# Daptomycin Dosing in Obesity: Which weight is the right weight?

Ashley N. Fox, PharmD
PGY2 Internal Medicine Resident
OU College of Pharmacy
Oklahoma City, Oklahoma
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Abstract # 12
IRB Approved

## Disclosure Statement

- Ashley N. Fox, PharmD
- Potential Conflicts of Interest: None
- Sponsorship: None
- Proprietary information or results of ongoing research may be subject to different interpretations
- Speaker's presentation is educational in nature and indicates agreement to abide by the non-commercialism guidelines provided

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## Learning Objectives

1. Describe concerns regarding daptomycin use in obese patients that could impact safety and efficacy of the drug.
2. Identify patients who might benefit from adjusted body weight (AdjBW) dosing of daptomycin based on the results of this study.

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## Study Institution

- 350-bed academic medical center
- Level 1 trauma center
- Infectious diseases section with ID specialists and fellows

https://www.oumedicine.com/ou-medical-center/hospital-Information

In 2014, OU Medical Center approved a protocol to dose daptomycin based on AdjBW in patients with body mass index (BMI) ≥ 30 kg/m$^2$

BMI = Body mass index

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## Pre-Assessment Questions

1. Which of the following adverse effects have occurred more commonly in obese patients taking daptomycin?
   A. Seizures
   B. Increased creatine phosphokinase
   C. Thrombocytopenia
2. At what BMI would you consider dosing daptomycin with an adjusted body weight?
   A. BMI ≥ 30 kg/m$^2$
   B. BMI 18.5 -25 kg/m$^2$
   C. BMI 25-30 kg/m$^2$

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## Daptomycin Overview and Activity in Obesity

- Concentration dependent, bactericidal activity against most gram-positive bacteria – MRSA and VRE
  - Pharmacokinetic parameter associated with efficacy: AUC/MIC
- In a pharmacokinetic study comparing obese patients to non-obese controls dosed with actual body weight (ABW)
  - AUC increased ~ 30%
  - $C_{max}$ increased ~ 30%

Higher daptomycin exposure in obese patients

Dvorchik BH, *J Clin Pharmacol*. 2005;45:48-56.

AUC = area under the curve (drug exposure over time)
MIC = minimum inhibitory concentration
$C_{max}$ = maximum concentration

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## Daptomycin Use in Obesity

- Daptomycin received FDA approval with doses studied of 4-6 mg/kg/day ABW in patients with normal renal function
- When approved, limited data was available for dosing in obese patients
- Retrospective studies suggest increased adverse drug events (creatine phosphokinase elevations) in populations with:
  - Obesity (BMI ≥ 30 kg/m$^2$)
  - Concomitant statin therapy

Bookstaver PB, et al. *Pharmacotherapy.* 2013;33:1322-30.
Bhavnani SM, et al. *Clin Infect Dis.* 2010;50:1568-74

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## Daptomycin Dosing in Obesity

| | |
|---|---|
| Ng, et al., 2014 | • Retrospective review<br>• Actual body weight (ABW) vs. ideal body weight (IBW) in patients with a BMI ≥ 30kg/m$^2$<br>• Staphylococcus aureus, Enterococcus, CONS<br>• Variety of infections<br>• No difference in clinical success or adverse events |
| Bookstaver, et al., 2013 | • Retrospective review<br>• Daptomycin dosed with ABW in patients with BMI ≥ 30 kg/m$^2$<br>• Stratified by BMI Classification<br>• No difference in ADEs between BMI classifications<br>• No difference in clinical effectiveness |

Ng, et al. Antimicrob Agents Chemother. 2014;58(1):88-93.
Bookstaver PB, et al. *Pharmacotherapy.* 2013;33:1322-30

CONS = Coagulase negative staph. sp.
ADE = Adverse drug event
ULN = Upper limit of normal

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## Daptomycin Dosing in Obesity

- Retrospective review
- Daptomycin mean dose 8mg/kg ABW
- Daptomycin mean treatment duration 25 days
- 61 patients included
  - 45 BMI Class 1
  - 16 BMI Class 3
- CPK elevation > 10x ULN in 3 patients
- No difference in safety for doses 8mg/kg versus lower doses

- Limited clinical and safety data for obese patients with normal renal function prescribed daptomycin regimens ≥ 8 mg/kg/day

Figueroa, et al., *Clin Infect Dis.* 2009;15;49(2):177-80.

CPK = Creatine phosphokinase
BMI Class 1: ≥ 30 kg/m$^2$ - 34.9 kg/m$^2$
BMI Class 2: 35 kg/m$^2$ – 39.9kg/m$^2$
BMI Class 3:≥ 40kg/m$^2$

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## Study Objective and Primary Endpoint

### Objective:

- Compare clinical and safety endpoints for obese patients (BMI ≥ 30 kg/m$^2$) receiving daptomycin dosing based on AdjBW to a historical cohort receiving daptomycin dosed based on ABW

### Primary Endpoint:

- Daptomycin clinical failure in obese patients dosed with ABW compared to AdjBW

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## Secondary Endpoints

- Microbiologic success
- Mortality at 90 days
- Readmission within 90 days
- Combined safety endpoint
  - Creatine phosphokinase (CPK) elevation
  - Patient reported myopathy
  - Rhabdomyolysis


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## Definitions

| | |
|---|---|
| Clinical Failure | • Development of resistance as noted on subsequent culture results<br>• Recurrent signs or symptoms of infection necessitating antibiotic therapy modification as documented in the patient's electronic medical record |
| Microbiologic Success | • At least 1 documented culture showing microbiologic eradication and no evidence of subsequent clinical failure |
| Creatine phosphokinase (CPK) elevation | • No CPK elevations at baseline or no CPK checked at baseline followed by CPK elevations ≥ 3x upper limit of normal (ULN)<br>• Baseline CPK greater than the ULN followed by CPK elevations ≥ 5x ULN<br>• Or daptomycin stopped by the treating physician due to concern for CPK elevation |
| Rhabdomyolysis | • Documented rhabdomyolysis on admission (secondary to trauma admission, seizure activity, or volume depletion)<br>• Elevation in CPK concentration as defined above PLUS<br>  • Positive urine myoglobin<br>  • Or acute kidney injury |

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## Methodology

- Retrospective chart review
  - Approved by University of Oklahoma HSC IRB
  - Identified patients by daptomycin order and BMI
- Evaluation of daptomycin dosing in separate cohorts
  - AdjBW: January 2014 - December 2015
  - ABW: January 2012 - December 2013
- Data collected utilizing a standardized form
  - Demographic data and daptomycin indication/dosing
  - Efficacy data: Clinical and microbiologic success
  - Safety data: rhabdomyolysis, CPK elevation, and patient reported myalgias
- Statistical analysis
  - Descriptive statistics (Fisher's exact, Mann-Whitney U test, Chi square)
  - Multivariate logistic regression

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## Inclusion and Exclusion Criteria

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| • Adult patients > 18 years<br>• BMI ≥ 30 kg/m²<br>• Daptomycin duration of therapy > 72 hours | • Renal dysfunction<br>  • CrCl < 30 mL/min<br>  • Q48H dosing<br>  • CRRT or HD<br>• Daptomycin therapy prior to admission<br>• Isolates not susceptible to daptomycin<br>• Infections with retained hardware<br>• Patients with rhabdomyolysis on admission<br>• Variations of documented weight of ≥ 20% during admission |

CRRT = continuous renal replacement therapy
HD = hemodialysis

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## Interim Demographics

| Characteristic | ABW Cohort (n=30) % (n) | AdjBW Cohort (n=26) % (n) | p-value |
|---|---|---|---|
| Age Median (IQR) | 47 (32-55) | 51 (42-58) | 0.2971 |
| Female | 60 (18) | 42 (11) | 0.1864 |
| BMI Class | | | |
| • Class I (30-34.9 kg/m²): | 47 (14) | 47 (14) | 0.3103 |
| • Class II (35-39.9 kg/m²): | 27 (8) | 35 (9) | |
| • Class III (> 40 kg/m²): | 27 (8) | 38 (10) | |
| BMI Median (IQR) | 35 (32-45) | 37 (34-41) | 0.3503 |
| Doses | | | |
| • 4-5.5 mg/kg/day | 13 (4) | 19 (5) | |
| • 5.6-7.49 mg/kg/day | 70 (21) | 15 (4) | 0.0093 |
| • ≥ 7.5 mg/kg/day | 17 (5) | 65 (17) | |
| Concurrent statin therapy | 23 (7) | 12 (3) | 0.3102 |

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## Interim Demographics

| Micro Data | ABW Cohort n=30 % (n) | AdjBW Cohort n=26 % (n) | p-value |
|---|---|---|---|
| Indication | | | |
| • Empiric | 7 (2) | 4 (1) | |
| • BSI | 3 (1) | 24 (6) | |
| • SSTI | 7 (2) | 16 (4) | |
| • Osteomyelitis | 43 (13) | 24 (6) | 0.089 |
| • Abscess | 17 (5) | 8 (2) | |
| • UTI | 10 (3) | 0 (0) | |
| • Neutropenic fever | 10 (3) | 8 (2) | |
| • Intra-abdominal | 3 (1) | 12 (2) | |
| • Pacemaker/ endocarditis | 0 (0) | 4 (1) | |
| | 0(0) | | |
| Organism (n) | | | |
| • MRSA | 4 | 4 | * No statistical analysis |
| • MSSA | 2 | 0 | |
| • VRE | 4 | 8 | |

BSI = Blood stream infection
SSTI = Skin soft tissue infection

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## Interim Results

| Endpoint | ABW Cohort (n=30) % (n) | AdjBW Cohort (n=26) % (n) | p-value |
|---|---|---|---|
| Clinical Failure | 0 (0) | 4 (1) | 0.4643 |
| Adverse Event | 10 (3) | 23 (6) | 0.2771 |
| All-cause Mortality at 90 days | 10 (3) | 4 (1) | 0.6151 |
| Readmission within 90 days | 20 (6) | 8 (2) | 0.2627 |
| Micro Success | 60 (6) | 92 (12) | 0.1269 |

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## Limitations

- Retrospective, single center trial
- Small sample size
- No statistical power calculation
- Microbiological success dependent upon repeated cultures from primary site of infection with demonstrated clearance
- Admissions related to primary infection at OSH not captured by medical record
- Weights obtained for antibiotic dosing may not be uniform (bed weight versus standing weights)

OSH = Outside hospital

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## Conclusions

- Interim data suggests there is no difference in clinical failure or adverse effects when patients are dosed using an adjusted body weight
- Secondary endpoints regarding microbiological cure, mortality at 90 days and readmission within 90 days were not statistically different between the groups
- Daptomycin doses have increased in clinical practice
  - This project could provide clinical and safety information for patients with obesity and high dose daptomycin

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## Self-Assessment Question

1. Which of the following has been identified as a concern regarding daptomycin dosing in obesity?
   A. Increased creatine kinase
   B. Decreased daptomycin area under the concentration-time curve
   C. Increased daptomycin drug clearance
   D. Increased daptomycin volume of distribution

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## Self-Assessment Question

1. For which of the following patients could the data presented assist in determining the daptomycin dosing strategy?
   A. 29 YO M with BMI 38 kg/m$^2$, CrCl of 98 mL/min, and surgical site infection with retained hardware
   B. 75 YO M with BMI 32 kg/m$^2$, CrCl < 30 mL/min, and diagnosis of VRE bacteremia
   C. 60 YO M with BMI of 28 kg/m$^2$, CrCl of 85 mL/min, and diagnosis of VRE intra-abdominal abscess
   D. 45 YO F with BMI of 45 kg/m$^2$, CrCl of 55 mL/min, and diagnosis of osteomyelitis

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## Daptomycin Dosing in Obese Patients:
### Analysis of Adjusted Body Weight VS. Actual Body Weight


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