Obesity Is Not Associated with Antimicrobial Treatment Failure for Intra-Abdominal Infection

Zachary C. Dietch,¹ Therese M. Duane,³ Charles H. Cook,⁴ Patrick J. O'Neill,⁵ Reza Askari,⁶ Lena M. Napolitano,⁷ Nicholas Namias,⁸ Christopher M. Watson,⁹ Daniel L. Dent,¹⁰ Brandy L. Edwards,¹ Puja M. Shah,¹ Christopher A. Guidry,¹ Stephen W. Davies,¹ Rhett N. Willis,¹ and Robert G. Sawyer^{1,2}

Abstract

Background: Obesity and commonly associated comorbidities are known risk factors for the development of infections. However, the intensity and duration of antimicrobial treatment are rarely conditioned on body mass index (BMI). In particular, the influence of obesity on failure of antimicrobial treatment for intra-abdominal infection (IAI) remains unknown. We hypothesized that obesity is associated with recurrent infectious complications in patients treated for IAI.

Methods: Five hundred eighteen patients randomized to treatment in the Surgical Infection Society Study to Optimize Peritoneal Infection Therapy (STOP-IT) trial were evaluated. Patients were stratified by obese (BMI ≥ 30) versus non-obese (BMI < 30) status. Descriptive comparisons were performed using Chi-square test, Fisher exact test, or Wilcoxon rank-sum tests as appropriate. Multivariable logistic regression using a priori selected variables was performed to assess the independent association between obesity and treatment failure in patients with IAI.

Results: Overall, 198 (38.3%) of patients were obese (BMI ≥ 30) versus 319 (61.7%) who were non-obese. Mean antibiotic d and total hospital d were similar between both groups. Unadjusted outcomes of surgical site infection (9.1% vs. 6.9%, $p = 0.36$), recurrent intra-abdominal infection (16.2% vs. 13.8%, $p = 0.46$), death (1.0% vs. 0.9%, $p = 1.0$), and a composite of all complications (25.3% vs. 19.8%, $p = 0.14$) were also similar between both groups. After controlling for appropriate demographics, comorbidities, severity of illness, treatment group, and duration of antimicrobial therapy, obesity was not independently associated with treatment failure (c-statistic: 0.64).

Conclusions: Obesity is not associated with antimicrobial treatment failure among patients with IAI. These results suggest that obesity may not independently influence the need for longer duration of antimicrobial therapy in treatment of IAI versus non-obese patients.

OBESITY AFFECTS a large and increasing percentage of the American population, with more than one in three American adults considered obese. Unfortunately, little is known about the implications of obesity on the clinical efficacy of most pharmaceutical agents [1]. With few exceptions,

dosing guidelines for pharmaceuticals, including most antimicrobial agents, do not advise weight-based dosing adjustments. Although a growing number of studies have identified altered pharmacodynamics (PD) and pharmacokinetic (PK) parameters in various populations of obese patients, few drug

¹Department of Surgery, ²Division of Patient Outcomes, Policy and Population Research, Department of Public Health Sciences, The University of Virginia Health System, Charlottesville, Virginia.

³Department of Surgery, Virginia Commonwealth University, Richmond, Virginia.

⁴Department of Surgery, Beth Israel Deaconess Medical Center, Boston, Massachusetts.

⁵Department of Surgery, Maricopa Integrated Health System, Phoenix, Arizona.

⁶Department of Surgery, Brigham and Women's Hospital, Boston, Massachusetts.

⁷Department of Surgery, University of Michigan, Ann Arbor, Michigan.

⁸Department of Surgery, University of Miami Miller School of Medicine, Miami, Florida.

⁹Department of Surgery, University of South Carolina, Columbia, South Carolina.

¹⁰Department of Surgery, University of Texas Health Science Center at San Antonio, San Antonio, Texas.

Presented at the Thirty-fifth Annual Meeting of the Surgical Infection Society, Westlake Village, California, April 16, 2015.

studies are designed to evaluate potentially unique dosing needs for the obese population [2]. Similarly, few studies have been conducted among surgical patients with intra-abdominal infection to evaluate whether treatment failure occurs at greater rates among the obese with conventional dosing strategies versus normal weight comparators.

The successful treatment of infection balances the need to achieve therapeutic serum and tissue antibiotic concentrations to facilitate the eradication of pathogens against the risks of pharmacologic toxicity. In short, insufficient dosing risks treatment failure, whereas more aggressive dosing strategies may increase the risk of toxicity. The parameters that influence serum antimicrobial concentrations such as absorption, volume of distribution, metabolism, and excretion, among others, may vary greatly among individual patients as a result of underlying disease or an acute physiologic disturbance. How the obese body habitus further compounds these complex interactions largely remains unclear for most antimicrobial agents, as well as most other prescription medications.

We sought to evaluate whether obesity is associated with antimicrobial treatment failure for intra-abdominal infection, which could suggest that standard antimicrobial dosing strategies are insufficient in obese patients. Using data from the recently completed Study to Optimize Peritoneal Infection Therapy (STOP-IT) trial [3], we hypothesized that obesity is associated with increased treatment failure for IAI versus normal weight comparators.

Patients and Methods

Data source

The STOP-IT trial was an investigator-initiated, open-label, multi-center trial conducted to define the optimal duration of antimicrobial therapy in patients after adequate source control of complicated IAI (cIAI). Five hundred eighteen patients were enrolled at 23 sites in the United States and Canada over a 5-y study period. The study was coordinated through the Surgical Infection Society and the University of Virginia. Institutional Review Boards at all participating sites approved the study.

Patient characteristics

Eligible patients were 16 y of age or older with cIAI and either fever (temperature $\geq 38.0^{\circ}\text{C}$), leukocytosis (peripheral white blood cell [WBC] count $>11,000/\text{mL}$), or gastrointestinal dysfunction because of IAI precluding intake of more than half of their normal diet, and had undergone either percutaneous or surgical intervention to achieve source control [3]. Source control is recognized as an essential component of treatment for cIAI. For the purposes of STOP-IT, source control was defined as elimination of infectious foci, control of factors that promote ongoing infection, and correction or control of anatomic derangements to restore normal physiologic function. Patients with non-infectious, inflammatory causes of peritonitis, such as non-perforated cholecystitis or necrotic but non-perforated bowel, were excluded.

Statistical analysis

Data analyses were designed to test the null hypothesis that obesity, defined as body mass index (BMI) ≥ 30 , is not associated with treatment failure—defined as a composite outcome of recurrent IAI, surgical site infection, or death—in

the study population. Additional analyses were performed using thresholds to define obesity of BMI ≥ 35 and BMI ≥ 40 . Statistical significance was determined using the standard alpha value of <0.05 . All data analyses were performed using the open-source programming language R and user interface RStudio (RStudio, Boston, Massachusetts), as well as open-source packages [4–8].

Descriptive, univariate statistics were utilized to characterize baseline demographic characteristics, co-morbid disease states, treatment characteristics, and outcomes, stratified by obesity status. Additional comparisons were performed to assess treatment failures by antibiotic class, again stratified by obesity status.

Continuous data are reported as median values [interquartile range] and were compared using the Wilcoxon rank-sum test. Categorical values are reported as a percentage of the total population of each group, and were compared using Fisher exact or Chi-square tests where appropriate.

Multivariable logistic regression was performed to determine associations with treatment failure and included a combination of a priori selected variables and others identified in univariate analysis. Modeled factor likelihood ratios (Wald 2 statistic) were utilized to estimate the predictive strength and relative contribution of each covariate with the odds of treatment failure. Results are reported as adjusted odds ratios with 95% confidence intervals. Model performance was assessed using the calculated Area Under the Receiver Operating Characteristic Curve. All calculated test statistics were used to derive reported two-tailed *p* values.

Results

Patient demographics and disease characteristics are presented in Table 1, stratified by obesity status. Five hundred seventeen patients were included for analysis after exclusion of one study participant because of missing data. Mean BMI for the entire study population was 29.0 ± 8.8 , 23.8 ± 3.5 for non-obese patients, and 37.3 ± 8.3 for obese patients. There were few other differences between obese and non-obese patients. Not surprisingly, diabetes mellitus was observed more frequently among obese patients, as was insulin-dependent diabetes mellitus. The incidence of chronic kidney disease was not substantially different in obese versus non-obese patients.

Characteristics of cIAI affecting patients and disease severity, as well as original STOP-IT treatment group assignments (i.e., control group vs. experimental), are presented in Table 2. Patients were evenly distributed between study groups by weight class and demonstrated comparable severity of illness scores. Likewise, the sites of IAI infection were similarly distributed among obese and non-obese patients. Overall, total antibiotic d and total length of stay did not differ between obese and non-obese patients.

Procedures used to gain source control and clinical outcomes are detailed in Table 3. Although the composite outcome of surgical site infection, recurrent intra-abdominal infection, or death, approached or exceeded 20% in both groups, these outcomes were comparable between obese and non-obese patients.

Bivariate analysis of the rates of treatment failure by antibiotic class, as measured by the composite outcome, is presented in Table 4, stratified by obesity status. β -lactam-penicillins were the antibiotic most commonly utilized

TABLE 1. PATIENT DEMOGRAPHICS AND DISEASE CHARACTERISTICS STRATIFIED BY OBESITY STATUS

<i>Risk factor</i>	<i>n</i>	<i>Non-obese</i>	<i>Obese</i>	<i>p</i>
Total	517	319 (61.7%)	198 (38.3%)	
Age		53 [39–65]	53 [42–62]	0.91
Body mass index		24.0 [22–27]	35.0 [31–40]	<0.001
Female	229	41.2 %	48.5 %	0.13
White	403	76.5 %	80.3 %	0.31
Black	94	18.2 %	18.2 %	1.00
American Indian/Alaskan Native	3	0.63%	0.51%	0.86
Asian	11	3.50%	0.0 %	0.01
Hispanic	35	0.1 %	0.1 %	0.35
Comorbidities				
Cardiac disease	70	11.9 %	16.2 %	0.17
Cerebrovascular disease	19	3.5 %	4.0 %	0.73
Peripheral vascular disease	15	3.1 %	2.5 %	0.69
Diabetes mellitus (total)	78	11.9 %	20.2 %	0.01
IDDM	36	4.7 %	10.6 %	0.01
NIDDM	42	7.2 %	9.6 %	0.33
Steroid use	31	3.8 %	2.0 %	0.27
Inflammatory bowel disease	53	12.2 %	7.1 %	0.06
Malignant disease	59	13.5 %	8.1 %	0.06
Chronic kidney disease	25	6.0 %	3.0 %	0.13
Dialysis dependence	9	1.9 %	1.5 %	1.00
Chronic liver disease	17	3.8 %	2.5 %	0.44
Chronic pulmonary disease	28	6.3 %	4.0 %	0.28
Red blood cell transfusion since admission	43	8.8 %	7.6 %	0.63

IDDM=Insulin-dependent diabetes mellitus; NIDDM=Non-insulin-dependent diabetes mellitus.

as part of the antibiotic regimen for study participants. Treatment failure rates did not differ in obese patients for any antibiotic class, with the exception of the subset of patients that received triazoles, for which failure rates among the obese exceeded those of non-obese patients.

This relation, however, was not observed in subsequent analyses using thresholds to define obesity of BMI ≥ 35 and BMI ≥ 40 .

The results of multivariable logistic regression to determine the association of obesity with treatment failure and

TABLE 2. DISEASE CHARACTERISTICS STRATIFIED BY OBESITY STATUS

<i>Risk factor</i>	<i>n</i>	<i>Non-obese</i>	<i>Obese</i>	<i>p</i>
APACHE-II score	517	9.0 [6–14]	9.0 [5–13]	0.37
Maximum white blood cell count	517	15 [11–20]	16.2 [13–19]	0.12
Maximum temperature	517	37.5 [37–38]	37.8 [77–38]	0.01
Total antibiotic days	517	5.0 [4–10]	5.0 [4–8]	0.12
Total hospital days	517	6.0 [4–11]	7.0 [4–10]	0.34
STOP-IT study group				0.52
4 d	257	48.5%	51.5%	
Clinical resolution	260	51.4%	48.5%	
Setting of IAI				
Community-acquired	321	61.4%	63.1%	0.70
Healthcare-associated	127	24.5%	24.8%	0.94
Hospital-acquired	69	14.1%	12.1%	0.52
Organ site of IAI				
Colon or rectum	177	37.3%	29.3%	0.06
Biliary tree including gallbladder	56	10.0%	12.1%	0.46
Duodenum	23	4.4%	4.6%	0.93
Small intestines	73	14.7%	13.1%	0.61
Esophagus	3	0.0%	1.5%	0.06
Stomach	31	5.3%	7.1%	0.42
Appendix	73	13.2%	15.7%	0.43
Pancreas	16	4.4%	1.0%	0.04
Liver	18	2.8%	4.6%	0.30
Abdominal wall surgical site	13	1.6%	4.0%	0.09
Other	34	6.3%	7.1%	0.72

IAI=Intra-abdominal infection.

TABLE 3. SOURCE CONTROL PROCEDURE AND CLINICAL OUTCOMES STRATIFIED BY OBESITY STATUS

<i>Risk factor</i>	<i>n</i>	<i>Non-obese</i>	<i>Obese</i>	<i>p</i>
Source control procedure				
Resection with proximal diversion	64	11.6%	13.6%	0.49
Resection with anastomotic closure	133	26.3%	24.8%	0.69
Simple closure	32	4.1%	9.6%	0.01
Percutaneous drainage	172	36.7%	27.8%	0.04
Open/surgical drainage	109	20.1%	22.7%	0.47
Diversion and drainage without resection	7	1.3%	1.5%	0.80
Outcomes				
Surgical site infection	40	6.9%	9.1%	0.36
Recurrent intra-abdominal infection	76	13.8%	16.2%	0.46
Death	5	0.9%	1.0%	1.00
Composite outcome	113	19.8%	25.3%	0.14
STOP-IT group—4 d	55	18.7%	25.5%	0.19
STOP-IT group—clinical resolution	58	20.7%	25.0%	0.42

model performance are presented in Table 5, which suggest that obesity is not associated with treatment failure in patients with cIAI. Table 6 displays the association of obesity with treatment failure for analyses performed using BMI thresholds to define obesity of greater than or equal to 30, 35, and 40. None of these analyses identifies a substantial relation between obesity and treatment failure. Complete results of analyses performed using obesity thresholds of BMI ≥ 35 and BMI ≥ 40 are available in supplementary Appendices A and B, respectively.

Discussion

In this post-hoc subgroup analysis of the STOP-IT trial, obesity was not associated with treatment failure for cIAIs, nor were noteworthy differences in treatment failure rates observed across antibiotic classes. The present study provides reassurance that the diverse antimicrobial regimens employed across the 23 participating sites did not result in disproportionate treatment failures among obese patients with cIAI. Similarly, obesity was not found to be an independent predictor of treatment failure in multivariable regression, although it approached significance when obesity was defined as BMI ≥ 30 .

Importantly, patients in this study all underwent adequate intervention to achieve cIAI source control, and the principal findings of the STOP-IT trial were non-inferiority of 4 d of antibiotics versus an extended course based on clinical parameters. Thus, our findings should only be considered in

the context of this specific patient population, where appropriate source control may be more important than the specific antibiotic class, duration of therapy, or the optimization of antimicrobial concentrations.

Although previous literature have reported differences in pharmacokinetics and pharmacodynamics between obese and normal weight patients, the clinical implications of these differences are largely unknown, because of a lack of well-designed studies to evaluate the effect of obesity on outcomes. Although differences in antimicrobial PK or PD among obese patients would seemingly support greater dosing or longer duration of treatment versus normal weight patients, our findings challenge this concept for patients with cIAI by demonstrating comparable clinical outcomes under current antimicrobial dosing parameters.

On the other hand, an inverse relation between obesity and death has been identified in surgical ICUs [9], elective general surgery [10], pneumonia [11], heart failure, coronary heart disease, and patients with diabetes mellitus. Similarly, this finding of the “obesity paradox” was identified in patients with surgical peritonitis with improved short-term but not long-term outcomes [12]. In contrast, our current study did not find evidence of the obesity paradox. This may, in part, be related to the requirement for adequate source control of cIAI to be achieved for enrollment in this clinical trial. Our results suggest that antimicrobial dosing strategies may not require adjustment for obesity in the treatment of cIAI.

TABLE 4. TREATMENT FAILURE BY ANTIBIOTIC CLASS STRATIFIED BY OBESITY STATUS

<i>Antibiotic class</i>	<i>n</i>	<i>Non-obese</i>	<i>Obese</i>	<i>p</i>
β -Lactams-penicillins	312	19.6%	26.3%	0.17
Fluoroquinolones	177	19.8%	26.2%	0.33
Nitroimidazoles	163	21.3%	27.3%	0.39
Glycopeptides (vancomycin)	128	26.9%	32.0%	0.54
β -Lactams-cephalosporins	81	22.2%	16.7%	0.53
Carbapenems	75	27.5%	25.7%	0.86
Triazoles	75	18.5%	46.9%	0.01
Lincosamides	11	37.5%	0.0%	0.49
Macrolides	7	20.0%	0.0%	1.00
Lipopeptides	6	50.0%	100.0%	0.47

TABLE 5. RESULTS OF MULTIVARIABLE LOGISTIC REGRESSION FOR TREATMENT FAILURE^a

Variable	Wald χ^2	Odds of treatment failure (95% CI)	p
Obesity	3.8	1.55 (0.999–2.41)	0.0501
Age	0.5	0.99 (0.98 –1.01)	0.48
Male gender	0.02	1.03 (0.67 –1.60)	0.89
APACHE II	4.8	1.04 (1.00 –1.08)	0.03
Control treatment group	0.31	1.13 (0.74 –1.74)	0.58
Diabetes mellitus	2.6	0.57 (0.28 –1.10)	0.11
Healthcare-associated infection	1.67	0.7 (0.39 –1.19)	0.20
Hospital-acquired infection	2.6	1.63 (0.89 –2.94)	0.11
Chronic steroid use	4.26	2.32 (1.02 –5.09)	0.04
Chronic kidney disease	0.64	1.48 (0.53 –3.76)	0.42

^ac-statistic = 0.64

APACHE = Acute Physiology and Chronic Health Evaluation.

Despite the increasing prevalence of obesity and the known associations between obesity and infectious disease, including surgical infections, the dosing of antibiotics in overweight patients remains “as much an art as a science” given the absence of evidence-based dosing strategies [13,14]. Prevailing uncertainty about the need to alter pharmaceutical dosing strategies in the obese results in large part from the lack of drug studies evaluating dosing recommendations in the obese, which are not required of drug manufacturers by the Food and Drug Administration [2]. As a result, the bulk of existing research evaluates alterations in PK and PD in the obese, rather than clinical efficacy.

The effectiveness of antimicrobial therapy depends on achieving therapeutic concentrations to enable pathogen elimination while limiting toxicity. Various physiological and pharmacokinetic parameters are altered in the obese patient, which may impact the efficacy and toxicity of antimicrobial agents. Delays in gastric emptying have been reported to occur in the obese that may affect drug absorption, although most evidence suggests this effect is not sizeable [15]. The volume of distribution (V_d), which represents the degree to which a drug distributes in plasma volume and tissues, may be increased versus lean comparators, thus resulting in lower concentrations. This phenomenon is magnified for lipophilic medications, which tend to more readily distribute than hydrophilic drugs. Previous work has identified larger V_d in obese patients for most classes of antimicrobial agents, including penicillins, cephalosporins, carbapenems, aminoglycosides, vancomycin, and others [16–25]. The extent to which

a medication is protein-bound also affects V_d , and obesity has been shown to alter lipoproteins and alpha1-acid glycoprotein [2]. Physiologic changes in the liver, including fatty infiltration and altered cytochrome P450 activity, may also impact drug metabolism [15]. Similarly, baseline renal clearance is generally increased in obesity because of concomitant increases in cardiac output and blood volume that result in elevated glomerular filtration rate, although the presence of commonly associated conditions such as hypertension may reverse this phenomenon by causing chronic renal disease [2,26].

Considering the scope of potential physiologic alterations affecting drug absorption, distribution, metabolism, and elimination in obesity, it is not surprising that many studies report pharmacokinetic differences in obese versus normal weight patients. For example, at least 11 pharmacokinetic studies of aminoglycosides have been conducted in human beings, most of which support dose adjustment in obesity using adjusted body weight [2]. Similarly, most studies of vancomycin pharmacokinetics support weight-based dosing adjustments using actual body weight [2]. In general, pharmacokinetic studies that have observed increases in V_d and renal clearance among obese patients have described suboptimal antimicrobial concentrations in blood and tissues, thus supporting weight-based dosing adjustments [27].

Unfortunately, few studies have evaluated the clinical implications of altered pharmacokinetics for cIAI or, for that matter, any infectious disease. A recent population-based cohort study of Canadian outpatients treated with antibiotics for infection reported obesity as a predictor of treatment failure, defined as any additional antibiotic prescriptions or hospitalization for infections within 30 d of the initial therapy [27]. These findings led the authors to hypothesize that antimicrobial dosing adjustments may be required to achieve therapeutic concentrations in obese patients because of the pharmacokinetic differences earlier described. In a post-hoc subgroup analysis of the effect of obesity on antibiotic treatment failure in patients with cIAI who had undergone intervention to achieve source control, greater failure rates were reported among obese versus normal weight patients, although the differences were not substantial and the data were limited by a small sample of obese patients [28]. These limited data reflect a glaring absence of evidence that requires further investigation.

The strengths of this study are its relatively large sample size and well-matched study groups. This study has several important limitations. First, this post-hoc analysis was performed on data generated by the STOP-IT trial for which obesity was not a pre-defined subgroup. Thus, these results must be interpreted with caution and with recognition of the limitations associated with post-hoc analyses. Second, although the STOP-IT trial required that antimicrobial therapy adhere to published guidelines from the Surgical Infection Society and the Infectious Diseases Society of America [29], the specific dosing of antimicrobial therapy was not reported. Therefore, any off-label weight-based dosing for obese patients would not be accounted for in our analysis, although the extent of this practice is presumably limited as it would diverge from consensus guidelines [29]. Finally, despite the size of this study, the potential for type II error must be acknowledged, particularly with respect to conclusions about the efficacy of specific antibiotic classes that were only rarely administered in the STOP-IT trial. In addition, it should be recognized that type II error may explain the failure to

TABLE 6. ASSOCIATION OF OBESITY AND TREATMENT FAILURE AT BMI THRESHOLDS

Obesity threshold	Wald χ^2	Odds of treatment failure	p
BMI ≥ 30	3.8	1.55 (0.999–2.41)	0.0501
BMI ≥ 35	1.3	1.35 (0.79 –2.28)	0.26
BMI ≥ 40	1.7	1.58 (0.77 –3.09)	0.19

BMI = Body mass index.

demonstrate obesity as an independent predictor for treatment failure. Nevertheless, these results are reassuring that conventional treatment for cIAI does not result in large failure rates among obese patients.

In summary, obese patients with cIAI and adequate source control have similar outcomes as more lean comparators. These results suggest that current antimicrobial regimens in this specific patient population are efficacious in obese patients and may not require weight-based modification beyond existing practice; however, these conclusions should be interpreted with caution in light of the potential for type II error. Additional studies with clinical outcomes as endpoints are required to further evaluate the need for weight-based antimicrobial dosing in cIAI and other infectious diseases.

Author Disclosure Statement

The authors have no relevant financial disclosures.

This work was supported by National Institutes of Health grants R01GM081510 and T32 AI078875.

References

- Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. *JAMA* 2014;311:806–814.
- Polso AK, Lassiter JL, Nagel JL. Impact of hospital guideline for weight-based antimicrobial dosing in morbidly obese adults and comprehensive literature review. *J Clin Pharm Ther* 2014;39:584–608.
- Sawyer RG, Claridge JA, Nathens AB, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. *N Engl J Med* 2015;372:1996–2005.
- Studio R. RStudio: Integrated development environment for R. Boston; 2014.
- R Core Team. R: A Language and Environment for Statistical Computing. Vienna: R Foundation for Statistical Computing; 2014.
- Warnes GR. gmodels: Various R programming tools for model fitting. Includes R source code and/or documentation contributed by Ben Bolker, Thomas Lumley, Randall C Johnson. Contributions from Randall C. Johnson are Copyright SAIC-Frederick, Inc. Funded by the Intramur. 2013.
- Lesnoff M, Lancelot R. aod: Analysis of Overdispersed Data. 2012.
- Fellows I. Deducer: A data analysis GUI for R. *J Stat Softw* 2012;49:1–15.
- Hutagalung R, Marques J, Kobylka K, et al. The obesity paradox in surgical intensive care unit patients. *Intensive Care Med* 2011;37:1793–1799.
- Valentijn TM, Galal W, Hoeks SE, et al. Impact of obesity on postoperative and long-term outcomes in a general surgery population: A retrospective cohort study. *World J Surg* 2013;37:2561–2568.
- Nie W, Zhang Y, Jee S, et al. Obesity survival paradox in pneumonia: A meta-analysis. *BMC Med* 2014;12:61.
- Utzolino S, Ditzel CM, Baier PK, et al. The obesity paradox in surgical intensive care patients with peritonitis. *J Crit Care* 2014;29:887.e1–887.e5.
- Erstad BL. Dosing of medications in morbidly obese patients in the intensive care unit setting. *Intensive Care Med* 2004;30:18–32.
- Huttunen R, Syrjänen J. Obesity and the risk and outcome of infection. *Int J Obes* 2013;37:333–340.
- Jain R, Chung SM, Jain L, et al. Implications of obesity for drug therapy: Limitations and challenges. *Clin Pharmacol Ther* 2011;90:77–89.
- Rich BS, Keel R, Ho VP, et al. Cefepime dosing in the morbidly obese patient population. *Obes Surg* 2012;22:465–471.
- Pieracci FM, Barie PS, Pomp A. Critical care of the bariatric patient. *Crit Care Med* 2006;34:1796–1804.
- Chiba K, Tsuchiya M, Kato J, et al. Cefotiam disposition in markedly obese athlete patients, Japanese sumo wrestlers. *Antimicrob Agents Chemother* 1989;33:1188–1192.
- Yost RL, Derendorf H. Disposition of cefotaxime and its desacetyl metabolite in morbidly obese male and female subjects. *Ther Drug Monit* 1986;8:189–194.
- Newman D, Scheetz MH, Adeyemi OA, et al. Serum piperacillin/tazobactam pharmacokinetics in a morbidly obese individual. *Ann Pharmacother* 2007;41:1734–1739.
- Demian H, Verhaegen J, Willems L, Spriet I. Dosing of piperacillin/tazobactam in a morbidly obese patient. *J Antimicrob Chemother* 2012;67:782–783.
- Chen M, Nafziger AN, Drusano GL, et al. Comparative pharmacokinetics and pharmacodynamic target attainment of ertapenem in normal-weight, obese, and extremely obese adults. *Antimicrob Agents Chemother* 2006;50:1222–1227.
- Bauer LA, Edwards WA, Dellinger EP, Simonowitz DA. Influence of weight on aminoglycoside pharmacokinetics in normal weight and morbidly obese patients. *Eur J Clin Pharmacol* 1983;24:643–647.
- Schwartz SN, Pazin GJ, Lyon JA, et al. A controlled investigation of the pharmacokinetics of gentamicin and tobramycin in obese subjects. *J Infect Dis* 1978;138:499–505.
- Grace E. Altered vancomycin pharmacokinetics in obese and morbidly obese patients: What we have learned over the past 30 years. *J Antimicrob Chemother* 2012;67:1305–1310.
- Janson B, Thursky K. Dosing of antibiotics in obesity. *Curr Opin Infect Dis* 2012;25:1.
- Longo C, Bartlett G, Macgibbon B, et al. The effect of obesity on antibiotic treatment failure: A historical cohort study. *Pharmacoepidemiol Drug Saf* 2013;22:970–976.
- Zakrison TL, Hille DA, Namias N. Effect of body mass index on treatment of complicated intra-abdominal infections in hospitalized adults: Comparison of ertapenem with piperacillin-tazobactam. *Surg Infect* 2012;13:38–42.
- Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2010;50:133–164.

Address correspondence to:

Dr. Zachary C. Dietch

Department of Surgery

University of Virginia Medical Center

PO Box 800681

Charlottesville, VA 22908-0681

E-mail: zd8a@virginia.edu

(Appendices follow →)

APPENDIX A: RESULTS WHEN OBESITY IS DEFINED AS BMI $\geq$ 35

APPENDIX TABLE 1. PATIENT DEMOGRAPHICS AND DISEASE CHARACTERISTICS STRATIFIED BY OBESITY STATUS

<i>Risk factor</i>	<i>n</i>	<i>Non-obese</i>	<i>Obese</i>	<i>p</i>
Total	517	417 (80.7%)	100 (19.3)%	
Age		53.0 [40–64]	51.5 [39–60]	0.56
Body mass index		26.0 [22–29]	40.0 [37–46]	<0.001
Female	229	42.7%	51.0%	0.13
White	403	76.3%	85.0%	0.06
Black	94	19.2%	14.0%	0.23
American Indian/Alaskan Native	3	0.5%	1.0%	0.54
Asian	11	2.6%	0.0%	0.13
Hispanic	35	6.5%	8.0%	0.59
Comorbidities				
Cardiac disease	70	12.7%	17.0%	0.26
Cerebrovascular disease	19	3.6%	4.0%	0.77
Peripheral vascular disease	15	3.4%	1.0%	0.32
Diabetes mellitus (total)	78	12.7%	25.0%	0.002
IDDM	36	5.0%	15.0%	<0.001
NIDDM	42	7.7%	10.0%	0.44
Steroid use	31	6.5%	4.0%	0.35
Inflammatory bowel disease	53	11.5%	5.0%	0.054
Malignant disease	59	12.7%	6.0%	0.06
Chronic kidney disease	25	5.0%	4.0%	0.80
Dialysis dependence	9	1.7%	2.0%	0.69
Chronic liver disease	17	3.4%	3.0%	0.89
Chronic pulmonary disease	28	5.3%	6.0%	0.77
Red cell transfusion since admission	43	7.9%	10.0%	0.50

IDDM=Insulin-dependent diabetes mellitus; NIDDM=Non-insulin-dependent diabetes mellitus.

APPENDIX TABLE 2. DISEASE CHARACTERISTICS STRATIFIED BY OBESITY STATUS

<i>Risk factor</i>	<i>n</i>	<i>Non-obese</i>	<i>Obese</i>	<i>p</i>
APACHE-II score	517	9.0 [6 –13]	8.0 [5 –15]	0.89
Maximum white blood cell count—per mm ³	517	15.5 [11.1–19.9]	16.2 [13.1–18.9]	0.30
Maximum temperature—°C	517	37.6 [37.0–38.3]	38.1 [37.3–38.5]	<0.001
Total antibiotic d	517	5.0 [4 –9]	5.0 [4 – 8]	0.14
Total hospital d	517	7.0 [4 –11]	6.5 [4 –10]	0.66
STOP-IT study group				0.70
4 d	257	50.1%	48.0%	
Clinical resolution	260	49.9%	52.0%	
Setting of IAI				
Community-acquired	321	61.2%	66.0%	0.37
Healthcare-associated	127	25.2%	22.0%	0.51
Hospital-acquired	69	13.7%	12.0%	0.66
Organ site of IAI				
Colon or rectum	177	35.7%	28.0%	0.14
Biliary tree including gallbladder	56	11.0%	10.0%	0.77
Duodenum	23	5.3%	1.0%	0.10
Small Intestines	73	14.6%	12.0%	0.50
Esophagus	3	0.2%	2.0%	0.10
Stomach	31	6.0%	6.0%	1.00
Appendix	73	13.0%	19.0%	0.12
Pancreas	16	3.6%	1.0%	0.33
Liver	18	2.6%	7.0%	0.03
Abdominal wall surgical site	13	2.6%	2.0%	1.00
Other	34	5.3%	12.0%	0.01

APACHE=Acute Physiology and Chronic Health Evaluation; IAI=Intra-abdominal infection.

APPENDIX TABLE 3. SOURCE CONTROL PROCEDURE AND CLINICAL OUTCOMES STRATIFIED BY OBESITY STATUS

<i>Risk factor</i>	<i>n</i>	<i>Non-obese</i>	<i>Obese</i>	<i>p</i>
Source control procedure				
Resection with proximal diversion	64	12.0%	14.0%	0.30
Resection with anastomotic closure	133	26.9%	21.0%	0.23
Simple closure	32	5.8%	8.0%	0.40
Percutaneous drainage	172	34.3%	29.0%	0.31
Open/surgical drainage	109	19.9%	26.0%	0.18
Diversion and drainage without resection	7	1.2%	2.0%	0.63
Outcomes				
Surgical site infection	40	7.2%	10.0%	0.35
Recurrent intra-abdominal infection	76	14.6%	15.0%	0.92
Death	5	0.7%	2.0%	0.25
Composite outcome	113	21.1%	25.0%	0.40
STOP-IT group—4 d	55	20.6%	25.0%	0.50
STOP-IT group—clinical resolution	58	21.6%	25.0%	0.60

APPENDIX TABLE 5. RESULTS OF MULTIVARIABLE LOGISTIC REGRESSION FOR TREATMENT FAILURE^a

<i>Variable</i>	<i>Wald χ^2</i>	<i>Odds of Treatment Failure</i>	<i>p</i>
Obesity	1.3	1.35 (0.79–2.28)	0.26
Age	0.46	0.99 (0.98–1.01)	0.50
Male gender	0.01	1.02 (0.66–1.58)	0.92
APACHE II	4.6	1.04 (1.00–1.08)	0.03
Control treatment group	0.19	1.1 (0.72–1.69)	0.67
Diabetes mellitus	2.3	0.59 (0.29–1.13)	0.13
Healthcare-associated infection	1.6	0.70 (0.40–1.20)	0.21
Hospital-acquired infection	2.5	1.61 (0.88–2.90)	0.11
Chronic steroid use	4.1	2.26 (1.00–4.97)	0.04
Chronic kidney disease	0.46	1.40 (0.50–3.51)	0.50

^ac-statistic=0.64

APACHE= Acute Physiology and Chronic Health Evaluation.

APPENDIX TABLE 4. TREATMENT FAILURE BY ANTIBIOTIC CLASS STRATIFIED BY OBESITY STATUS

<i>Antibiotic class</i>	<i>n</i>	<i>Non-obese</i>	<i>Obese</i>	<i>p</i>
β -Lactams-penicillins	312	21.8%	23.3%	0.80
Fluoroquinolones	177	21.1%	28.0%	0.44
Nitroimidazoles	163	21.9%	30.7%	0.33
Glycopeptides (vancomycin)	128	27.9%	33.3%	0.60
β -Lactams-cephalosporins	81	18.8%	23.5%	0.73
Carbapenems	75	28.8%	21.7%	0.52
Triazoles	75	30.8%	30.0%	1.00
Lincosamides	11	27.3%	-	-
Macrolides	7	14.3%	-	-
Lipopeptides	6	66.7%	-	-

APPENDIX B: RESULTS WHEN OBESITY IS DEFINED AS BMI $\geq$ 40

APPENDIX TABLE 1. PATIENT DEMOGRAPHICS AND DISEASE CHARACTERISTICS STRATIFIED BY OBESITY STATUS

<i>Risk factor</i>	<i>n</i>	<i>Non-obese</i>	<i>Obese</i>	<i>p</i>
Total	517	466 (90.1%)	51 (9.9%)	
Age		53 [40–64]	52 [39–59]	0.42
Body mass index		26.0 [23–30]	27.0 [23–33]	<0.001
Female	229	43.0%	56.9%	0.06
White	403	77.0%	86.3%	0.13
Black	94	18.9%	11.8%	0.21
American Indian/Alaskan Native	3	0.4%	2.0%	0.17
Asian	11	2.40%	0.0%	0.27
Hispanic	35	0.1%	0.1%	0.75
Comorbidities				
Cardiac disease	70	13.3%	15.7%	0.64
Cerebrovascular disease	19			
Peripheral vascular disease	15	3.0%	2.0%	0.67
Diabetes mellitus (total)	78	13.3%	31.4%	<0.001
IDDM	36	5.6%	19.6%	<0.001
NIDDM	42	7.7%	11.8%	0.32
Steroid use	31	6.5%	2.0%	0.20
Inflammatory bowel disease	53	11.0%	3.9%	0.12
Malignant disease	59	12.0%	5.9%	0.19
Chronic kidney disease	25	5.0%	3.9%	0.75
Dialysis dependence	9	1.7%	2.0%	0.90
Chronic liver disease	17	3.7%	0.0%	0.16
Chronic pulmonary disease	28	5.2%	7.8%	0.42
Red blood cell transfusion since admission	43	8.6%	5.9%	0.50

IDDM=Insulin-dependent diabetes mellitus; NIDDM=Non-insulin-dependent diabetes mellitus.

APPENDIX TABLE 2. DISEASE CHARACTERISTICS STRATIFIED BY OBESITY STATUS

<i>Risk factor</i>	<i>n</i>	<i>Non-obese</i>	<i>Obese</i>	<i>p</i>
APACHE-II score	517	9 [6 –13]	10 [6 –16]	0.22
Maximum white blood cell count	517	15.6 [11.4–19.7]	15.1 [12.5–18.7]	0.91
Maximum temperature	517	37.6 [37.0–38.3]	38.2 [37.6–38.6]	<0.001
Total antibiotic d	517	5.0 [4 – 9]	5 [4 – 8]	0.17
Total hospital d	517	7.0 [4 –11]	7.0 [5 –11]	0.57
STOP-IT study group				0.28
4d	257	48.8%	56.9%	
Clinical resolution	260	51.2%	43.1%	
Setting of IAI				
Community-acquired	321	61.9%	62.8%	0.91
Healthcare-associated	127	24.5%	25.5%	0.88
Hospital-acquired	69	13.6%	11.8%	0.72
Organ Site of IAI				
Colon or rectum	177	35.1%	25.5%	0.17
Biliary tree including gallbladder	56	10.8%	11.8%	0.83
Duodenum	23	5.0%	0.0%	0.10
Small intestines	73	14.0%	15.7%	0.74
Esophagus	3	0.4%	2.0%	0.17
Stomach	31	5.8%	7.8%	0.56
Appendix	73	14.0%	15.7%	0.74
Pancreas	16	3.2%	2.0%	0.62
Liver	18	3.4%	3.9%	0.86
Abdominal wall surgical site	13	2.6%	2.0%	0.79
Other	34	5.8%	13.7%	0.03

IAI=Intra-abdominal infection; APACHE=Acute Physiology and Chronic Health Evaluation.

APPENDIX TABLE 3. SOURCE CONTROL PROCEDURE AND CLINICAL OUTCOMES STRATIFIED BY OBESITY STATUS

<i>Risk factor</i>	<i>n</i>	<i>Non-obese</i>	<i>Obese</i>	<i>p</i>
Source control procedure				
Resection with proximal diversion	64	11.8%	17.7%	0.23
Resection with anastomotic closure	133	26.7%	17.7%	0.16
Simple closure	32	5.8%	9.8%	0.26
Percutaneous drainage	172	33.1%	33.3%	0.98
Open/surgical drainage	109	21.1%	21.6%	0.93
Diversion and drainage without resection	7	1.5%	0.0%	0.38
Outcomes				
Surgical site infection	40	7.5%	9.8%	0.56
Recurrent intra-abdominal infection	76	14.2%	19.6%	0.30
Death	5	0.9%	2.0%	0.45
Composite outcome	113	21.3%	27.5%	0.31
STOP-IT group—4 d	55	20.3%	31.0%	0.18
STOP-IT group—Clinical resolution	58	22.3%	22.7%	0.96

APPENDIX TABLE 5. RESULTS OF MULTIVARIABLE LOGISTIC REGRESSION FOR TREATMENT FAILURE^a

<i>Variable</i>	<i>Wald χ^2</i>	<i>Odds of treatment failure</i>	<i>p</i>
Obesity	1.7	1.58 (0.77–3.09)	0.19
Age	0.36	1.00 (0.98–1.01)	0.55
Male gender	0.02	1.03 (0.67–1.59)	0.89
APACHE II	4.2	1.04 (1.00–1.08)	0.04
Control treatment group	0.25	1.12 (0.73–1.72)	0.61
Diabetes mellitus	2.48	0.58 (0.28–1.11)	0.12
Healthcare-associated infection	1.65	0.7 (0.40–1.19)	0.20
Hospital-acquired infection	2.56	1.62 (0.89–2.91)	0.11
Chronic steroid use	4.25	2.31 (1.02–5.08)	0.04
Chronic kidney disease	0.51	1.42 (0.51–3.55)	0.48

^ac-statistic = 0.64

APACHE = Acute Physiology and Chronic Health Evaluation.

APPENDIX TABLE 4. TREATMENT FAILURE BY ANTIBIOTIC CLASS STRATIFIED BY OBESITY STATUS

<i>Antibiotic class</i>	<i>n</i>	<i>Non-obese</i>	<i>Obese</i>	<i>p</i>
β -Lactams-penicillins	312	21.9%	24.1%	0.78
Fluoroquinolones	177	21.2%	36.4%	0.24
Nitroimidazoles	163	22.8%	30.8%	0.52
Glycopeptides (vancomycin)	128	29.7%	23.5%	0.60
β -Lactams-cephalosporins	81	18.9%	28.6%	0.54
Carbapenems	75	26.7%	26.7%	1.00
Triazoles	75	31.3%	25.0%	0.71
Lincosamides	11	27.3%	-	-
Macrolides	7	14.3%	-	-
Lipopeptides	6	66.7%	-	-