptible isolates.^{10, 33} Several studies have demonstrated increased
201 activity with higher daptomycin doses using daptomycin non-susceptible MRSA, hVISA, and
202 VISA isolates^{33, 34}, though daptomycin non-susceptible isolates are likely rare as a trend
203 analysis of 12,181 MRSA isolates from medical centers in the United States only found 0.11%
204 that were daptomycin non-susceptible.³⁷

205
206 Prior to the present study, the most relevant work in determining the impact of higher
207 daptomycin dose on clinical outcomes in MRSA BSI has been from simulation modeling
208 performed using data from a randomized, non-inferiority study comparing daptomycin to the

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

219

220 Two studies have suggested fixed daptomycin dose may be an alternative to a mg/kg dose.^{27, 39}
221 One study evaluated fixed dose and clinical outcomes among 50 critically ill patients receiving
222 6-8 mg/kg/day of daptomycin for *Staphylococcus* species-related infections. Using those data,
223 Monte Carlo simulations (MCS) were performed to determine the cumulative fraction of
224 response (CFR) and risk for muscle toxicity achieved by various fixed dose regimens. Fixed
225 dose regimens (500 mg and 750 mg for non-septic and septic patients, respectively) achieved
226 higher CFR than mg/kg dose strategies while simultaneously decreasing probabilities of muscle
227 toxicities. In our sensitivity analyses, fixed dose was not found to be predictive of 30-day
228 mortality. Moreover, the small, fixed dose study calculated probabilities of daptomycin trough
229 levels associated with risk for muscle toxicity to be 4.88-11.0% among non-septic patients. In
230 contrast, using our more direct surrogate measure of muscle toxicity, CPK, we found elevations
231 to be infrequent in our cohort, and lower in higher dose group than in the label dose group. Our
232 results of infrequent CPK elevations are consistent with a recent larger cohort of 911 patients
233 among whom CPK elevations were rare (<1%) among those receiving higher than label
234 daptomycin dose.²⁸

235
236 Several considerations should be made when interpreting our results. As a retrospective
237 observational study, unmeasured residual confounding may be present. Although all patients
238 were initiated on vancomycin, vancomycin minimum inhibitory concentrations (MICs) were not
239 analyzed, however the effect of these on outcomes remains unclear.⁴⁰ Similarly, daptomycin
240 MIC was not analyzed, yet MRSA isolates with daptomycin non-susceptibility remains rare.³⁷
241 We did not evaluate the impact of concomitant or prior MRSA active agents that some patients
242 may have received. Some data has suggested combination therapy with daptomycin and
243 another antibiotic may increase effectiveness for MRSA.^{41, 42} Future studies should consider the
244 impact of these factors on clinical outcomes. Identification of source control was not available
245 from our data. Our safety evaluation for CPK elevation was among a limited sample due to lack
246 of baseline testing for many patients. However, two recent studies evaluating higher daptomycin
247 dose regimens in VRE have suggested similar rates of elevations compared to label dose.^{28, 29}
248 Finally, while our CART analysis suggests a benefit with doses of ≥ 7 mg/kg among patients with
249 higher (>51%) predicted probabilities of 30-day mortality, CART analyses may be sensitive in
250 determining cutoffs based on the number of observations occurring at a splitting node (N=54 for
251 the high risk patients).⁴³ As a larger node of patients could have resulted in an alternative cutoff,
252 we recommend, and believe our data supports, the use of guideline recommended dosing of 8-
253 10 mg/kg for MRSA bacteremia with or without infective endocarditis.⁶

254

255 **Conclusion**

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

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283

284

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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

Comorbidities

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.

^aWithin 72 h of index culture; ^bModified APACHE III score; ^cCulture-confirmed source of infection; ^dSource of infection defined by ICD-9-CM code; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*

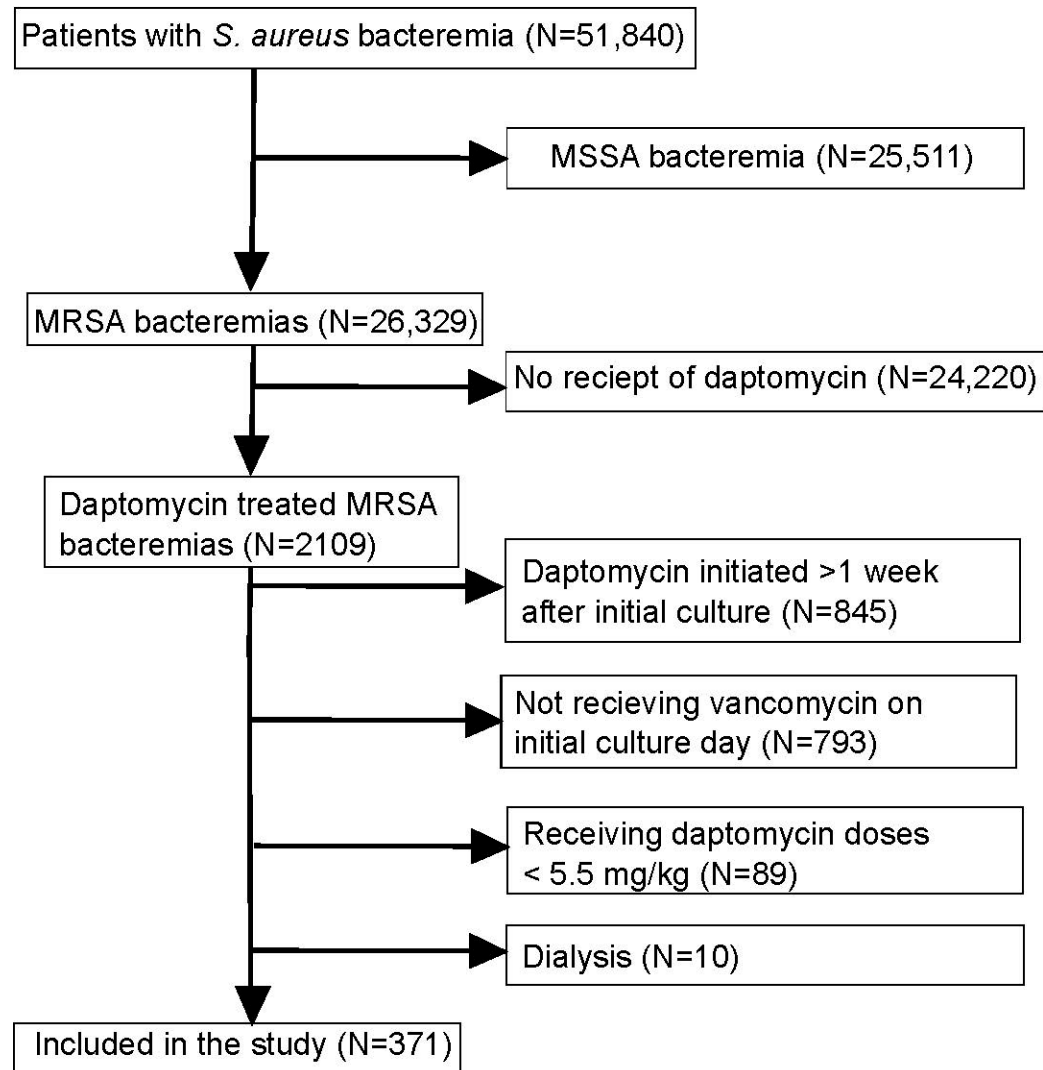
Figure 1. Flow diagram for inclusion and exclusion

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).

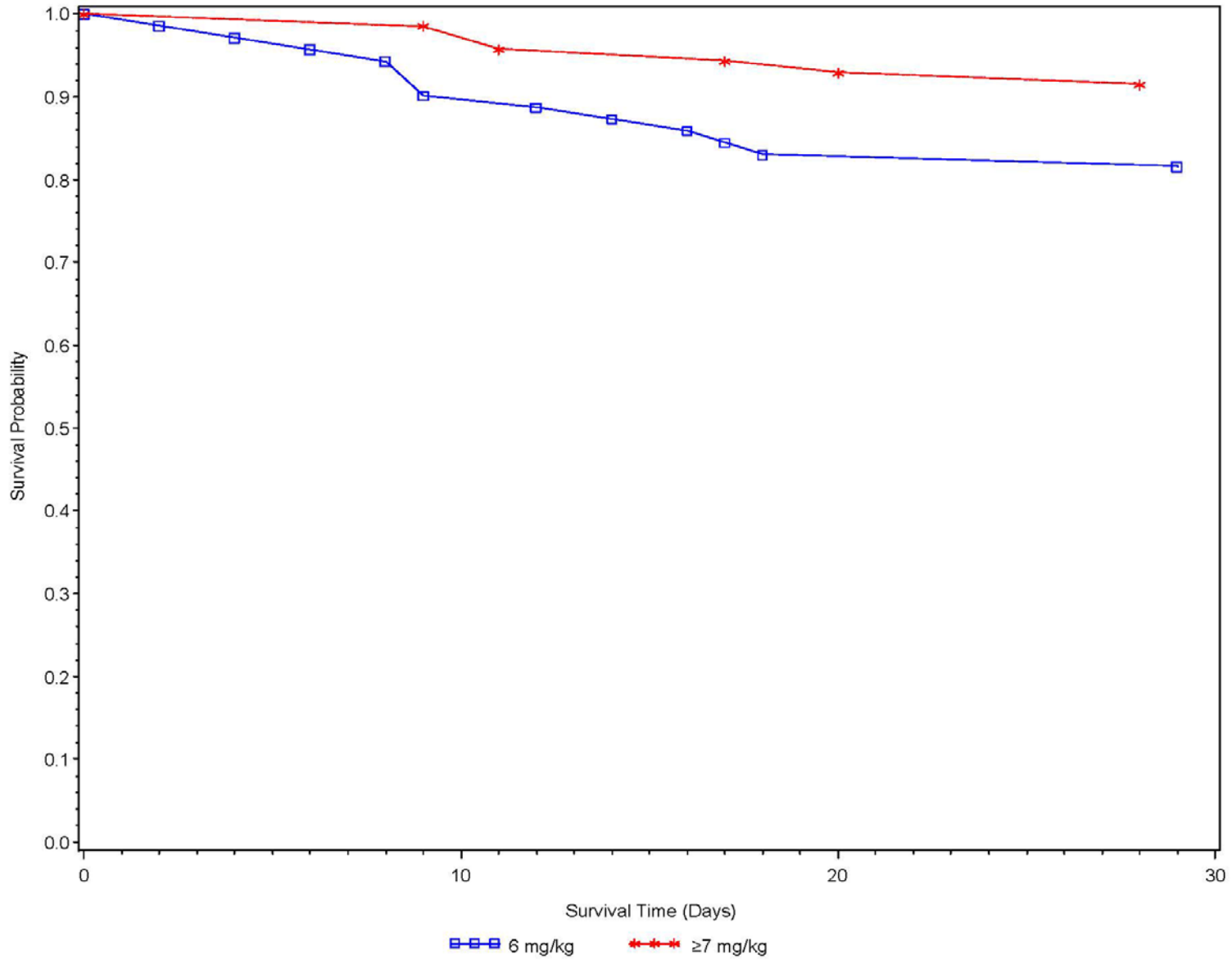
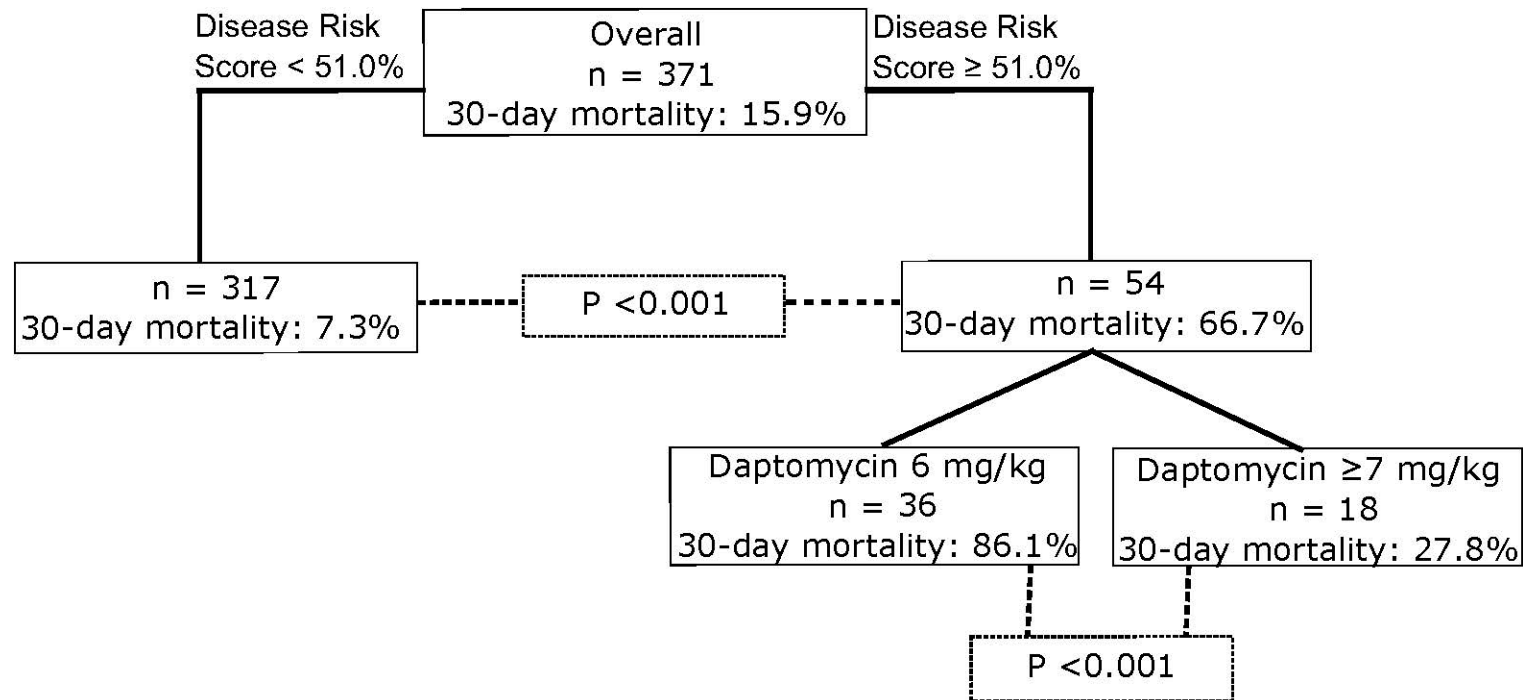


Figure 3. Comparison of 30-day all-cause mortality by classification and regression tree (CART)-derived breakpoints on disease risk score (DRS) and daptomycin mg/kg dose

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

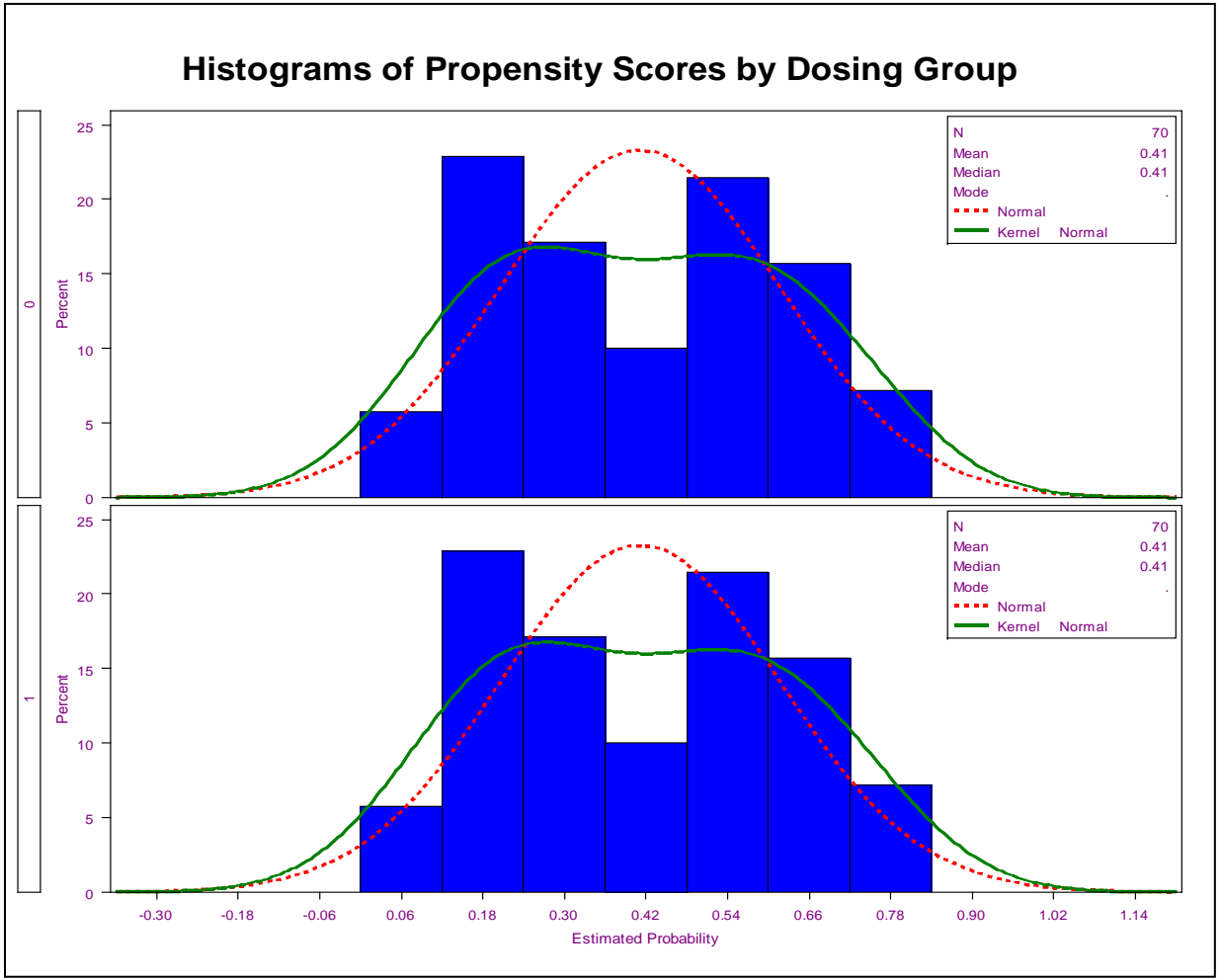


Supplemental Tables

Table S1: Variables included in final model

Propensity model	Disease risk score model
<ul style="list-style-type: none"> • Year, ≥65, ICU admission, sex, hospital (center effects), APACHE III, community onset, hepatic failure, ID consult • Current diagnosis <ul style="list-style-type: none"> • 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) <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • Skin (culture) 	<ul style="list-style-type: none"> • Year, ≥65, ICU admission, hospital (center effects), severe sepsis, ID consult, albumin level, operation during current admission • Current diagnosis <ul style="list-style-type: none"> • Respiratory failure, residual • Historical <ul style="list-style-type: none"> • Depression, bacterial infection, lower respiratory, osteoporosis • Source <ul style="list-style-type: none"> • Endocarditis (ICD-9)

Figure S1: Probability distributions by exposure



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