


Original Research

Efficacy and Safety of Weight-based Dosing of Daptomycin in Obese Patients: A Systematic Review

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Abstract

Purpose: To provide a comprehensive review of daptomycin weight-based dosing methods for obese patients. **Methods:** PubMed, Embase, Web of Science, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched through December 31, 2022. Studies relevant to daptomycin weight-based dosing methods in obese adult patients were included. **Results:** Sixteen studies were included, of which five were case reports and 11 were cohort studies. Obese patients were included in all case reports, of which one was pregnant. The infections improved after receiving a daptomycin dose based on actual body weight (ABW) in all cases. Seven studies demonstrated that ABW, ideal body weight (IBW), and adjusted body weight (AjbW)-based daptomycin dosing differed in terms of treatment success, microbiological clearance, and creatinine phosphokinase (CPK) elevation. However, AjbW was not statistically equivalent to ABW in all evaluated outcomes, except for treatment success. Three studies showed a higher area under the concentration-time curve (AUC) by 60% in obese patients, whereas two studies indicated a higher maximum plasma concentration (C_{max}) of ~2 folds. One study demonstrated that obese patients had higher levels of total clearance and volume of distribution, whereas other pharmacokinetic parameters were comparable between obese and non-obese patients. **Conclusion:** While most of the available evidence reported daptomycin dosing based on actual or total body weight, a few other studies have reported the use of ideal or adjusted body weight. A significant elevation in CPK was observed when daptomycin was administered based on AdjBW, but not with ABW and IBW. Further research is required to determine the optimal daptomycin weight-based dosing method in obese patients.

Keywords: daptomycin; obesity; body weight; creatine phosphokinase; drug dosage calculation

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INTRODUCTION

Obesity has been identified as an independent risk factor for increased mortality in patients with critical illnesses. In addition, it is linked to the impairment of the immune system, leading to an increased risk of infection.¹ Although antibiotic treatment plays a pivotal role in decreasing the mortality risk associated with infections, questions have often been raised regarding optimal antibiotic dosing to ensure positive outcomes and minimize side effects.² This can be achieved using different dosing strategies and understanding the pharmacokinetics and pharmacodynamics of each medication in different patient populations.¹

The obese population has been found to have increased kidney size and glomerular filtration rate (GFR), which has the potential to alter renal clearance and volume of distribution (V_d) of medications, including antibiotics.³ Commonly influenced pharmacodynamic parameters related to antibiotics include the area under the concentration-time curve to the minimum inhibitory concentration ratio (AUC:MIC), the peak concentration (C_{max}):MIC ratio, and the percentage of time that the antimicrobial concentration remains above the MIC (T>MIC).⁴



Daptomycin, a novel lipopeptide antibiotic used to treat severe infections caused by gram-positive bacteria, is cleared mainly by the kidneys, and its efficacy is predominantly correlated with AUC:MIC and C_{max} :MIC. It is currently administered based on the total body weight (TBW) in obese patients to achieve adequate therapeutic levels. Because daptomycin can accumulate when creatinine clearance (CrCl) falls below 30 mL/min, monitoring of creatine phosphokinase (CPK) and adverse events should be increased, as there is a potential risk for skeletal muscle toxicity.³

This systematic review aimed to summarize the evidence to determine the appropriate weight-based dosing strategy for daptomycin, resulting in optimal clinical outcomes in obese patients.

METHODS

Research Question and PICOS Criteria

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [5] were followed. A focused question in a PICOS format (Patient, Intervention, Comparison, Outcome, and Study design) was formulated to answer the following: “In adult obese patients requiring treatment with daptomycin, what is the optimal weight-based dosing method?”

PICOS Definition

Population: Adults (age ≥ 18 years) who were identified as overweight or obese, defined as having a body mass index (BMI) of 25 - 29.9 kg/m² for overweight and ≥ 30 kg/m² for obesity.⁶

Intervention: An intravenous daptomycin dose was administered based on the actual (total) body weight (ABW) for treating the corresponding infection.

Comparison: Administration of intravenous daptomycin that was dosed based on weights other than ABW [i.e., ideal body weight (IBW), adjusted body weight (AdjBW)]

Outcome: Study outcomes should include at least one of the following: clinical cure or microbiological cure and safety measurements for the elevation of creatine kinase level from the baseline.

Data Sources and Study Selection

We searched electronic databases, including the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, PubMed, Web of Science, and Scopus, using the following keywords: “daptomycin”, “dosing”, “obesity”, and “body weight”. The search was performed from inception to December 31, 2022. The references of the included studies were checked to identify additional relevant studies. The titles and abstracts were first screened to identify eligible studies. Full-text publications were retrieved. Studies were excluded based on the following criteria: no report of efficacy or safety outcomes, review articles, letters, editorials, animal studies, and studies published in languages other than English. Two

reviewers independently screened each database (SA, NA, JA, ZA, SMK, and NA). Discrepancies were resolved through discussions. The primary investigator (HAW) adjudicated the final decision to include the studies.

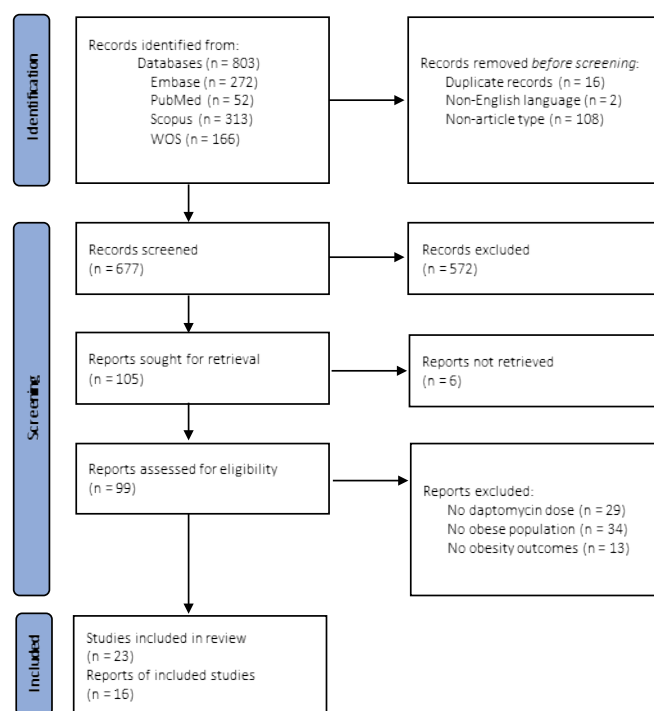
Data Extraction

A pre-specified data form was used to extract the following information: study characteristics (first author’s name, year of publication, study design, country, sample size, number of obese patients), patients’ baseline characteristics (characteristics of included patients, the proportion of obese patients, sex, age, weight, BMI, type of infection, infective organism), daptomycin administration (dose, weight used for dosing), and outcomes of interest (clinical cure, microbiological cure, creatine phosphokinase level, and adverse events).

RESULTS

Search Results

The database search yielded a total of 802 relevant records. After removing duplicates (n=16), articles published in languages other than English (n=2), and non-research article publications (n=108), 677 publications were screened for eligibility. After title and abstract screening, 23 articles were found to be initially eligible for inclusion in the full-text review. Of these, 16 met the inclusion criteria and were included in the systematic review to assess the effect of extreme weight on patients receiving daptomycin. The studies were conducted in four countries. The PRISMA flow diagram of study selection is shown in Figure 1.



WOS: Web of Science

Figure 1. Flowchart of the literature search process and extraction of studies that met the inclusion criteria



Study Characteristics

Sixteen studies, including four clinical pharmacokinetic studies, one of which was a pharmacokinetic simulation analysis; seven observational studies; and five case reports, with a total of 1570 subjects, were included in this systematic review, 805 of which were obese subjects. All the articles were published in English between 2005 and 2020. The ages of the participants ranged from 23 to 87 years. The baseline characteristics of the patients in the included studies are shown in Table 1.

Data Synthesis

Qualitative Evidence from Published Case Reports

Our search identified five case reports published between 2005 and 2020 (Table 2). Methicillin-resistant *Staphylococcus aureus* (MRSA) was the predominant microorganism, and skin and soft tissue infections (SSTIs) were the predominant types of infections. ABW was used as the standard weight for daptomycin dosing in all the cases.

Table 1. Baseline characteristics of the patient population in the included studies

Study (Year)	Study Design	No. of Patients	No. of Obese Patients	Weight (Kg), Mean (SD)	BMI Mean (SD)	Type of Infection	Organism
Dvorchik et al. (2005)	PK study	25	Moderately obese ^a : 6 Morbidly obese ^b : 7	Moderately obese: 85.7 (9) Morbidly obese: 125.8 (17) Matched control: 64.3 (7)	Moderately obese: 33.2 (4) Morbidly obese: 46.2 (6) Matched control: 24.3 (1)	Not reported	Not reported
Burns (2006)	Case report	One	One	158	Not reported	Bacteremia secondary to chronic right hip arthroplasty	MRSA
Pai et al. (2006)	Case report	One	One	209	66	Infected wound and cellulitis	MRSA
Pai et al. (2007)	PK study	14	Morbidly obese ^b : 7	Morbidly obese: 114.3 (15.8) Normal weight: 58.8 (6.2)	Morbidly obese: 46.2 (5.5) Normal weight: 21.8 (1.9)	Not reported	Not reported
Figueroa et al. (2009)	Cohort study	61	Grade I obesity ^c : 45 Grade III obesity ^b : 16	Not reported	Not reported	Skin and soft tissue infection, bloodstream infection, infective endocarditis, and intra-abdominal infection, bone, and joint infection.	MRSA, MSSA, MRSE, <i>E. faecium</i> , <i>E. faecalis</i> , GBS.
Traunmuller et al. (2010)	PK study	9	Morbidly obese ^b : 2 Obese ^d : 7	Morbidly obese: 166 (9) Obese: 92.1 (14.5)	Morbidly obese: 45.3 (1.6) Obese: 30.1 (3.3)	Diabetic foot infection	Not reported
Pea et al. (2011)	Case report	One	One	250	81.6	Severe cellulitis with possible early necrotizing fasciitis	No growth
Bookstaver et al. (2013)	Cohort study	126	Class I ^e : 39 Class II ^f : 39 Class III ^g : 48	Class I: 103.52 (9.31) Class II: 113.94 (10.05) Class III: 140.39 (29.86)	Not reported	Bacteremia, endocarditis, skin and soft tissue infection, osteomyelitis, urinary tract infections, and intraabdominal infections	MRSA, MSSA, <i>Enterococcus</i> spp., VRE, CoNS, and polymicrobial Gram-positive bacteria.

Ng et al. (2014)	Cohort study	117	53	Case: 91.4 (21.9) Control: 91.0 (24.8)	Case: 31.0 (6.2) Control: 30.9 (8.7)	Bacteremia, skin and soft tissue infection, intra-abdominal infection, osteomyelitis, and urinary tract infection	MRSA, MSSA, <i>Enterococcus</i> spp., and CoNS
Klibanov et al. (2014)	Case report	One	One	159	71.5	Panniculitis	Presumed to be MRSA
Britt et al. (2017)	Cohort study	911	Obese ^c : 279 Extremely obese ^b : 56	Not reported	Standard-dose ^e : 27.4 (23.7–31.7) Medium-dose: 26.3 (22.5–31.3) High-dose: 26.3 (22.4–30.5) ^h	Bloodstream infection	VRE
Butterflied-Cowper et al. (2018)	PK study	14	7	114.3 (15.8)	46.2 (5.5)	Not reported	Not reported
Fox et al. (2019)	Cohort study	101	101	Not reported	ABW group: 35 (32–43) AdjBW group: 37 (34–43) ^h	Urinary tract infection, skin and soft tissue infection, abscess, osteomyelitis, endocarditis, bacteremia, intra-abdominal infection, neutropenic fever	MRSA, MSSA, MRSE, VRE, <i>Enterococcus</i> spp.
Cojutti et al. (2020)	Case report	One	One	185	51.2	Bloodstream infection	MRSE
Lorenzo et al. (2020)	Cohort study	16	16	113.5 (23.4)	37.6 (8.7)	Bloodstream infection	MRSA, MSSA

^aBMI=25-39.9 kg/m²; ^bBMI≥40 kg/m²; ^cBMI=30–34.9 kg/m²; ^dBMI<40 kg/m²; ^eBMI≥30 kg/m²; ^fBMI≥35 kg/m².

^gFor the definition of doses, please refer to Table 2.

^hValues are reported as median (interquartile range).

Kg: kilogram; SD: Standard deviation; BMI: Body mass index; PK: Pharmacokinetic; MRSA: Methicillin-resistant *Staphylococcus aureus*; MSSA: Methicillin-sensitive *Staphylococcus aureus*; MRSE: Methicillin-resistant *Staphylococcus epidermidis*; GBS: Group B streptococcus; VRE: Vancomycin-resistant enterococci; CoNS: Coagulase-negative staphylococci; ABW: actual body weight; AdjBW: adjusted body weight.

Table 2. Daptomycin dosing and outcome information from the case reports and observational studies

Study (Year)	Daptomycin Dose	Dosing Weight	Maximum Daily Daptomycin Dose (mg)	Clinical Outcome	Microbiological Outcome	CPK Level (U/L)	Adverse Effects
Burns (2006)	6 mg/kg q24h	ABW	948	Clinical cure	Cure	60 – 172	None
Pai et al. (2006)	6 mg/kg q48h	TBW	1200	Clinical cure	Not reported	Not reported	None
Figueroa et al. (2009)	Mean, 8 mg/kg (Range, 7–11 mg/kg q24h)	ABW	Not reported	Not reported	Not reported	Not reported	Constitutional and/or musculoskeletal symptoms accompanying CPK levels >10 times ULN
Pea et al. (2011)	4.8 mg/kg q36-48h	TDM-based	1200	Clinical cure	Not reported	657 – 2241	None



Bookstaver et al. (2013)	Class I: 6.49 mg/kg Class II: 6.51 mg/kg Class III: 5.83 mg/kg ^a	ABW	1600	Clinical success: Class I: 66.7% Class II: 68.4% Class III: 77.1%	Not reported	132 ^b - 15,354	Myalgias; hypokalemia; arthralgias; <i>Clostridium difficile</i> infection
Ng et al. (2014)	4-6 mg/kg q24h	IBW or ABW	Not reported	Clinical cure: IBW: 69.6% ABW: 57.1%	Microbiological success: IBW: 91.5% ABW: 90.8%	437.5 ^c	Presumed daptomycin pulmonary toxicity; eosinophilia
Klibanov et al. (2014)	4 mg/kg q24h	TBW	800	Clinical cure	Not reported	36 – 49	None
Britt et al. (2017)	Standard dose: 6 mg/kg Medium dose: 8 mg/kg High dose: ≥10 mg/kg	TBW	Not reported	Compared to the high dose, the standard dose and medium dose were associated with poorer survival	Compared with the standard dose, the medium dose and high dose were associated with improved microbiological clearance	33.1, 33.5, 30.9 ^d	None
Fox et al. (2019)	Low: ≤6 mg/kg Medium: 6.1–8.0 mg/kg High: >8.0 mg/kg	ABW or AdjBW	Not reported	Clinical failure: ABW: 2% AdjBW: 6.1%	Microbiologic success: ABW: 10/18 (55.6%) AdjBW: 18/26 (69.2%)	Not reported	CPK elevation; patient-reported myopathy; rhabdomyolysis
Cojutti et al. (2020)	14 mg/kg	LBW	1250	Clinical cure	Microbiological cure	Not reported	Not reported
Lorenzo et al. (2020)	Fixed dose: 750 mg	N/A	750	Clinical cure: 9/16 (56.3%)	Microbiological cure	169 (51.3-286) ^e	Not reported

^aClass I, BMI ≥ 30 kg/m²; class II, BMI ≥ 35 kg/m²; class III, BMI ≥ 40 kg/m².

^bThe patient developed myalgia at this CPK level. The patient had a creatinine clearance of 13.58 mL/min at the time of daptomycin initiation.

^cReported in one patient in the ABW group.

^dMedian (IQR) normalized CPK: Standard-dose 33.1 U/L (IQR, 18.8–71.4); medium-dose 33.5 U/L (IQR, 19.3–73.5); high-dose 30.9 U/L (IQR, 17.3–66.7).

^ePeak CPK, median (IQR).

The first case involved a 54-year-old morbidly obese male weighing 158 kg infected with MRSA bacteremia secondary to chronic right hip arthroplasty infection. The bacteremia resolved 48 hours after adding daptomycin-rifampin to the vancomycin-gentamicin therapy. The daptomycin dose was 6 mg/kg based on ABW (948 mg every 24 h).⁷

Pai et al. reported the case of a 46-year-old morbidly obese man weighing 209 kg (BMI 66 kg/m²) who failed a 42-day course of vancomycin therapy to treat an MRSA-infected wound and cellulitis. A 6 mg/kg dose based on ABW (1200 mg) was administered every 48 h, based on the estimated clearance from the measured vancomycin concentrations. The patient demonstrated remarkable improvement without apparent side effects.⁸

Furthermore, Pea et al. reported a case of a 63-year-old man with morbid obesity weighing 250 kg (BMI 81.6 kg/m²) and a history of chronic leg ulceration due to peripheral vascular disease who was admitted to the emergency department with severe cellulitis. Broad-spectrum antimicrobial therapy was initiated with daptomycin and meropenem. The daptomycin dose was determined using the following formula: $LD = V_d \times C_{target}$. Based on therapeutic drug monitoring, the daptomycin

dosage was varied from 1200 mg every 48 h to 1200 mg every 36 h. Clinical response was observed within 72 h, and on day 29, antimicrobial therapy was switched to amoxicillin/clavulanate plus levofloxacin and then discontinued at discharge on day 53.⁹

Klibanov et al. reported a 34-year-old, 27-week pregnant, morbidly obese woman (weight 195 kg, BMI 71.5 kg/m²). She was diagnosed with panniculitis, and on hospital day 5, antimicrobial therapy was switched to daptomycin 4 mg/kg based on ABW (800 mg) every 24 hours. On hospital day 6, a significant clinical improvement in the infection site was noted, and she was discharged the next day and instructed to continue daptomycin with home health utilization for 14 days.¹⁰

Cojutti et al. reported a case of a 45-year-old critically ill, morbidly obese man weighing 185 kg; BMI:51.2 kg/m² who had methicillin-resistant *Staphylococcus epidermidis* (MRSE) and *Candida albicans* bloodstream infections. After 12 days of treatment for severe bilateral pneumonia with piperacillin/tazobactam and linezolid in the intensive care unit, the patient improved clinically with the resolution of pneumonia. One day after completing antibiotic therapy, he had signs of infection, and caspofungin was initiated when his blood cultures yielded



C. albicans on days 1 and 3. Daptomycin (1250 mg every 48 h) was started on day eight, following positive cultures with MRSE on days 5, 7, and 8. Based on real-time TDM, the daptomycin dose was increased to 1500 mg every 24 h, and fluconazole and ceftobiprole were added for synergism. On day 18, the patient's clinical status improved significantly.¹¹

Qualitative Evidence from Observational Studies

Seven observational studies published between 2005 and 2021 reported daptomycin dosing in obese patients, comprising 1,517 patients (Table 2).

In a retrospective chart review by Figueroa et al., 61 patients received a mean daptomycin dose of 8 mg/kg (range, 7-11 mg/kg) based on ABW for a median of 25 days. Grade I obesity was reported in 45 of the 61 patients, while grade III obesity was reported in the remaining 16 patients. The isolated microorganisms included but were not limited to (MRSA, MSSA, and *Enterococcus faecalis*). CPK elevation (levels >1000 U/L) and/or musculoskeletal symptoms occurred in 3 of 61 patients; two had grade III obesity. Daptomycin treatment was discontinued, and patients had a resolution of symptoms.¹²

Bookstaver et al. included 126 obese (BMI > 30 kg/m²) hospitalized patients in a multicenter retrospective cohort study. The mean daptomycin dose was 6 mg/kg based on the ABW (maximum dose was 10.31 mg/kg) for a mean duration of 20 days. Clinical effectiveness was documented in 71% of the patients and was consistent across BMI classes. MRSA was a predominantly isolated microorganism. Discontinuation due to ADEs occurred in eight patients (6.3%). The incidence of CPK elevation was 13.7% and 8.4% for CKP levels > 500 units/L and 1000 units/L, respectively. One patient developed rhabdomyolysis on day 9 of therapy.¹³

Ng et al. compared daptomycin dosing based on IBW versus ABW in 117 patients; 53 were obese (BMI > 30 kg/m²). Clinical success was not significantly different between the treatment groups: 88.9% in the ABW group vs. 89.1% in the IBW group (P = 0.97). Similarly, no difference in microbiological success was observed between the ABW and IBW groups (90.8% vs. 91.5%, P = 0.48). Daptomycin therapy was discontinued in one patient due to CPK elevation by two and a half times the upper limit of normal.¹⁴

Britt et al. included 911 patients in a retrospective cohort that compared standard-dose (6 mg/kg), medium-dose (8 mg/kg), and high-dose (≥10 mg/kg) daptomycin for vancomycin-resistant *Enterococcus* (VRE) bloodstream infection, 279 of them were obese, and 56 were morbidly obese. High-dose daptomycin was associated with improved survival and microbiological clearance in VRE-BSI, whereas no difference in the risk of CPK elevation was observed between the treatment groups (P = 0.504).¹⁵

AdjBW- versus ABW-based daptomycin dosing in obese patients was compared in a retrospective cohort study in which 101 patients were analyzed. The two daptomycin dosing cohorts were statistically equivalent for clinical failure and 90-day mortality.²

Lorenzo et al. retrospectively evaluated fixed-dose daptomycin (750 mg) in 16 obese patients with bloodstream infections caused by *Staphylococcus aureus*. Nine patients (56.3%) achieved clinical cure, and five (31.3%) died during admission. All patients cleared their bacteremia while admitted to the hospital, with a median (IQR) duration of bacteremia of 8 (6-12) days.¹⁶

Quantitative Evidence from Clinical Pharmacokinetic Studies

Four pharmacokinetic (PK) studies were included in this systematic review. A summary of the pharmacokinetic parameters is presented in Table 3.

An open-label, single-dose, parallel-group study of daptomycin pharmacokinetics included 25 subjects, six of them were moderately obese (BMI = 25-39.9 kg/m²), and seven were morbidly obese (BMI ≥40 kg/m²), and 12 matched (gender, age, renal function) nonobese (BMI = 18.5-24.9 kg/m²) control group. All subjects received a 4 mg/kg daptomycin dose based on TBW. Daptomycin plasma half-life, fraction of the dose excreted unchanged in the urine, and daptomycin absolute renal clearance (mL/h) were unchanged as a function of obesity. The absolute volume of distribution (V_d and V_{ss}) and plasma clearance (CL) of daptomycin were higher in obese subjects than in non-obese controls. The rate of change of V_d and CL with increasing BMI was greater when these pharmacokinetic parameters were expressed in absolute terms than when they were normalized for TBW or IBW. This suggests that the

Table 3. Daptomycin dosing and outcome information from the pharmacokinetic studies

Study (Year)	Daptomycin Dose	Dosing Weight	C _{max} (µg/mL), mean (SD)		AUC ₀₋₂₄ (µg•h/mL), mean (SD)		V _d (L/kg), mean (SD)	
			Morbidly Obese ^a	Normal Weight ^b	Morbidly Obese	Normal Weight	Morbidly Obese	Normal Weight
Dvorchik et al. (2005)	4 mg/kg/day	TBW	67.00 (6.95)	53.22 (6.02)	473.19 (80.11)	353.15 (71.23)	11.33 (1.20)	7.44 (1.26)
Pai et al. (2007)	4 mg/kg/day	TBW	67.3 (12.3)	42.3 (11.9)	494 (62)	307 (54)	10.04 (2.04)	7.69 (1.05)
Butterflied-Cowper et al. (2018)	6 mg/kg/day dose or a 500-mg daily fixed dose	TBW	6 mg/kg: 97.1 (30.1) 500 mg: 70.8 (19.4)	6 mg/kg: 55.4 (12.8) 500 mg: 78.5 (16.1)	6 mg/kg: 877 (236) 500 mg: 511 (130)	6 mg/kg: 638 (144) 500 mg: 658 (94)	5.13 (1.63)	5.57 (1.39)

^aBody mass index [BMI] ≥ 40 kg/m². ^bBMI = 18–25 kg/m².

TBW: Total body weight; C_{max} = Maximum plasma concentration; AUC₀₋₂₄ = Area under the concentration-time curve; V_d = apparent volume of distribution; SD: Standard deviation.



increase in body mass associated with obesity is proportionally higher than the corresponding increases in Vd and CL. Exposure to daptomycin in obese subjects (C_{max} , AUC) increased by 25% and 30%, respectively, compared to non-obese matched controls, well within the range previously determined to be safe and well-tolerated.¹⁷

Another single-dose (4 mg/kg TBW) pharmacokinetics study enrolled 14 subjects; seven of them were morbidly obese (BMI > 40 kg/m²), and seven were matched normal weight (BMI 18-25 kg/m²) subjects. The maximum plasma concentration and area under the concentration-time curve from dosing to 24 h were approximately 60% higher ($P < 0.05$) in the morbidly obese group than in the normal-weight group, and these were a function of the higher total dose received in the morbidly obese group. No differences in daptomycin volume of distribution (Vd), total clearance, renal clearance, or protein binding were observed between the two groups.¹⁸

In a nonparametric population pharmacokinetic analysis, the 6 mg/kg/day daptomycin dose was compared with a 500-mg daily fixed dose in obese and non-obese subjects using Monte Carlo simulations. No significant differences were observed in clearance, volume of distribution at steady state, or terminal half-life between morbidly obese and non-obese PK models. Daptomycin at 6 mg/kg/day resulted in AUC, C_{max} , and C_{min} values that were ~2-fold higher in morbidly obese subjects than in non-obese individuals. In contrast, fixed dosing (500 mg/day) yielded relatively isometric exposure. The fraction of simulated morbidly obese subjects with a C_{min} target associated with CPK elevation was 10.8% at 6 mg/kg/day and 2.0% at 500 mg/day.¹⁹

Traunmuller et al. enrolled nine patients; two of them were morbidly obese (BMI > 40 kg/m²), and seven were overweight (BMI < 40 kg/m²). The samples were divided into two groups (A and B), where serial sampling of specimens at steady state was performed from 0 to 8 h post-dose in five patients (Group A) and from 8 to 16 h after drug administration in another group of four patients (Group B). The microdialysis technique was used to collect interstitial space fluid from inflamed subcutaneous adipose tissue and metatarsal bone in diabetic patients with diabetic foot infection (DFI) requiring surgical debridement. The daptomycin dose was 6 mg/kg/day, based on TBW for four consecutive days. The plasma AUCs of daptomycin were higher in two morbidly obese patients than in subjects in the same group with a BMI < 40 kg/m² (349 versus 231.1 mg.h/L, respectively). However, tissue pharmacokinetic profiles were comparable between obese and nonobese patients.

DISCUSSION

Pharmacokinetics of Daptomycin

The kinetics of daptomycin were linear, with approximately 20% accumulation following repeated once-daily doses. Daptomycin is distributed primarily in extracellular fluid, does not readily cross cell membranes, and is bound (approximately 87%-94%) to serum proteins. Elimination is mainly caused by renal excretion of daptomycin.²¹

Daptomycin exhibits concentration-dependent bactericidal activity against gram-positive bacteria with C_{max}/MIC or AUC/MIC ratios, representing pharmacodynamic parameters predictive of success.¹⁵ Thus, higher doses of daptomycin (> 6 mg/kg daily) may be warranted in special populations to maximize the bioactivity and treatment success. Nevertheless, using a dose higher than the standard dose of daptomycin may contribute to an increased incidence of musculoskeletal toxicity, which is evident with elevated CPK.¹³

Daptomycin Dosing and Plasma Concentration with Obesity

The maximum plasma concentration of daptomycin and the area under the concentration-time curve from dosing to 24 h was approximately 60% higher ($P < 0.05$) in the morbidly obese group than in the normal-weight group [18]. The probability of elevated CPK levels demonstrated an association between daptomycin C_{min} values and CPK elevation. At a $C_{min} \geq 24.3$ mg/L, the probability of CPK elevation was significantly higher than that for $C_{min} < 24.3$ mg/L (50% vs. 2.9%; $P = 0.002$).²²

Efficacy and Safety of Daptomycin Dosing Methods with Obesity

The efficacy and safety of daptomycin dosing based on ABW were assessed in 126 hospitalized obese patients (BMI > 30 kg/m²) with varying degrees of renal function. The maximum dose administered was 1600 mg or 10.31 mg/kg based on ABW. This study suggests that daptomycin dosing based on ABW in obese patients has higher rates of CPK elevation and discontinuation of therapy owing to adverse events.¹³ In addition, in patients with class I, II, or III obesity, when daptomycin (4 – 6 mg/kg) was administered using adjBW versus TBW, no difference was observed in the clinical failure rate.²

When assessing the safety of a daptomycin dose of 8 mg/kg (range, 7-11 mg/kg) using ABW in 61 patients, three patients had constitutional and/or musculoskeletal symptoms accompanying CPK levels >10 times the upper limit of normal (grade 3). All cases occurred after 24 days of treatment and improved after the daptomycin treatment was discontinued. Two of the three patients were morbidly obese (BMI >40).¹² In addition, elevated CPK levels were reported as an adverse event in 49 (1.0%), 9 (2.0%), and 18 (2.8%) patients who received daptomycin doses ≤ 6 , >6 to <8 , and ≥ 8 mg/kg/day, respectively.²³

Fixed dosing rather than weight-based dosing has been proposed as an alternative approach to dosing with daptomycin.^{16,19,24} A pharmacokinetic study supports fixed-dosing strategies to effectively balance the efficacy and toxicity of daptomycin in obese populations.²⁴ In addition, in a Monte Carlo simulation used to model two doses, 6 mg/kg TBW/day and 500 mg/day, fixed-dose modeling showed similar AUC_{0-24h}, C_{max} , and C_{min} between the obese and non-obese groups.¹⁹ Finally, a clinical cure rate of 56.3% was reported when a fixed dose of 750 mg of daptomycin was used in obese patients, with a reported median peak CPK of 169.¹⁶

Pharmacists' Role in Optimizing Daptomycin Dosing

With their extensive education and training in the



pharmacokinetics and pharmacodynamics of medications, pharmacists can play an essential role in optimizing the dosing and monitoring of daptomycin, especially in obese patients. Ross and colleagues assessed the impact of implementing a high-dose daptomycin algorithm. Daptomycin dosing was 4-6 mg/kg for skin and soft tissue infections and 6-10 mg/kg for severe or difficult-to-treat infections, depending on the pathogen, disease state, and prior treatment as per the dosing algorithm. A statistically significant decrease in the mean daptomycin dose from 9.01 mg/kg to 7.51 mg/kg ($p < 0.005$) was observed, resulting in an annual cost savings of over \$75,000 without adversely affecting readmission rates due to infection.²⁵ Although the study included obese patients, the outcomes for this subpopulation were not presented. However, the overall positive results of the study might also indicate promising results in the obese population.

Implications for Further Research

Several knowledge gaps were identified based on this comprehensive systematic review. First, the optimization of daptomycin dosing in obese patients requires further research because there is a lack of prospective, randomized clinical trials assessing the appropriate daptomycin dosing methods in overweight or obese patients. Second, the number of obese patients included in the studies was relatively low, which may have overestimated the results. Future large-scale studies, including those with obesity who require daptomycin treatment, are warranted. Finally, investigating the mechanisms by which pharmacokinetic parameters change may help us determine whether this phenomenon is misleading. For example, one PK study reported that obese patients had higher Vd and Cl levels than non-obese patients. However, two studies reported that obesity does not affect Cl and Vd, and there is no statistically significant difference between obese and non-obese patients regarding these parameters.

Strengths and Limitations

To the best of our knowledge, this is the first comprehensive review of daptomycin dosing optimization in obese patients. The characteristics of each study and the key results are presented in Tables 1, 2, and 3, which provide specific details for pharmacists, physicians, and researchers. However, no quantitative analysis was performed because the available evidence was limited and diverse. Across studies, clinical heterogeneity existed, represented by the different types of infections with various degrees of severity and the inconsistent definition of clinical cure or treatment success. Nevertheless, this systematic review mapped the relevant literature on this

topic, allowing us to focus on optimizing daptomycin dosing in overweight or obese patients.

CONCLUSION

Our systematic review indicated that there is insufficient data on daptomycin dosing in obese patients. While most available evidence reported daptomycin dosing based on actual or total body weight, a few other studies have reported using ideal or adjusted body weight. A significant elevation in CPK was observed when daptomycin was administered based on AdjBW, but not with ABW and IBW. Therefore, the optimal daptomycin dosing method in these populations cannot be determined based on available evidence. Large randomized clinical trials are needed to investigate the appropriate method for daptomycin dosing.

AUTHORS' CONTRIBUTIONS

Haytham A. Wali and Abdulaziz S. Almulhim contributed to the study's conception and design. Sara Al-Maghem, Noura Al-Dughaim, Jawaher Al-Shamrani, Zainab Al-Omran, Sawsan M. Kurdi, Nura Alshehab, and Mohammed Y. Alshami performed material preparation, data collection, and analysis. Sara Al-Maghem, Noura Al-Dughaim, Jawaher Al-Shamrani, and Zainab Al-Omran wrote the first draft of the manuscript. All authors commented on the previous versions of the manuscript. All authors have read and approved the final manuscript.

REGISTRATION AND PROTOCOL

This systematic review was not registered, and a protocol was not prepared.

CONFLICTS OF INTEREST DISCLOSURE

The authors declare no potential conflicts of interest.

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DATA AVAILABILITY STATEMENT

The dataset is available upon request from the corresponding author.

References

1. Janson B, Thursky K. Dosing of antibiotics in obesity. *Current Opinion in Infectious Diseases*. 2012;25(6):634-49. <https://doi.org/10.1097/qco.0b013e328359a4c1>
2. Fox AN, Smith WJ, Kupiec KE, et al. Daptomycin dosing in obese patients: analysis of the use of adjusted body weight versus actual body weight. *Ther Adv Infect Dis*. 2019;6:2049936118820230. <https://doi.org/10.1177%2F2049936118820230>
3. Payne KD, Hall RG 2nd. Dosing of antibacterial agents in obese adults: does one size fit all? *Expert Rev Anti Infect Ther*. 2014;12(7):829-54. <https://doi.org/10.1586/14787210.2014.912942>



4. Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients: insights from the society of infectious diseases pharmacists. *Pharmacotherapy*. 2007;27(8):1081-91. <https://doi.org/10.1592/phco.27.8.1081>
5. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. <https://doi.org/10.1136/bmj.n71>
6. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. *The American Journal of Clinical Nutrition*. 1998;68(4):899-917. <https://doi.org/10.1093/ajcn/68.4.899>
7. Burns CA. Daptomycin-rifampin for a recurrent MRSA joint infection unresponsive to vancomycin-based therapy. *Scandinavian Journal of Infectious Diseases*. 2006;38(2):133-6. <https://doi.org/10.1080/00365540500277292>
8. Pai MP, Mercier RC, Allen SE. Using vancomycin concentrations for dosing daptomycin in a morbidly obese patient with renal insufficiency. *Ann Pharmacother*. 2006;40(3):553-8. <https://doi.org/10.1345/aph.1g509>
9. Pea F, Cojutti P, Sbrojavacca R, et al. TDM-guided therapy with daptomycin and meropenem in a morbidly obese, critically ill patient. *Ann Pharmacother*. 2011;45(7-8):e37. <https://doi.org/10.1345/aph.1p745>
10. Klibanov OM, Vickery S, Nortey C. Successful treatment of infective panniculitis with daptomycin in a pregnant, morbidly obese patient. *Ann Pharmacother*. 2014;48(5):652-5. <https://doi.org/10.1177/1060028014523731>
11. Cojutti PG, Carnelutti A, Mattelig S, et al. Real-Time Therapeutic Drug Monitoring-Based Pharmacokinetic/Pharmacodynamic Optimization of Complex Antimicrobial Therapy in a Critically Ill Morbidly Obese Patient. *Grand Round/A Case Study. Ther Drug Monit*. 2020;42(3):349-352. <https://doi.org/10.1097/ftd.0000000000000740>
12. Figueroa DA, Mangini E, Amodio-Groton M, et al. Safety of high-dose intravenous daptomycin treatment: three-year cumulative experience in a clinical program. *Clin Infect Dis*. 2009;49(2):177-80. <https://doi.org/10.1086/600039>
13. Bookstaver PB, Bland CM, Qureshi ZP, et al. SERGE-45 Investigators. Safety and effectiveness of daptomycin across a hospitalized obese population: results of a multicenter investigation in the southeastern United States. *Pharmacotherapy*. 2013;33(12):1322-30. <https://doi.org/10.1002/phar.1298>
14. Ng JK, Schulz LT, Rose WE, et al. Daptomycin dosing based on ideal body weight versus actual body weight: comparison of clinical outcomes. *Antimicrob Agents Chemother*. 2014;58(1):88-93. <https://doi.org/10.1128/aac.01018-13>
15. Britt NS, Potter EM, Patel N, et al. Comparative Effectiveness and Safety of Standard-, Medium-, and High-Dose Daptomycin Strategies for the Treatment of Vancomycin-Resistant Enterococcal Bacteremia Among Veterans Affairs Patients. *Clin Infect Dis*. 2017;64(5):605-613. <https://doi.org/10.1093/cid/ciw815>
16. Lorenzo MP, Housman EL, Housman ST. Evaluation of Fixed-Dose Daptomycin in Obese Patients With Bloodstream Infections Caused by *Staphylococcus aureus*. *Ann Pharmacother*. 2020;54(3):290-291. <https://doi.org/10.1177/1060028019883810>
17. Dvorchik BH, Dampousse D. The pharmacokinetics of daptomycin in moderately obese, morbidly obese, and matched nonobese subjects. *J Clin Pharmacol*. 2005;45(1):48-56. <https://doi.org/10.1177/0091270004269562>
18. Pai MP, Norenberg JP, Anderson T, et al. Influence of morbid obesity on the single-dose pharmacokinetics of daptomycin. *Antimicrob Agents Chemother*. 2007;51(8):2741-7. <https://doi.org/10.1128/aac.00059-07>
19. Butterfield-Cowper JM, Lodise TP Jr, Pai MP. A Fixed versus Weight-Based Dosing Strategy of Daptomycin May Improve Safety in Obese Adults. *Pharmacotherapy*. 2018;38(9):981-985. <https://doi.org/10.1002/phar.2157>
20. Traunmüller F, Schintler MV, Metzler J, et al. Soft tissue and bone penetration abilities of daptomycin in diabetic patients with bacterial foot infections. *J Antimicrob Chemother*. 2010;65(6):1252-7. <https://doi.org/10.1093/jac/dkq109>
21. Cubicin (daptomycin) [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp; February 2022.
22. Bhavnani SM, Rubino CM, Ambrose PG, et al. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. *Clin Infect Dis*. 2010;50(12):1568-74. <https://doi.org/10.1086/652767>
23. Seaton RA, Menichetti F, Dalekos G, et al. Evaluation of Effectiveness and Safety of High-Dose Daptomycin: Results from Patients Included in the European Cubicin® Outcomes Registry and Experience. *Adv Ther*. 2015;32(12):1192-205. <https://doi.org/10.1007/s12325-015-0267-4>
24. Falcone M, Russo A, Venditti M, et al. Considerations for higher doses of daptomycin in critically ill patients with methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2013;57(11):1568-76. <https://doi.org/10.1093/cid/cit582>
25. Ross JL, Rankin S, Marshik P, et al. Antimicrobial Stewardship Intervention and Feedback to Infectious Disease Specialists: A Case Study in High-Dose Daptomycin. *Antibiotics (Basel)*. 2015;4(3):309-20. <https://doi.org/10.3390/antibiotics4030309>

