Impact of Body Size Descriptors on Initial Treatment Response and Thirty-Day Mortality in Patients with Gram-Negative Infections

Meghan N. Jeffres, PharmD[1,2,3]

Sean M. Barclay, PharmD[1,2,3,]

Michael W. Daly, PharmD[4]

Mark C. Decerbo, PharmD[1,2,3]

Peter Golenia, PharmD[5]

[1]*Roseman University of Health Sciences College of Pharmacy*
[2] *University Medical Center of Southern Nevada Department of Pharmacy*
[3]*University of Nevada School of Medicine Department of Internal Medicine*
[4]*St. Louis College of Pharmacy Department of Pharmacy Practice*
[5]*Boston Medical Center Department of Pharmacy*

Meghan N. Jeffres, PharmD, BCPS
Roseman University of Health Sciences, College of Pharmacy
11 Sunset Way
Henderson, NV 89014
Phone: 702-968-2084
Fax: 702-990-4435
mjeffres@roseman.edu

Disclosures:
This study was funded through an intramural grant from Roseman University of Health Sciences

KEY WORDS: Obesity, body mass index, weight, infection

ABSTRACT

Objective

To determine the body size descriptor that is most predictive of clinical outcome in patients with gram-negative infections treated with beta-lactam antibiotics.

Design

A retrospective-cohort analyzing association between various body size descriptors and initial patient response to antibiotic therapy and 30-day mortality.

Subjects

Hospitalized patients with sterile site gram-negative infections receiving appropriate beta-lactam therapy at an academic county hospital between January 2005 and January 2010 were screened for inclusion. Patients were excluded for a delay in therapy greater than 24 hours from time of culture collection or a creatinine clearance less than 60 ml/min during antibiotic therapy.

Results

A total of 234 patients were included in the analysis, of which 38 (16.2%) experienced initial treatment failure and 12 (5.1%)

expired. Differences in baseline characteristics and process of care variables between patients with complete or partial response vs treatment failure were APACHE II scores (11.4 vs 14.9, p<0.001), intensive care unit stay (60.7% vs. 86.8%, p=0.001), and mechanical ventilation (34.2% vs 76.3%, p<0.001). Significant differences in body size descriptors between patients with complete response versus treatment failure were total body weight (77.1 vs 88.4 kg, p=0.025), body mass index (26.5 vs 29.9 kg/m2, p=0.038), body surface area (1.9 vs 2.0 m2, p=0.043), and lean body weight2005 (53.9 vs 59.5 kg, p=0.029). Total body weight was statistically higher in non-survivors (79.3 vs 96.2 kg, p=0.014). Logistic regression identified total body weight, APACHE II score and mechanical ventilation as predictors for both initial treatment failure and 30 day mortality.

Conclusion

Increased total body weight was associated with initial treatment failure and 30-day mortality in patients with gram-negative infections. This discrepancy in treatment outcomes warrants further investigation into potential causes, including pharmacokinetic and pharmacodynamic changes, as well the potential presence of a sick patient bias conferred by higher total body weight.

INTRODUCTION

Based on 2008 World Health Organization (WHO) estimates, 1.5 billion adults were overweight, with over 200 million men and nearly 300 million women being classified as obese.[1] Even with this increasing prevalence of obesity, there continues to be a void in the scientific literature regarding the impact of body habitus in relation to clinical outcomes in patients with bacterial infections. Thus far, the only body size descriptor studied in relation to infection associated outcomes has been body mass index (BMI). Multiple studies have found obesity (BMI ≥ 30 kg/m^2) or morbid obesity (BMI ≥ 40 kg/m^2) to be associated with increased mortality in patients with bacterial infections.[2-5] Limitations of the current literature include the dichotomization of patients into either obese or non-obese instead of analysis of body size descriptors as continuous data. Additionally, no other body size descriptors have been evaluated for their precise predictive value on infection related treatment outcomes.

The objective of this study is to determine which body size descriptors, if any, are associated with poor treatment outcomes and mortality in hospitalized patients with gram-negative infections treated with anti-pseudomonal beta-lactam antibiotics.

METHODS

Patients

Adult inpatients at University Medical Center of Southern Nevada with cultured sterile site gram-negative infections that received an anti-pseudomonal beta-lactam antibiotics between August 2005 through February 2010 were screened for inclusion. Only the first sterile site infection for each patient was included in the analysis. To control for pharmacokinetic and pharmacodynamic confounders patients were excluded if their estimated creatinine clearance less than 60 ml/minute during antibiotic receipt, receipt of multiple anti-pseudomonal beta-lactams, or changes in dose or frequency during first 120 hours of treatment.

Microbiology Identification

Species identification and susceptibility testing was performed using Phoenix Automated Microbiology System (BD Biosciences, USA).

Study Design and Data Collection

A retrospective observational cohort study was conducted to identify the relationship between multiple size descriptors and treatment outcomes of patients with sterile site gram-negative infections treated with anti-pseudomonal beta-lactams. Medical records of all patients were reviewed. The data collected included age, sex, weight, height, site of infection, antibiotic regimen, receipt of immunosuppressive medications, receipt of vasopressors for hemodynamic support, severity of illness at the time of culture draw

Table 1. *Body size descriptor formulas*

	Abbreviation, unit	Formula
Body mass index (20)	BMI, kg/m^2	TBW(kg)/ht (m^2)
Body surface area (21)	BSA, m^2	$TBW^{0.425}$ x HT $(cm)^{0.725}$ x 0.007184
Lean body weight (22, 23)	LBW, kg	For males: (1.1 x TBW) – (0.0128 x BMI x TBW) For females: (1.07 x TBW) – (0.0148 x BMI x TBW)
Lean body weight (24)	LBW_{2005}, kg	For males: (9270 x wt (kg)) / 6680 + 216 x BMI (kg/m2) For females: (9270 x wt (kg))/8780 + 244 x BMI (kg/m2)

(calculated by the APACHE II score,[6] use of mechanical ventilation, receipt of vasopressors, intensive care unit stay, duration of hospital stay before and after onset of infection, length of hospital stay, and select comorbid conditions including malignancy, diabetes, and cirrhosis. Body size descriptors were calculated for each patient using equations found in Table 1.

The main outcome measures were the initial response to treatment and 30-day mortality. The initial response to treatment was assessed between hours 96 and 120 after starting antibiotic therapy and designated into one of three groups as follows: complete response (patients who showed resolution of fever, leukocytosis, and all other signs of infection); partial response (patients who showed an abatement of the above, but not complete resolution); failure (no abatement, or a deterioration, in any of their clinical parameters); or death (7).

Definitions

Infection was defined as a sterile site gram-negative culture and at least two systemic inflammatory response and syndrome (SIRS) criteria. Sterile site infection was defined as a finding of a gram-negative pathogen in either blood, respiratory (bronchial or tracheal wash or bronchoalveolar lavage), or peritoneal fluid. Infections were categorized as polymicrobial if two or more pathogens were recovered from cultures.

Appropriate empiric beta-lactam therapy was defined as initiation of either cefepime, piperacillin/tazobactam, meropenem, or imipenem within 24 hours of the culture being drawn, with confirmed in vitro activity against the gram-negative pathogen.8

Statistical Analysis

Student's t-test was used to compare continuous variables, and the Chi-Square test was used to compare categorical variables. Univariate logistic regression was used to determine the odds ratio of treatment failure and mortality for each body size descriptor. Multivariate logistic regression was used to identify the independent risk factors of treatment failure and mortality and control for confounding variables. All p-values were two-tailed, and values less than 0.05 were considered to be statistically significant. SPSS software, version 19.0, was used for the analyses.

RESULTS

Patient Characteristics

A total of 234 patients were included in the analysis, of which 38 (16.2%) experienced initial treatment failure and 12 (5.1%) expired. Baseline characteristics of patients with complete or partial response to antibiotic therapy and patients experiencing treatment failure are presented in Table 2.

Table 2. *Baseline characteristics and process of care variables*

Male, n (%)	119 (60.7)	23 (60.5)	0.560
Age, years ± SD	47.3 ± 15.6	47.4 ± 14.9	0.970
Malignancy, n (%)	30 (15.3)	10 (26.3)	0.083
Diabetes, n (%)	36 (18.4)	7 (18.4)	0.575
Cirrhosis, n (%)	8 (4.1)	1 (2.6)	0.555
Steroids, n (%)	31 (15.8)	8 (21.2)	0.281
APACHE II ± SD	11.4 ± 5.0	14.9 ± 4.4	<0.001
Intensive care stay, n (%)	119 (60.7)	33 (86.8)	0.001
Mechanical ventilation, n (%)	67 (34.2)	29 (76.3)	<0.001
Vasopressor use, n (%)	35 (17.9)	11 (28.9)	0.091
Site of infection			
Pulmonary, n (%)	35 (17.9)	12 (31.6)	
Blood, (%)	139 (70.9)	20 (52.6)	0.078
Intra-abdominal, n (%)	22 (11.2)	6 (15.8)	
Concurrent bacteremia, n (%)	20 (10.2)	7 (18.4)	0.123
Persistent cultures, n (%)	19 (9.7)	4 (10.5)	0.533
Pseudomonas sp., n (%)	21 (10.7)	4 (10.5)	0.618
Beta-lactam			
Cefepime 1g q12 hours, n (%)	38 (19.4)*	2 (5.3)*	
Cefepime 2g q12 hours, n (%)	29 (14.8)	9 (23.7)	
Cefepime 1g q8 hours, n (%)	2 (1.0)	1 (2.6)	
Cefepime 2g q8 hours, n (%)	3 (1.5)	2 (5.3)	0.045
Meropenem 1g q8 hours, n (%)	77 (39.3)	15 (39.5)	
Imipenem 500mg q6 hours, n (%)	8 (4.1)*	5 (13.2)*	
Piperacillin/tazobactam 3.375g q6 hours, n (%)	33 (16.8)	3 (7.9)	
Piperacillin/tazobactam 4.5g q6 hours, n (%)	6 (3.1)	1 (2.6)	
Aminoglycoside adjunct, n (%)	52 (26.5)	13 (34.2)	0.218
Fluoroquinolone adjunct, n (%)	52 (26.5)	9 (23.7)	0.444
Time to antibiotic, hours ± SD	14.0 ± 15.5	13.9 ± 13.6	0.969
Duration of antibiotic, days ± SD	9.8 ± 9.2	9.1 ± 5.3	0.665
Length of stay after culture, days ± SD	22.1 ± 25.7	19.6 ± 21.7	0.798

Significant differences between patients with complete or partial response to antibiotic therapy, and patients experiencing treatment failure were APACHE II scores (11.4 vs. 14.9, p<0.001), intensive care unit stay (60.7% vs. 86.8%, p=0.001), and mechanical ventilation (34.2% vs. 76.3%, p<0.001).

Outcome Measures

Initial treatment response to antibiotic therapy (complete, partial, failure) based on body size descriptors is presented in Table 3. Total body weight (TBW), BMI, body surface area (BSA), and lean body weight 2005 (LBW2005) were significantly higher in patients experiencing treatment failure compared to patients experiencing a complete response to therapy. Non-survivors also had statistically higher TBW, BMI, BSA, and LBW than survivors (Table 4).

Table 3. *Initial response to treatment and body size descriptors*

	Complete response n=131	Partial response n=65	Treatment failure n=38	p value
TBW (kg) ± SD	*77.1 ± 22.2	81.6 ± 22.2	*88.4 ± 27.4	0.025
BMI (kg/m2) ± SD	*26.5 ± 7.6	28.3 ± 7.9	*29.9 ± 8.5	0.038
BSA (m2) ± SD	*1.9 ± 0.3	1.9 ± 0.3	*2.0 ± 0.3	0.043
LBW (kg) ± SD	51.3 ± 7.6	52.1 ± 7.6	53.4 ± 7.3	0.328
LBW2005 (kg) ± SD	*53.9 ± 11.2	55.9 ± 10.9	*59.5 ± 13.1	0.029

** Indicates statistical significance when compared to treatment failure*

Logistic Regression

To determine which body size descriptor was most predictive of initial treatment failure and 30-day mortality, a univariate logistic regression analysis was performed (Table 5). All descriptors (except LBW) were predictive of treatment failure at 120 hours of treatment. Only TBW and BSA were predictive of 30-day mortality. Multiple regression analyses identified TBW, APACHE II scores, and mechanical ventilation as independent predictors of both initial treatment failure and 30 day mortality (Table 6). The multivariate analysis shows the odds of initial treatment failure increase by 1.6% for every increase in patient weight by 1 kilogram, with the odds of dying within 30 days of infection increasing 2.4% for every increase in patient weight by 1 kilogram.

DISCUSSION

Patient TBW, BMI, BSA, and LBW_{2005} were statistically higher in patients experiencing initial treatment failure compared to patients showing a complete response. Trends towards higher TBW, BMI, BSA, LBW, and LBW_{2005} were seen between complete and partial responders as well. Additionally, larger patients had a significantly higher risk of mortality. These results indicate that increased body size, as determined by multiple measures, is associated with poor treatment outcomes in patients infected with gram-negative pathogens treated with beta-lactams. The univariate analysis of body size descriptors identified TBW and BSA as predictors of both initial treatment failure and 30-day mortality. Comparing each of these body size predictors based on the univariate analysis is difficult because although the odds ratios for TBW are smaller than BSA so are the units of measure. Interpreting the odds ratio for 30-day mortality using TBW indicates a 2.5% increase in death with each kilogram increase. The odds of death increase 12-fold when BSA increases by 1 unit. A 70 kg, 5'9" male has a BSA of 1.85 m,2 to reach a BSA of 2.85 m2 a 5'9" male must weigh 194 kg, thus BSA is a much less sensitive marker than TBW.

Previous studies evaluating body size in relationship to infection related outcomes

Table 4. *30 day mortality and body size descriptors*

Means	Survivors n=222	Non-survivors n=12	p value
TBW (kg) ± SD	79.3 ± 22.9	96.2 ± 28.1	0.014
BMI (kg/m^2) ± SD	27.3 ± 7.8	32.0 ± 9.9	0.046
BSA (m^2) ± SD	1.9 ± 0.3	2.1 ± 0.3	0.014
LBW (kg) ± SD	51.7 ± 7.5	56.1 ± 11.1	0.049
LBW2005 (kg) ± SD	55.0 ± 11.5	61.7 ± 11.1	0.051

***Table 5**. Univariate logistic regression of body size descriptors for predictors of initial treatment failure and 30 day mortality*

	Initial treatment outcome OR	95% CI	30 day mortality OR	95% CI
TBW (kg)	1.017	1.003-1.031	1.025	1.004-1.046
BMI (kg/m^2)	1.041	1.000-1.084	1.060	0.999-1.125
BSA (m^2)	4.353	1.211-12.643	12.120	1.537-95.557
LBW (kg)	1.032	0.985-1.081	1.082	0.999-1.172
LBW_{2005} (kg)	1.038	1.007-1.070	1.050	0.999-1.104

have focused exclusively on BMI, which establish patient groups based on WHO definitions of normal weight, obese and, morbid obesity. This dichotomization implies a patient with a BMI of 29 is at a lower risk of poor treatment outcomes than a patient with a BMI of 31, while it has been hypothesized by Falagas et al9 that the risk of adverse outcomes is a continuous J-shape curve since both low BMI and high BMI have been identified as risks for poor infection related outcomes. The results of this study support the upper end of this hypothesis when using TBW.

Factors potentially related to poor treatment outcomes in large patients were summarized in a recent review article.[9] One of the hypothesized reasons is inadequate antibiotic dosing. Obese patients may be underdosed with the use of fixed, or "standard" doses of beta-lactams due to unrecognized pharmacokinetic and pharmacodynamic alterations of antibiotics in obesity. The pharmacodynamic parameter associated with efficacy of beta-lactams is percent time over the minimum inhibitory concentration (%T > MIC). The target %T > MIC for cephalosporins is 60-70%, 50% for penicillins, and 40% for carbapenems.[10] Several studies have associated unmet pharmacodynamic goals with poor treatment outcomes, including an increase in mortality.[11-13] Previous studies in obese patients revealed an altered volume of distribution (Vd) which may decrease the probability of meeting the aforementioned pharmacodynamic goals.[14-18] Only one previous study has analyzed beta-lactam pharmacokinetic parameters in relation to treatment outcomes for obese vs non-obese patients.[19] Obese patients (mean 127 kg) undergoing gastric bypass surgery were given either cefazolin 1 gram or cefazolin 2 grams prior to surgery. A group of normal-weight patients undergoing upper abdominal surgery were used as controls. At incision and closure, both blood and tissue levels of cefazolin were significantly lower for all morbidly obese patients who received 1 gram of cefazolin when compared with the blood and tissue levels found in normal-weight patients. Only when the morbidly obese patients received 2 grams of cefazolin were both the serum and adipose tissue levels adequate to meet pharmacodynamic goals. Based on this analysis, the authors changed dosing practices and administered

***Table 6.** Multivariate logistic regression for initial treatment failure and 30 day mortality*

	Initial treatment failure OR	95% CI	30 day mortality OR	95% CI
TBW (kg)	1.016	1.000-1.032	1.024	1.001-1.048
APACHE II	1.140	1.054-1.233	1.171	1.041-1.317
Mechanical ventilation	5.220	2.274-11.979	5.720	1.181-27.714

2 grams cefazolin to all obese patients. Using historical controls, they determined an infection rate of 16.5% in morbidly obese patients. This rate dropped to 5.6% when obese patients received 2 grams of cefazolin.

In an effort to explore the hypothesis of inadequate antibiotic dosing, our study excluded patients with an estimated creatinine clearance of less than 60 mL/min and varying beta-lactam dosing regimens during initial 120 hours of antibiotic therapy to eliminate the pharmacodynamic confounding variable. However, an association between antibiotic regimen and treatment outcomes was not possible due to small numbers in each regimen and unequal APACHE II scores, with sicker patients more likely to receive larger antibiotic doses regardless of body size, thereby skewing the analysis.

This study has several important limitations. First is the study's retrospective design. The potential for bias exists as some information that may be necessary to analyze patient cases is not always available. However the use of objective endpoints minimized this potential bias. Additionally, the inclusion of multiple dosing regimens and multiple sites of infection increases the generalizability of the results but also increases variability of severity of illness and heterogeneity of the study population.

Despite the limitations of study design, this is the first study evaluating multiple body size descriptors to determine their predictive value and the first to show TBW as a better predictor of 30 day mortality than BMI. We believe the body size descriptor of TBW is the strongest predictor of poor treatment outcomes in this patient population and the easiest for clinicians to recognize as a risk factor of poor infection related outcomes. Prospective trials are necessary to determine the true impact of patient body size on infection related treatment outcomes and patients with increasing TBW warrant specific study to determine which factors are negatively influencing their outcome.

ACKNOWLEDGEMENTS

This research was supported by an intramural grant from Roseman University of Health Sciences.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. WHO. Obesity and overweight. World Health Organization; 2011 [updated March 2011; cited 2011 September 16, 2011]; Available from: http://www.who.int/mediacentre/factsheets/fs311/en/index.html.
2. Huttunen R, Laine J, Lumio J, Vuento R, Syrjanen J. Obesity and smoking are factors associated with poor prognosis in patients with bacteraemia. *BMC Infect Dis*. 2007;7:13.
3. Bochicchio GV, Joshi M, Bochicchio K, Tracy K, Scalea TM. A time-dependent analysis of intensive care unit pneumonia in trauma patients. *J Trauma*. 2004 Feb;56(2):296-301; discussion -3.
4. El-Solh A, Sikka P, Bozkanat E, Jaafar W, Davies J. Morbid obesity in the medical ICU. *Chest*. 2001 Dec;120(6):1989-97.
5. Carratala J, Roson B, Fernandez-Sabe N, Shaw E, del Rio O, Rivera A, et al. Factors associated with complications and mortality in adult patients hospitalized for infectious cellulitis. *Eur J Clin Microbiol Infect Dis*. 2003 Mar;22(3):151-7.
6. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med.* 1985 Oct;13(10):818-29.
7. Kang CI, Kim SH, Park WB, Lee KD, Kim HB, Oh MD, et al. Bloodstream infections caused by Enterobacter species: predictors of 30-day mortality rate and impact of broad-spectrum cephalosporin resistance on outcome. *Clin Infect Dis*. 2004 Sep 15;39(6):812-8.
8. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. *Chest*. 2002 Jul;122(1):262-8.
9. Falagas ME, Athanasoulia AP, Peppas G, Karageorgopoulos DE. Effect of body mass index on the outcome of infections: a systematic review. *Obes Rev*. 2009 May;10(3):280-9.
10. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis.* 1998 Jan;26(1):1-10.
11. Tam VH GE, Weston JS, et al. Outcomes of bacteremia due to Pseudomonas aeruginosa with reduced susceptibility to piperacillin-tazobactam: implications on the appropriateness of the resistance breakpoint. *Clin Infect Dis.* 2008;46:862-7.
12. Lorente L, Jimenez A, Martin MM, Iribarren JL, Jimenez JJ, Mora ML. Clinical cure of ventilator-associated pneumonia treated with piperacillin/tazobactam administered by continuous or intermittent infusion. *Int J Antimicrob Agents*. 2009 May;33(5):464-8.

13. Lorente L, Lorenzo L, Martin MM, Jimenez A, Mora ML. Meropenem by continuous versus intermittent infusion in ventilator-associated pneumonia due to gram-negative bacilli. *Ann Pharmacother.* 2006 Feb;40(2):219-23.
14. Burkhardt O, Brunner M, Schmidt S, Grant M, Tang Y, Derendorf H. Penetration of ertapenem into skeletal muscle and subcutaneous adipose tissue in healthy volunteers measured by in vivo microdialysis. *J Antimicrob Chemother*. 2006 Sep;58(3):632-6.
15. Chiba K, Tsuchiya M, Kato J, Ochi K, Kawa Z, Ishizaki T. Cefotiam disposition in markedly obese athlete patients, Japanese sumo wrestlers. *Antimicrob Agents Chemother*. 1989 Aug;33(8):1188-92.
16. Yost RL, Derendorf H. Disposition of cefotaxime and its desacetyl metabolite in morbidly obese male and female subjects. *Ther Drug Monit.* 1986;8(2):189-94.
17. Mann HJ, Buchwald H. Cefamandole distribution in serum, adipose tissue, and wound drainage in morbidly obese patients. *Drug Intell Clin Pharm.* 1986 Nov;20(11):869-73.
18. Lovering AM, Walsh TR, Bannister GC, MacGowan AP. The penetration of ceftriaxone and cefamandole into bone, fat and haematoma and relevance of serum protein binding to their penetration into bone. *J Antimicrob Chemother.* 2001 Apr;47(4):483-6.
19. Forse RA, Karam B, MacLean LD, Christou NV. Antibiotic prophylaxis for surgery in morbidly obese patients. *Surgery*. 1989 Oct;106(4):750-6; discussion 6-7.