Daptomycin dosing based on ideal body weight versus actual body weight: comparison of clinical outcomes

Daptomycin ideal body weight dosing
24 Byline

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Abstract

Daptomycin use at our institution changed to ideal body weight dosing based on a published analysis of pharmacokinetic-pharmacodynamic efficacy target attainment, bacterial ecology, and a desire to reduce drug toxicity. The current study compared outcomes between actual body weight and ideal body weight dosing of daptomycin before and after this intervention. In the evaluable group, sixty-nine patients received doses based on actual body weight and 48 patients received doses based on ideal body weight. Patients were treated for documented Enterococcus sp, Staphylococcus aureus, or coagulase-negative Staphylococcus infections, including: bloodstream, intra-abdominal, skin and soft tissue, urinary, and bone. There was no statistically significant difference in clinical success between the groups (actual body weight 88.9% vs. ideal body weight 89.1%, p=0.97). After adjusting for gender, age, body mass index, concomitant HMG-CoA reductase inhibitors, infection type, and organism type, clinical success rates remained similar between groups (adjusted odds ratio=0.68 in favor of actual body weight, 95% CI 0.13-3.55). Microbiological outcomes, length of stay, mortality, and adverse effects were also similar between groups. Further studies are warranted to confirm that ideal body weight provides similar outcomes to actual body weight dosing for all patients and types of infections and organisms.
Introduction

Conventional daptomycin doses, based on actual body weight, result in sufficient drug exposure to meet effective area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio. Dvorchik et al demonstrated a single 4 mg/kg dose of daptomycin administered to non-obese patients resulted in an AUC of 418±25 ug·h/mL.(1) A 6 mg/kg dose resulted in AUC values of 726±79 ug·h/mL in healthy, non-obese patients.(2) In a mouse-thigh infection model, Safdar et al. determined the 24 hour AUC/MIC parameters associated with bacteriostatic effect were 388-537 for four ATCC Staphylococcus aureus strains and 0.94-1.67 for two clinical isolates of Enterococcus faecium.(3)

Pharmacokinetic parameters may change in some patient populations, including obesity. In two studies evaluating actual body weight dosed daptomycin pharmacokinetics in the morbidly obese (1, 4), the AUC increased 30 to 60% compared to normal weight individuals. Volume of distribution (Vd) and clearance (CL) were reduced when normalized for weight.

Daptomycin dosing can be limited by toxicity, especially myositis and creatine phosphokinase (CPK) elevations with exposures exceeding two weeks duration.(5) In an examination of data from a randomized trial of daptomycin treatment of bacteremia and endocarditis, a direct relationship between minimum serum concentration (Cmin) and incidence of CPK elevation was established. Patients weighing ≥ 111 kg had a significantly higher probability of elevated Cmin. Using a Monte Carlo evaluation, dosing daptomycin based on IBW in simulated patients weighing ≥ 111 kg predicted AUC values that were not significantly different than those obtained with ABW in

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simulated patients weighing < 111 kg. More significantly, IBW in obese patients was predicted to reduce the risk of elevated Cmin concentrations and hence reduce toxicity in this model.

An internal review of all *S. aureus* and *Enterococcus* organisms at University of Wisconsin Hospital and Clinics collected between 2009 and 2010 was conducted and found 98.9% of *S. aureus* and *Enterococcus sp* were susceptible (MIC ≤ 1 ug/ml or ≤ 4 ug/ml, respectively) by Etest method to daptomycin. Based on a highly susceptible bacterial ecology, two PK/PD investigations suggesting minimum efficacy parameters are attainable in all patients, and a potential to reduce the risk of drug toxicity in obese patients, our institution adopted daptomycin therapeutic dosing based on IBW in July 2010. The aim of this study was to describe and compare clinical and microbiological outcomes between ABW and IBW dosing.

**Methods**

Patients who received daptomycin at the University of Wisconsin Hospital and Clinics between July 1, 2009 and July 1, 2011 were included in this investigation. Patients were greater than 17 years of age, had a positive culture and received daptomycin therapy for at least 72 hours. Patients with endocarditis or prosthetic device-related infections, without device removal, were excluded due to the prolonged treatment course and primary need for surgical management. Other exclusion criteria included: ABW less than IBW, receipt of daptomycin at an outside institution within 24 hours of admission, causative isolates known to be nonsusceptible to daptomycin, renal impairment, and pre-existing rhabdomyolysis. Renal impairment was defined as a creatinine clearance less than 30 mL/min (calculated using Cockcroft-Gault or Salazar-
Corcoran for patients with ABW greater than 30% over IBW), daptomycin dosed every 48 hours, or renal replacement therapy. This retrospective analysis was approved by the institutional review board at our institution.

The primary outcome measure was clinical success. Clinical success was defined as the number of patients with clinical cure or improvement divided by the overall number of evaluable patients. Clinical cure was characterized as clinical signs and symptoms resolved and/or no additional antibiotics with gram positive coverage necessary. Clinical improvement included patients who required additional antibiotic therapy after daptomycin was stopped but whose condition allowed for de-escalation of therapy. Clinical failure was defined as resistant, worsening, or new/recurrent clinical signs and symptoms of infection or the need for a change in antibiotic therapy (i.e. to different antibiotic with similar coverage or increase in dosage of daptomycin).

Assessment of clinical cure, improvement, or failure was completed by a blinded physician and pharmacist panel which reviewed the patient cases but was unaware of daptomycin dosing weight cohort. The panel was provided patient demographic information, type of infection, culture results, antimicrobials used before, during, and/or after daptomycin therapy, duration of daptomycin therapy, and patient outcome if known.

If the assessment was discordant, a third panelist assessed the outcome. If there was discordance among the previous three panelists, a fourth panelist assessed the outcome. If panelists judged that a patient could not be fairly categorized as cure, improvement, or failure, the patient was classified as nonevaluable for clinical outcome assessment. Other
efficacy outcomes included microbiological success, hospital length of stay and in-
hospital mortality.

Microbiologic success was defined as the number of patients having at least one 
microbiologic result with microbiological cure (documented or presumed eradication) 
and no results with microbiological failure (documented or presumed failure) divided by 
the overall number of evaluable patients. Documented eradication was described as a 
subsequent negative culture that demonstrated elimination of the causative organism. 
Presumed eradication was used to classify those cases when no repeat cultures were 
obtained but the patient clinically improved and received no subsequent targeted therapy.
Documented microbiological failure was described as failure to eradicate the original 
causative organism as documented by subsequent positive cultures. Presumed 
microbiological failure was used to classify those cases when no repeat cultures were 
obtained in the setting of clinical deterioration. Patients with no documented 
microbiological outcome and who were also nonevaluable for clinical outcome were 
deemed nonevaluable for microbiological outcome.

Incidence of CPK elevation, myopathy, and rhabdomyolysis were retrospectively 
reviewed to assess safety. The criteria for CPK elevation was adapted from the 
definitions used in the study by Bhavnani et al. to allow for assessment of patients who 
did not have baseline CPK values drawn. The normal reference range for CPK at 
UWHC is 0-175 U/L. Patients were considered to have a CPK elevation if one of the 
following was true: no CPK elevations at baseline or no CPK checked at baseline 
followed by CPK elevations greater than three times the upper limit of normal (ULN), 
baseline CPK greater than the ULN followed by CPK elevations greater than five times
the ULN, or if daptomycin was stopped by the treating physician due to concern for CPK elevation even if the degree of elevation did not meet the aforementioned criteria. If a patient had CPK elevation, the chart was reviewed for patient-reported symptoms of myopathy.

Wilcoxon rank-sum tests were used to compare continuous variables between patient groups. Chi-squared tests were conducted to compare clinical and microbiological success rates, in-hospital mortality, and other categorical variables. Logistic regression was also used to compare clinical success, clinical cure, and microbiological success between groups including terms adjusting for potentially confounding baseline covariates. Covariates identified through clinical considerations included age, gender, body mass index (BMI), organism type (a term for each of *Enterococcus sp*, methicillin-resistant *S. aureus*, methicillin-susceptible *S. aureus*, or coagulase-negative *Staphylococcus* infections), and infection type (a single term distinguishing bacteremia or osteomyelitis from intra-abdominal, skin and soft tissue, or urinary tract). Concomitant 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitor use was significantly different between groups and so was also included. A sensitivity analysis was performed to assess the effect of model selection on results. Odds ratios (and adjusted odds ratios from logistic regression) were used to quantify group comparisons of success and cure rates. P-values < 0.05 were considered statistically significant.

**Results**

**Patients**
A total of 308 patients (n=185 in the ABW group, n=123 in the IBW group) received at least 72 hours of daptomycin during the study period. Number of patients and reasons for exclusion are presented in Figure 1. The main reason for exclusion was lack of positive cultures. Sixty-nine ABW patients and 48 IBW patients were available for clinical and microbiologic analysis. Six patients (8.7%) in the ABW group and two patients (4.2%) in the IBW group were judged to be clinically nonevaluable, and they were not included in the clinical outcome assessment. Nonevaluable classification reasons included inadequate information due to loss of follow-up, concomitant double gram-positive antibiotic therapies, or infections that significantly confounded the outcome assessment. Four patients (5.8%) in the ABW group and one patient (2.1%) in the IBW group were nonevaluable for microbiological outcome and were not included in that assessment. Of the clinically nonevaluable patients, two patients (2.9%) in the ABW group and one patient (2.1%) in the IBW group had microbiological results and were included in the microbiological outcome assessment. For the above reasons, the number of patients included in the clinical and microbiological analyses was different.

Most baseline characteristics were similar between groups (Table 1). Use of HMG-CoA reductase inhibitors during daptomycin therapy was significantly higher in the ABW group (49.3% vs. 22.9%, p<0.01). More patients in the IBW group had enterococcal infections (75.0% vs. 56.5%, p=0.04). Percentages of methicillin-resistant \textit{S. aureus} (MRSA), methicillin-susceptible \textit{S. aureus} (MSSA), and coagulase-negative \textit{Staphylococcus} were infrequent, but similar. More patients in the IBW group had urinary tract infections (25.0 % vs. 10.1%, p=0.03). There was a trend towards more osteomyelitis in the ABW group (10.1% vs. 2.1%, p=0.09). Rates of bacteremia, skin
and soft tissue infection, and intra-abdominal infection were similar. Twenty one patients (30.4%) in the ABW group and 18 patients (37.5%) in the IBW group had bacteremia. Excluding one IBW subject with outlying weight of 339.5 kg, mean weights were similar with 91.0 kg (range 49.3-185.0) and 91.4 kg (range 52.0-150.0) in the ABW and IBW groups respectively (p=0.61), and actual body weight was 142% and 141% of ideal body weight in the ABW and IBW groups respectively (p=0.40). Nominal dosing rates (4 mg/kg versus 6 mg/kg) were similar (p=0.98) as was duration of therapy (p=0.89). Actual daily dose was 441 ± 130 mg and 328 ± 84 mg in the ABW and IBW groups respectively (p<0.01). Excluding the subject with outlying weight, actual dosing in the IBW group was 135 ± 103 mg less than it would have been if ABW dosing had been used. On average, IBW group subjects received an actual dose of 73.8 ± 14.0% of their hypothetical ABW dose.

Outcomes

The blinded panel that determined clinical outcomes was concordant for 75.2% of patients. Discordance was resolved with a third reviewer for 19.7% of patients. A fourth reviewer was needed to resolve the remainder (5.1%). There were no statistically significant differences between overall clinical or microbiological outcomes between the ABW and IBW groups (Table 2, all p≥0.19). The effect of ABW versus IBW dosing on clinical success was similar overall and within subgroups defined by presence of each type of infection and type of organism (Figure 2, all p≥0.12). In particular, for patients with MRSA, clinical success was similar between ABW and IBW groups (76.9% vs. 100%, p=0.12). Similarly, there was no evidence that
the effect of ABW versus IBW dosing on clinical success differed by concomitant HMG-CoA reductase inhibitor use (p=0.31) or body mass index (p=0.44).

After adjusting for gender, age, BMI, concomitant HMG-CoA reductase inhibitors, infection type, and organism type, clinical cure rates were similar between ABW and IBW (adjusted odds ratio=2.10 for IBW, 95% CI 0.79-5.54, 80% CI 1.11-3.16). Clinical success rates were also similar between ABW and IBW (adjusted odds ratio=0.68 for ABW, 95% CI 0.13-3.55). A sensitivity analysis to assess the effect of model selection on results was performed for all subsets of the above covariates, and estimates and confidence intervals were insensitive to model choice.

A large number of patients did not have follow up cultures documented (65% of ABW, 50% of IBW group). Among patients with documented eradication or failure, there was no statistically significant difference in documented microbiological outcomes between groups (p=1.00).

Length of hospital stay was similar between ABW and IBW (Table 2). Duration of hospital stay from collection of first positive culture (15.7 ± 14.1 days vs. 16.3 ± 14.1 days, p=0.82) and from start of daptomycin therapy (12.7 ± 12.4 vs. 12.8 ± 13.7 days, p=0.48) did not differ between groups. Five patients (7.3%) in the ABW group and two patients (4.2%) in the IBW group died during the hospital stay (p=0.49).

Safety

There were no significant differences in the number of adverse events in either group. CPK monitoring was absent in 46 patients (29 in the ABW group, 17 in the IBW group, p=0.60) during therapy. As a result, these patients were unable to be assessed for elevations. Eight ABW patients (11.6%) and five IBW patients (10.4%) experienced an
adverse event. Of patients with CPK measurements, one patient in the ABW group (and zero patients in the IBW group) experienced a CPK elevation. In this patient, CPK values increased by two and a half times the ULN which did not meet the previously defined criteria for an elevation; however, daptomycin therapy was discontinued by the medical team due to concerns regarding the CPK elevation. One patient in each group developed presumed daptomycin pulmonary toxicity. Six ABW patients (8.7%) and four IBW patients (8.3%) developed eosinophilia.

Discussion

To our knowledge, this is the first study to report clinical outcomes of patients receiving daptomycin doses based on IBW. Conventional daptomycin dosing at 4 mg/kg or 6 mg/kg results in AUC values of 418 or 726 ug·h/mL in non-obese patients and significantly higher AUC values in obese patients, both of which exceed the minimum PK/PD parameters associated with efficacy, including *S. aureus* and *Enterococcus sp.* Our results suggest that IBW dosing has similar clinical and microbiological success rates to those achieved with ABW for some infections. Overall, the clinical and microbiologic success rates when using IBW dosing were 89.1% and 91.7%. These success rates are similar to a prior effectiveness study demonstrating 93% clinical success rate for a variety of *S. aureus* infection types.(6) Furthermore, there were no significant differences between hospital length of stay, in-hospital mortality, or incidence of adverse effects.

Daptomycin is often a target for antimicrobial stewardship programs because of the poor clinical outcomes associated with MRSA infection and the associated high costs of *Staphylococcal* infection and drug acquisition. Kullar et al recently reported the use of daptomycin in a MRSA bacteremia treatment pathway for high-vancomycin MIC.
organisms. They found clinical success rates improved after a switch to high dose daptomycin. The same group found that mortality and persistent bacteremia significantly decreased when daptomycin therapy was provided early in cases of MRSA bacteremia with a vancomycin MIC >1 µg/mL. Fortunately at our institution, the incidence of high-vancomycin MIC (>1 µg/mL) represents only 7% of MRSA isolates (internal data). Three studies have evaluated the use of high-dose (> 6 mg/kg/day) daptomycin in a variety of infection types, including endocarditis, bacteremia, osteomyelitis, skin and soft tissue, and urinary tract infection, with a variety of organisms, including S. aureus, coagulase-negative Staphylococcus and/or enterococcal infections. High-dose daptomycin was found to be safe and effective in all reports.

The majority of patients in our study received daptomycin for the treatment of enterococcal infections. Only 34 of 117 (29.1%) patients received therapy for S. aureus infection; however, it does not appear that organism type had a significant effect on clinical outcomes. In particular, clinical success was statistically indistinguishable between ABW and IBW groups among patients with S. aureus, but the success rate was higher in the IBW group. When adjusting for baseline variables including organism type, the odds ratio for clinical success favored ABW while the odds ratio for clinical cure favored IBW, but in neither case was the difference statistically significant. Given the small overall sample size and the low numbers of patients with S. aureus or coagulase-negative Staphylococcus, it is difficult to completely exclude any difference in outcomes between ABW and IBW groups when considering specific organism type. In models adjusting for age, gender, BMI, HMG-CoA reductase inhibitors, infection type, and organism type, there was no statistically significant difference in outcomes between
ABW and IBW groups, although both had large confidence intervals. With respect to clinical cure, our results can rule out an odds ratio of 0.9 or less (that is, ABW being 10% more effective or better than IBW) with 96% confidence (one-sided). It is difficult to rule out superiority of ABW to IBW with respect to clinical success due to the large variance. However, given the favorable odds ratio for clinical cure in the IBW group and similar overall clinical success rates in both groups, it seems unlikely that IBW treatment led to significantly poorer patient outcomes.

Our data demonstrated no difference in clinical or microbiologic outcomes when adjusted for body mass index. This is consistent with prior studies which suggest that ABW dosing produces significantly higher AUC values in obese individuals and the idea that AUC values obtained with IBW dosing are adequate to meet minimum PK-PD parameter. Physiochemically, daptomycin has a small Vd (0.1 L/kg) and is likely to remain serum-concentrated with minimal tissue distribution. Dvorchik et al confirmed this finding and demonstrated that in obesity, the Vd decreased when adjusted for body weight. Since this was a retrospective study, we were unable to collect blood samples for PK analysis and determination of AUC/MIC values. The number of adverse events in each group was small, but similar. It is interesting to note that the rate of CPK elevation in our study was much lower than reported by Bhavnani et al, which demonstrated an increased risk of this event with prolonged daptomycin duration. Our findings may be attributed to the fact that complex infections requiring prolonged antibiotic duration including endocarditis and prosthetic device-related infections, without device removal, were excluded from our study. Although HMG-CoA reductase inhibitors may increase the risk of CPK elevation and myopathy, patients who received
these medications during daptomycin therapy did not have a higher rate of CPK elevations or clinical failures in our study. Therapy with these agents may also be a surrogate marker for unaccounted baseline characteristics and overall health status of patients who receive them. The statistically significant reduction in use of HMG-CoA reductase inhibitors between ABW and IBW groups was due to adoption of an institutional guideline protocolizing IBW dosing and recommending discontinuation of HMG-CoA reductase inhibitors during daptomycin therapy. We adjusted for this imbalance in our models to correct for direct effects and any correlated unaccounted baseline characteristics.

There are several limitations of our results. Labs, cultures, and other data used to determine outcome assessments were limited by what was available in the electronic medical records. As a result, follow up cultures and CPK monitoring was not completed for all patients, and there was the potential for patients to be lost to follow up. Our evaluation of adverse effects, specifically CPK, is limited. Over one-third of our patients did not have CPK documented during therapy and the average duration of inpatient therapy, eight days, is shorter than the typical time course for CPK elevation, myalgia, and rhabdomyolysis to begin to develop. Clinical and microbiological outcome definitions were subjective and relied upon medical record documentation; however, they were based on those used in a previous study. The analysis may be complicated by potential confounders, such as concomitant antimicrobials; however, similar percentages of patients in the IBW and ABW group received antimicrobials with activity against the targeted organism. Given the small sample size, our study lacked the power to detect significant differences or superiority in outcomes or adverse events between ABW and
IBW groups. Although our sample size was small, it is consistent with other dose finding studies where the sample sizes were small. Four prior studies that evaluated various daptomycin dosing regimens included 15, 24, 36, and 96 patients, respectively. An extended-infusion piperacillin-tazobactam study included only 194 patients. There were 117 patients in our study, which is comparable to the sample sizes of other daptomycin and novel dosing strategy studies.

Dosing of daptomycin based on IBW may not be appropriate for all institutions for *Staphylococcal* infections. Empiric IBW dosing should be done cautiously and only after the incidence of high-vancomycin MIC organisms is evaluated and daptomycin MIC values are found to be highly susceptible. Targeted IBW dosing could be considered in this scenario. However, we have not evaluated this “step-down” method at our institution.

**Conclusion**

Our study was the first to present clinical outcomes for IBW dosing. Our results suggest that ABW and IBW dosing may provide similar clinical and microbiological outcomes. Certain patient and infection characteristics may favor one dosing weight over another and further study is warranted. Both infection and organism type did not appear to have a significant effect on outcomes in our study; however, more data and additional studies are needed to confirm that IBW is comparable to ABW for all infection types and organisms.
Acknowledgements

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References


Figure 1: Patients evaluated for inclusion and reasons for exclusion

Figure 2: Clinical success rates by dosing group, overall and by infection type and organism type subgroups. Odds ratio estimates with 95% confidence intervals are shown for those subgroups with sufficient data. Chi-square tests of an association between clinical success and dosing group are given by subgroup.
Patients receiving ≥72 hrs of daptomycin therapy during 24 months n = 308

Received ACTUAL body weight dosing  
 n = 185

Exclusion criteria met n = 116
- No positive cultures (n=75)
- Daptomycin prior to admission (n=5)
- Organism not *Staphylococcus* or *Enterococcus* (n=4)
- Endocarditis (n=10)
- Prosthetic device involvement (n=1)
- Renal impairment (n=3)
- ABW < IBW (n=18)

ABW Analysis group n = 69

Received IDEAL body weight dosing  
 n = 123

Exclusion criteria met n = 75
- No positive cultures (n=47)
- Daptomycin prior to admission (n=3)
- Organism not *Staphylococcus* or *Enterococcus* (n=2)
- Endocarditis (n=2)
- Prosthetic device involvement (n=6)
- Renal impairment (n=6)
- ABW < IBW (n=8)
- Daptomycin MIC intermediate (n=1)

IBW Analysis group n = 48
Table 1. Baseline Characteristics between ABW and IBW Groups

<table>
<thead>
<tr>
<th></th>
<th>ABW (n=69)</th>
<th>IBW (n=48)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Age (yr), mean (SD)</td>
<td>56.9 (13.6)</td>
<td>57.6 (12.4)</td>
<td>0.72</td>
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<tr>
<td>Weight (kg), mean (SD)</td>
<td>91.0 (24.8)</td>
<td>91.4 (21.9)</td>
<td>0.61</td>
</tr>
<tr>
<td>ABW/IBW (%), mean (SD)</td>
<td>142 (44.0)</td>
<td>141 (28.4)</td>
<td>0.40</td>
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<tr>
<td>Body Mass Index (BMI) (kg/m^2), mean</td>
<td>30.9 (8.7)</td>
<td>31.0 (6.2)</td>
<td>0.44</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL), mean (SD)</td>
<td>1.33 (0.66)</td>
<td>1.35 (0.73)</td>
<td>0.93</td>
</tr>
<tr>
<td>BMI&gt;30 kg/m^2, n (%)</td>
<td>28 (40.6%)</td>
<td>25 (52.1%)</td>
<td>0.22</td>
</tr>
<tr>
<td>General floor status, n (%)</td>
<td>57 (82.6%)</td>
<td>42 (87.5%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>37 (53.6%)</td>
<td>28 (58.3%)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Medical Conditions, n (%)

- Diabetes                           | 26 (37.7%)| 20 (41.7%)| 0.66    |
- Cancer                              | 10 (14.5%)| 12 (25.0%)| 0.15    |
- Transplant                          | 22 (31.9%)| 17 (35.4%)| 0.69    |
- Surgery within past 30 days         | 22 (31.9%)| 10 (20.8%)| 0.19    |

Concomitant HMG-CoA reductase inhibitors, n (%) | 34 (49.3%)| 11 (22.9%)| <0.01    |

Infection Type, n (%)^

- Bacteremia                          | 21 (30.4%)| 18 (37.5%)| 0.43    |
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<th>Condition</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>p-value</th>
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<tr>
<td>Skin and soft tissue</td>
<td>26 (37.7%)</td>
<td>14 (29.2%)</td>
<td>0.34</td>
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<tr>
<td>Osteomyelitis</td>
<td>7 (10.1%)</td>
<td>1 (2.1%)</td>
<td>0.09</td>
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<tr>
<td>Intra-abdominal</td>
<td>17 (24.6%)</td>
<td>15 (31.2%)</td>
<td>0.43</td>
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<tr>
<td>Urinary tract</td>
<td>7 (10.1%)</td>
<td>12 (25.0%)</td>
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<th>Organism Type, n (%)</th>
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<th>Treatment 2</th>
<th>p-value</th>
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<tr>
<td>Enterococcus</td>
<td>39 (56.5%)</td>
<td>36 (75.0%)</td>
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<td>CoNS</td>
<td>24 (34.8%)</td>
<td>13 (27.1%)</td>
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<td>MRSA</td>
<td>13 (18.8%)</td>
<td>9 (18.8%)</td>
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<tr>
<td>MSSA</td>
<td>9 (13.0%)</td>
<td>3 (6.25%)</td>
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<tr>
<th>Prior antimicrobial therapy with activity against the isolated organism, n (%)</th>
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<th>Treatment 2</th>
<th>p-value</th>
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<tr>
<td>35 (50.7%)</td>
<td>19 (39.6%)</td>
<td>0.23</td>
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<th>Treatment 1</th>
<th>Treatment 2</th>
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<tr>
<td>7 (10.3%)</td>
<td>8 (16.7%)</td>
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<tr>
<th>Daily daptomycin dose (mg), mean (SD)</th>
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<th>Treatment 2</th>
<th>p-value</th>
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<tr>
<td>441 (130)</td>
<td>328 (84.1)</td>
<td>&lt;0.01</td>
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<th>Daily daptomycin dosing rates</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 mg/kg</td>
<td>39 (56.5%)</td>
<td>27 (56.2%)</td>
</tr>
<tr>
<td>6 mg/kg</td>
<td>30 (43.5%)</td>
<td>21 (43.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of therapy (days), mean (SD)</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.8 (26.1)</td>
<td>20.6 (19.5)</td>
<td>0.89</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Completed therapy as outpatient, n (%)</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>33 (48.5%)</td>
<td>27 (56.2%)</td>
<td>0.41</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of inpatient daily doses of daptomycin, mean, (SD)</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.4 (5.7)</td>
<td>8.1 (7.5)</td>
<td>0.28</td>
<td></td>
</tr>
</tbody>
</table>
No. of outpatient daily doses of daptomycin, mean, (SD) & 13.3 (24.6) & 13.1 (17.6) & 0.47

*Excludes one outlying subject with weight 339.5kg.

# All infection types are off-label usage of daptomycin except bacteremia (S. aureus) and skin and soft tissue.

^Some patients had more than one infection or organism type identified that was treated with daptomycin, but number of patients was used as the denominator to calculate the percentage reported.
Table 2. Comparison of Outcomes between ABW and IBW Groups

<table>
<thead>
<tr>
<th></th>
<th>ABW (n=63)</th>
<th>IBW (n=46)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical success, n (%)</td>
<td>56 (88.9%)</td>
<td>41 (89.1%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Clinical cure, n (%)</td>
<td>36 (57.1%)</td>
<td>32 (69.6%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Microbiological success, n (%)</td>
<td>59 (90.8%)</td>
<td>43 (91.5%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Length of hospital stay (days), mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- overall</td>
<td>20.8 (16.8)</td>
<td>20.8 (22.2)</td>
<td>0.34</td>
</tr>
<tr>
<td>- since collection of first positive culture</td>
<td>15.7 (14.1)</td>
<td>16.3 (14.1)</td>
<td>0.82</td>
</tr>
<tr>
<td>- since start of daptomycin</td>
<td>12.7 (12.4)</td>
<td>12.8 (13.7)</td>
<td>0.48</td>
</tr>
<tr>
<td>In-hospital mortality, n (%)</td>
<td>5 (7.3%)</td>
<td>2 (4.2%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Death related to infection, n (%)</td>
<td>1 (1.5%)</td>
<td>0 (0.0%)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

*Six patients in the ABW group and two patients in the IBW group were classified as clinically nonevaluable. Of these patients, two in the ABW group and one in the IBW group had microbiological results and were included in the microbiological analysis.

#Four patients in the ABW group and one patient in the IBW group were classified as microbiologically nonevaluable.
### Overall Infection Type

<table>
<thead>
<tr>
<th>Organism Type</th>
<th>ABW Successes/Total (%)</th>
<th>IBW Successes/Total (%)</th>
<th>Odds Ratio (Est w/ 95% CI)</th>
<th>Chi sq.</th>
<th>P−value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>56/63 (88.9%)</td>
<td>41/46 (89.1%)</td>
<td>0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td>15/19 (78.9%)</td>
<td>14/17 (82.4%)</td>
<td>0.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra−abdominal</td>
<td>15/16 (93.8%)</td>
<td>13/15 (86.7%)</td>
<td>0.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and Soft Tissue</td>
<td>20/22 (90.9%)</td>
<td>12/13 (92.3%)</td>
<td>0.89</td>
<td>0.12</td>
<td>0.03</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>6/7 (85.7%)</td>
<td>1/1 (100.0%)</td>
<td>0.69</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Urinary Tract</td>
<td>7/7 (100.0%)</td>
<td>11/12 (91.7%)</td>
<td>0.43</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>33/36 (91.7%)</td>
<td>31/35 (88.6%)</td>
<td>0.66</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>CoNS</td>
<td>20/22 (90.9%)</td>
<td>10/12 (83.3%)</td>
<td>0.51</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>MRSA</td>
<td>10/13 (76.9%)</td>
<td>9/9 (100.0%)</td>
<td>0.12</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>MSSA</td>
<td>7/7 (100.0%)</td>
<td>2/2 (100.0%)</td>
<td>1.00</td>
<td></td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Favors ABW**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Favors IBW</td>
<td></td>
</tr>
</tbody>
</table>

---

**Note:** The table above shows the successes and total percentages for different infection types and organism types, along with the calculated odds ratios, chi-square values, and p-values. The graph to the right illustrates the comparison between ABW and IBW for each category.