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

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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 (≥7mg/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 ≥7mg/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 (≥7mg/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.

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.

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 (≥7mg/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 ≥7mg/kg yielding a 30-day mortality

165 benefit (P<0.001) among patients with higher DRS (≥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 ≥7mg/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 ≥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 (≥7mg/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 doses[9-11], 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 ≥7mg/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.

261

262 **Acknowledgments**

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402

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

| | Daptomycin Dose | | | | | |
| | Overall Cohort | | | Propensity Matched | | |
Characteristic	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
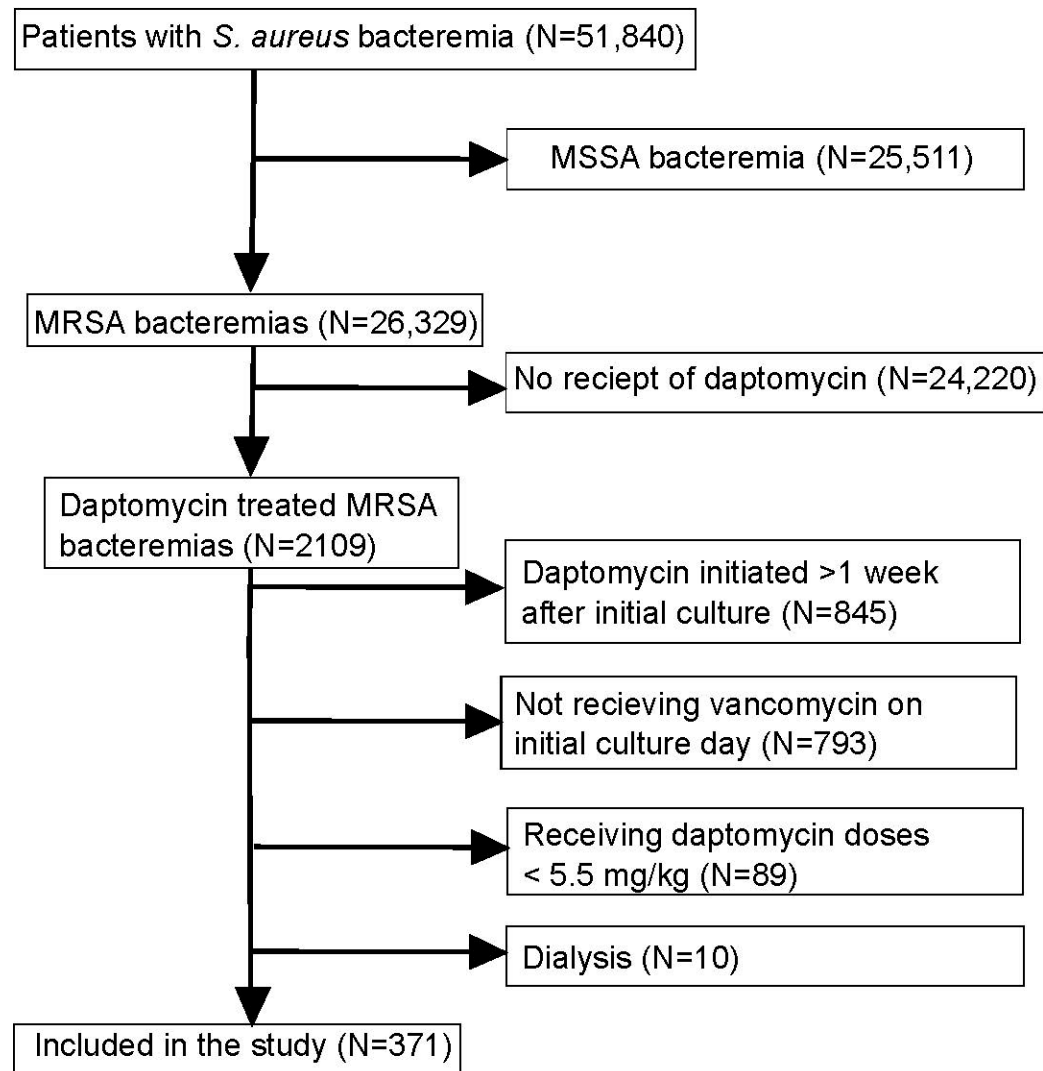
Figure 1. Flow diagram for inclusion and exclusion

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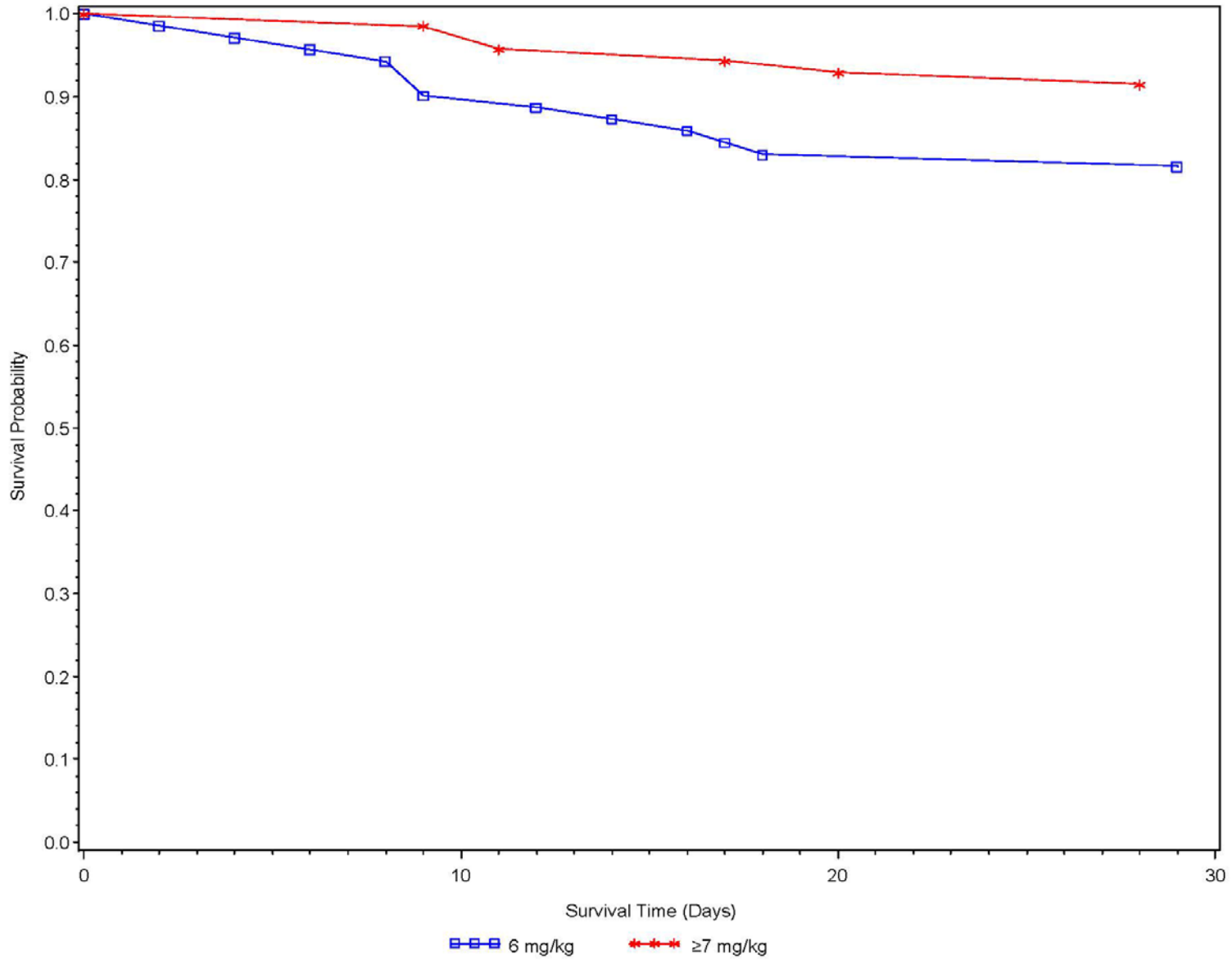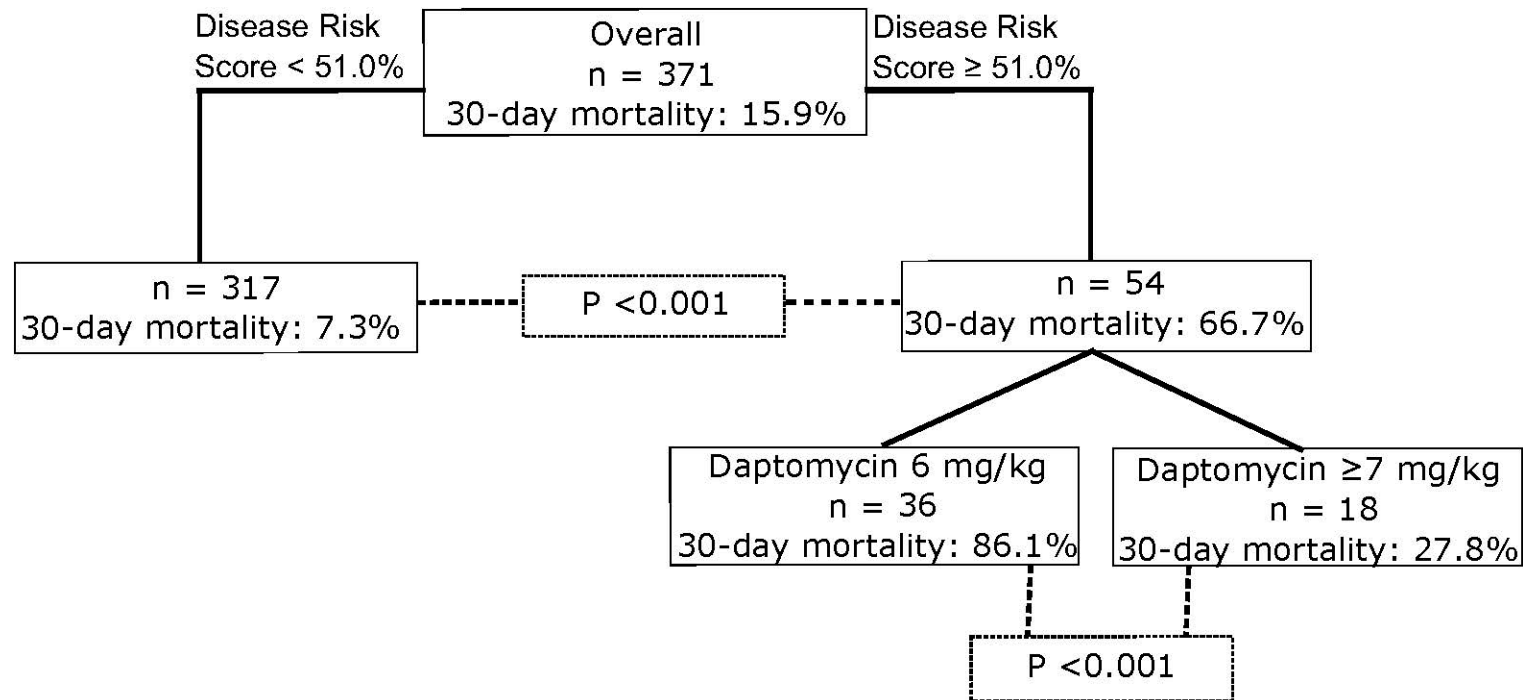
Figure 3. Comparison of 30-day all-cause mortality by classification and regression tree (CART)-derived breakpoints on disease risk score (DRS) and daptomycin mg/kg dose

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

Histograms of Propensity Scores by Dosing Group
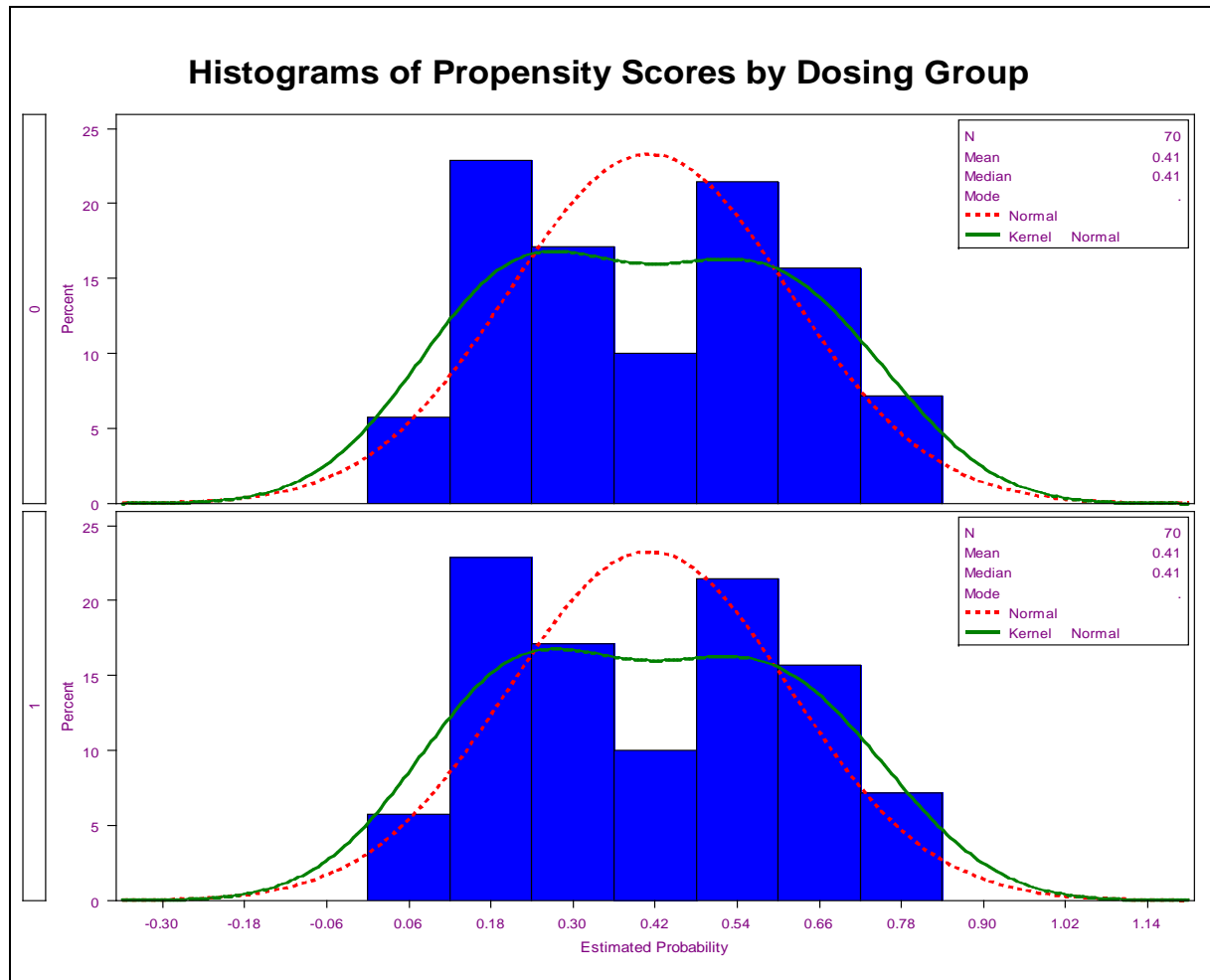
Note. Dosing group "0" for 6 mg/kg, "1" for ≥7mg/kg