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Pharmacokinetic and Pharmacodynamic Evaluation of a Weight-Based Dosing Regimen of Cefoxitin for Perioperative Surgical Prophylaxis in Obese and Morbidly Obese Patients

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The objective of this study was to determine the pharmacokinetics and pharmacodynamics (PK/PD) of a weight-based cefoxitin dosing regimen for surgical prophylaxis in obese patients. Patients received a single dose of cefoxitin at 40 mg/kg based on total body weight. Cefoxitin samples were obtained over 3 h from serum and adipose tissue, and concentrations were determined by validated high-performance liquid chromatography. Noncompartmental pharmacokinetic analysis was performed, followed by Monte Carlo simulations to estimate probability of target attainment (PTA) for *Staphylococcus aureus*, *Escherichia coli*, and *Bacteroides fragilis* over 4-h periods postdose. Thirty patients undergoing bariatric procedures were enrolled. The body mass index (mean ± standard deviation [SD])was 45.9 ± 8.0 kg/m^2 (range, 35.0 to 76.7 kg/m^2); the median cefoxitin dose was 5 g (range, 4.0 to 7.5 g). The mean maximum concentrations were 216.15 ± 41.80 μg/ml in serum and 12.62 ± 5.89 in tissue; the mean tissue/serum ratio was 8% ± 3%. In serum, weight-based regimens achieved ≥90% PTA (goal time during which free [unbound] drug concentrations exceed pathogen MICs [*f*T>MIC] of 100%) for *E. coli* and *S. aureus* over 2 h and for *B. fragilis* over 1 h; in tissue this regimen failed to achieve goal PTA at any time point. The 40-mg/kg regimens achieved higher PTAs over longer periods in both serum and tissue than did the standard 2-g doses. However, although weight-based cefoxitin regimens were better than fixed doses, achievement of desired pharmacodynamic targets was suboptimal in both serum and tissue. Alternative dosing regimens and agents should be explored in order to achieve more favorable antibiotic performance during surgical prophylaxis in obese patients.

Surgical site infections (SSIs) are the leading cause of postoperative morbidity and mortality and add significantly to the cost of care (1). Perioperative antibiotic prophylaxis is therefore a standard of care and a keystone for the prevention of SSIs (2–6). Recommendations regarding the use of specific antibiotics for prophylaxis during surgical procedures have been published since the early 1990s and have been frequently revisited since that time (1, 2, 5–9). More recently, specific recommendations provided by the National Surgical Infection Prevention (SIP) Project have focused on appropriate timing of administration of prophylactic antibiotics, appropriate drug selection, and the discontinuation of prophylactic antibiotics within 24 h after surgery (2, 9). However, the actual recommended drugs and dosing regimens for surgical prophylaxis have been relatively unchanged over the past 20 years. Limited published data exist regarding appropriate dosing of antimicrobials for prophylaxis. It is generally stated that the drug should be given in an adequate dose based on patient weight, adjusted dosing weight, or body mass index (BMI) (2, 6, 9). Furthermore, antibiotic administration should be repeated intraoperatively if the procedure continues beyond one to two pharmacokinetic (PK) half-lives after the first dose to ensure adequate antimicrobial concentrations until surgical closure (2, 6, 10, 11).

In the United States, greater than 1 in every 3 adults is obese (defined as a BMI of ≥30 kg/m^2) and nearly 1 in every 15 adults is morbidly obese (BMI ≥ 40 kg/m^2) (12). Obesity is a recognized risk factor for SSIs, with the incidence of wound infections positively correlated with increased BMI (13–16). Obese patients can no longer be regarded as a small subgroup and merit special consideration with respect to the appropriate dosing of antimicrobial agents (6, 17–22). Because the proper dosing of most antimicrobials has not been adequately studied in the context of obesity, the obese population poses a significant challenge to clinicians when considering optimal antimicrobial dosing for prophylaxis of SSIs (18–23). Limited literature regarding β-lactam pharmacokinetics suggests that an increase in drug dose may be warranted to better achieve desired concentrations and favorable outcomes during prophylaxis (6, 20).

Cefoxitin is commonly recommended and used for perioperative parenteral surgical prophylaxis in colorectal, abdominal, pelvic, bariatric, and gynecologic surgical procedures (2, 6). The 2005 SIP Project (2) recommended a standard intravenous (i.v.) cefoxitin dose of 1 to 2 g with a redosing interval of 2 to 3 h in the case of prolonged surgery, while the weight-based dose recommendation was 20 to 40 mg/kg (of body weight). In 2013, the American Society of Health-System Pharmacists (ASHP), the Infectious Dis-

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eases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA) recommended a standard i.v. cefoxitin dose of 2 g with a redosing interval of 2 h in the case of prolonged surgery (6). Although prophylactic antibiotic dosing was discussed in the context of obesity, a weight-based dosing recommendation for adults was not addressed due to a lack of clinical data (6). A recently published cefoxitin pharmacokinetic analysis in obese patients suggests that a 2-g dosing strategy may fail to provide adequate perioperative prophylaxis in obese patients with a BMI of >30 kg/m^2 (24).

Conclusive recommendations for weight-based dosing of cefoxitin for surgical prophylaxis in obese patients are not available. Therefore, the objective of this study was to evaluate cefoxitin pharmacokinetic and pharmacodynamic (PD) target attainment in obese surgical patients using a standardized weight-based dose of 40 mg/kg in order to determine whether this approach to dosing improves the PK/PD performance of the drug for surgical prophylaxis in this high-risk group of patients.

MATERIALS AND METHODS

Protocol. The study protocol was approved by the University of Colorado Denver institutional review board (IRB 09-0928) prior to patient enrollment. All patients participating in the study provided written informed consent. Inclusion criteria were obesity (defined as a BMI greater than 30 kg/m^2), age of 18 to 75 years, and being scheduled for elective bariatric surgery (laparoscopic Roux-en-y gastric bypass or gastric banding procedures) anticipated to last more than 2 h in duration. Exclusion criteria were a known history of allergy to cephalosporins, severe renal insufficiency (creatinine clearance of <40 ml/min calculated according to the Cockcroft and Gault formula [25]) or severe hepatic impairment (serum bilirubin concentration of >2 mg/dl). Cefoxitin is a standard antibiotic for prophylaxis in these patients. Patients underwent their surgical procedure and received a general anesthetic regimen not otherwise altered by enrollment in the study. An additional i.v. catheter for blood sampling was placed in the arm contralateral to that used for drug administration.

Immediately before the surgical incision, patients received a 40-mg/kg (total body weight [TBW]) cefoxitin dose administered i.v. over 5 min; calculated doses were rounded to the next highest 0.5-g increment. Venous blood samples were collected at time zero (immediately before beginning the antibiotic infusion), at 10, 30, 60, 120, and 180 min after cefoxitin administration, and at wound closure. If a second prophylactic cefoxitin dose was administered intraoperatively for procedures of longer duration, the final blood sample was collected just before administration of the second dose. Blood samples were collected in plain glass vacuum tubes, allowed to clot in an ice-water bath, promptly centrifuged, transferred to labeled polyethylene vials, and stored at −70°C until assayed. In addition, tissue samples of pericolonic/perirectal fat were obtained at the opening of the abdominal cavity and at 60 min after the initial cefoxitin dose. A final pericolonic/perirectal fat sample was obtained at either 180 min postdose, before administration of a second prophylactic dose, or at closing of the abdominal cavity, whichever occurred first. The reason for sampling of pericolonic/perirectal fat rather than subcutaneous fat tissues was because the most serious and potentially life-threatening SSIs are deep incisional and organ-space SSIs, which are associated with much higher morbidity and cost of treatment (26, 27). Superficial SSIs are more prevalent than deep/organ-space SSIs but generally require less aggressive interventions than do deep incisional/organ-space SSIs. We were thus more interested in drug penetration into these deeper tissues as a marker for adequate prophylaxis against the more severe and costly type of SSI. Additionally, previous studies of cefoxitin pharmacokinetics and tissue penetration sampled subcutaneous fat (24); penetration into pericolonic/perirectal fat has not been previously as well described. In light of the above-mentioned issues related to deep incisional/organ space SSIs, we were particularly interested in characterizing cefoxitin penetration in these deeper tissues.

Sample analysis. Cefoxitin concentrations in serum were determined using reversed-phase high-performance liquid chromatography (HPLC) with UV detection. The HPLC system utilized a Phenomenex Luna 5-μm C-18(2) 4.6-mm by 150-mm column (Phenomenex Inc., Torrance, CA), with the detector set at a wavelength of 254 nm. The mobile phase consisted of 0.005 M potassium phosphate buffer and acetonitrile (80:20 [vol/vol]). Cefazolin (Sigma-Aldrich Co., St. Louis, MO) was used as the internal standard and added to serum samples prior to the extraction process. Proteins were extracted from serum by vortexing with 600 μl of acetonitrile, followed by centrifugation and pipetting of 700 μl of supernatant into glass tubes and addition of 2 ml of dichloromethane. After vortexing, the organic and aqueous phases were separated by centrifugation and an aliquot of the aqueous phase was injected into the HPLC system. Coefficients of determination (r^2) for the serum cefoxitin assay were determined over a standard curve of 0.5 to 480 mg/liter in spiked serum. Assay procedures for tissue samples were similar to those for serum. Antibiotic-free swine tissues were spiked with known amounts of cefoxitin and cefazolin to validate the assay method in tissue, and a standard curve of 0.5 to 55 μg/g tissue was developed. Tissue samples were finely ground and homogenized after the addition of 10% acetonitrile (4 ml/g of tissue sample) and were centrifuged prior to solid-phase extraction of the supernatant. Tissue concentrations were converted from a percent weight to a percent volume to compare tissue concentrations. Standard curves for serum and tissue assays performed with an r^2 of >0.99 over the respective reference ranges and were reproducible, and single-blinded quality control (QC) samples dispersed throughout each run were analyzed for variability. All samples were analyzed in duplicate. Within-day assay variability across the standard calibration curve ranged from 2.6% to 8.4% in serum and from 3.8% to 9.2% in tissue at the upper and lower ranges of the standard curve (500 mg/liter and 2.0 mg/liter, respectively).

Pharmacokinetic analysis. Serum concentration-time data for cefoxitin were analyzed by standard noncompartmental pharmacokinetic methods with elimination of cefoxitin assumed to be first order. Peak drug concentrations in serum (C_{max}) and the times at which these concentrations were achieved (T_{max}) were estimated by visual inspection of the serum concentration-versus-time data. The dose-normalized peak concentrations in serum (C_{max}/D) were calculated as C_{max}/cefoxitin dose in grams. Minimum serum concentration (C_{min}) was also be determined by direct measurement. The apparent terminal elimination rate constant (k_{el}) was determined by least-squares regression analysis of the terminal portion of the natural log concentration-time curve. Elimination half-life ($t_{1/2}$) was calculated as $0.693/k_{el}$. The area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) was calculated by the linear trapezoidal summation method. Total systemic clearance (CL_s) was calculated as dose/$AUC_{0-\infty}$. The cefoxitin volume of distribution (V) was calculated by standard noncompartmental methods; the mean residence time (MRT) was calculated as $1/k_{el}$, and V was calculated as MRT × CL_s. Measures of central tendency and variability were evaluated for all pharmacokinetic parameters, with the results expressed as the means ± standard deviations (SD). Pharmacokinetic parameters (CL_s and V) were also calculated as normalized to each of four different weights: TBW, ideal body weight (IBW), lean body weight (LBW), and adjusted body weight (AdjBW). Ideal body weight was calculated according to the Devine equation (28). Lean body weight was calculated according to two methods, the Hume equation (29) and the LBW2005 equation (30). Adjusted body weight was calculated as follows: AdjBW = IBW + 0.3 × (TBW − IBW). Pharmacokinetic calculations were initially performed using Microsoft Excel 2013 (Microsoft Corporation, Redmond, WA) and certain parameters (e.g., k_{el} and $AUC_{0-\infty}$) verified with WinNonlin (version 4; Pharsight, Cary, NC, USA).

Analysis of pharmacodynamic targets. Pharmacodynamic parameters were evaluated in order to determine whether weight-based cefoxitin

TABLE 1 Subject demographics

Patient characteristic	Value for[a]: All patients ($n = 30$)	Patients with BMIs of <40 kg/m^2 ($n = 5$)	Patients with BMIs of ≥ 40 kg/m^2 ($n = 25$)	P value[b]
Age (yr)	40.6 ± 11.4	48.8 ± 6.3	38.9 ± 11.6	0.02
Sex (no. of females/no. of males)	26/4	3/2	23/2	0.12
Ht (cm)	166 ± 10	174 ± 8	164 ± 9	0.04
Total body wt (kg)	125.6 ± 22.4	112.4 ± 10.4	128.2 ± 23.4	0.03
Ideal body wt (kg)	58.6 ± 9.4	67.0 ± 8.2	56.9 ± 8.8	0.06
Lean body wt, Hume (kg)	63.6 ± 9.5	64.1 ± 6.3	63.5 ± 10.1	0.87
Lean body wt, LBW2005 (kg)	59.9 ± 9.6	63.6 ± 9.6	59.1 ± 9.6	0.38
Adjusted body wt (kg)	85.4 ± 11.9	85.2 ± 8.2	85.4 ± 12.6	0.96
BMI (kg/m^2)	45.9 ± 8.0	37.0 ± 2.2	47.6 ± 7.6	<0.0001
Baseline serum creatinine (mg/dl)	0.86 ± 0.28	0.97 ± 0.13	0.84 ± 0.30	0.14
Surgical procedure (no. of patients)	Laparoscopic Roux-en-y gastric bypass (29) Laparoscopic gastric band placement (1)			
Dose (mg)	5,020 ± 854	4,500 ± 500	5,124 ± 878	0.06
Duration of infusion (min)	5.1 ± 0.9	5.0 ± 0.7	5.1 ± 1.1	0.80
Time from end of drug infusion to incision (min)	1.2 ± 1.6	1.6 ± 0.9	1.3 ± 1.7	0.58

[a] Values are means ± SDs or numbers.
[b] Comparison of patients with BMIs of <40 kg/m^2 and those with BMIs of ≥ 40 kg/m^2.

doses resulted in serum and tissue concentrations adequate for prophylaxis of surgical site infections due to *Escherichia coli*, *Bacteroides fragilis*, and *Staphylococcus aureus*. These pathogens are the most representative pathogens causing SSIs in this setting and thus were targeted for PK/PD modeling in this analysis. Susceptibility data for wild-type organisms of these species were obtained from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) website (http://www.eucast.org/organization). The EUCAST database was chosen for this analysis because it provided the most current and comprehensive collection of MIC data for cefoxitin and the specific organisms of interest. For the purposes of this study, Monte Carlo simulations were performed using susceptibility data only for methicillin-susceptible *S. aureus* (MSSA). Susceptibility breakpoints used in this study are those currently recommended by the Clinical and Laboratory Standards Institute (CLSI) (31).

Monte Carlo simulation (Crystal Ball version 7; Oracle Corporation, Redwood Shores, CA) was used to calculate probability of target attainment (PTA) for pharmacodynamic goals. The time during which free (unbound) drug concentrations exceed pathogen MICs (fT>MIC) is the pharmacokinetic/pharmacodynamic parameter best correlated with bacterial killing and clinical efficacy of β-lactam antibiotics (32). Specific values for fT>MIC, expressed as a percentage of the dosing interval, that have been correlated with maximal bactericidal activity of cephalosporins are 50 to 70% (32). The PTA for desired fT>MIC goals was evaluated at MICs of 0.25 mg/liter, 0.5 mg/liter, 1 mg/liter, 2 mg/liter, 4 mg/liter, 8 mg/liter, and 16 mg/liter; these MICs represent susceptibilities of target organisms for prophylaxis regimens during colorectal and other gastrointestinal (GI) surgeries (e.g., *E. coli* and *B. fragilis*), up to and including the established susceptibility breakpoint. The model randomly applied pharmacokinetic values derived from experimental data obtained in this study. Custom MIC frequency distributions were constructed and used in the Monte Carlo simulations based on susceptibility derived from the EUCAST database as previously described. Five thousand simulations were performed at each MIC and for each of the selected pathogens. For pharmacodynamic evaluation of free (unbound) drug levels, the approximate free fraction of cefoxitin in human blood (average, 0.30; range, 0.21 to 0.48) was incorporated into Monte Carlo simulations to obtain corresponding pharmacodynamic parameters for free drug (fT>MIC) (33). The targeted pharmacodynamic goal was the cefoxitin concentration above the MIC of these common pathogens (T>MIC) for 100% of the prophylactic dosing interval (i.e., fT>MIC = 100%) as suggested by previous literature (34). The more traditional cephalosporin PD target of fT>MIC of 70% has been previously used for evaluation of drug dosing during surgical prophylaxis (35) and was also modeled for purposes of direct comparison with the proposed target of fT>MIC of 100%. Guidelines for surgical prophylaxis state that antibiotics with short pharmacokinetic half-lives should be readministered at intervals of 1 to 2 times the half-life of the drug; therefore, cefoxitin is recommended to be redosed at intervals of 2 to 3 h during longer procedures (6). Since the goal of perioperative antimicrobial prophylaxis is to achieve free (unbound) serum and tissue drug levels that exceed the MICs for likely pathogens across the duration of the procedure, and since redosing of cefoxitin is recommended every 2 to 3 h during colorectal procedures (6), the PK/PD performance of cefoxitin over that time frame was therefore of particular interest. Additionally, since bacterial contamination of surgical sites may potentially occur at any time between incision and closure, maintaining adequate drug concentrations throughout the duration of the procedure is a reasonable goal of perioperative prophylaxis. Since the importance of adequate antibiotic concentrations at surgical closure on wound infection rates following colorectal procedures has been clearly shown (36), for the purposes of this study PD targets were defined as fT>MIC of 100% over periods of up to 3 h in duration; PTAs were also calculated and reported at 4 h for completeness, since in actual practice cefoxitin may not always be redosed at 2 to 3 h if the surgical procedure is nearing completion. Achieving PTA of ≥90% for the specified fT>MIC goal was considered adequate for the use of cefoxitin as surgical prophylaxis in this population.

Differences among patient characteristics and pharmacokinetic parameters between patients with BMIs of <40 kg/m^2 compared to those with BMIs of ≥ 40 kg/m^2 were evaluated using either Mann-Whitney U test or unpaired t test with Welch correction for nonparametric data. All statistical tests were performed by using GraphPad InStat software, v.3.00 for Windows (GraphPad Software, San Diego, CA). P values less than 0.05 was considered significant for all statistical tests.

RESULTS

A total of 30 patients were enrolled; demographics are provided in Table 1. A majority of patients were female (87%); 25 patients

TABLE 2 Cefoxitin serum and tissue pharmacokinetic parameters in obese surgical patients with BMIs of >30 kg/m^2

Parameter	Value for[a]: All patients (n = 30)	Patients with BMIs of <40 kg/m^2 (n = 5)	Patients with BMIs of ≥40 kg/m^2 (n = 25)	P value[b]
Serum pharmacokinetics				
Observed C_{max} (mg/liter)	216.15 ± 41.80	205.35 ± 27.60	218.31 ± 44.21	0.42
Observed C_{max}/D (mg/liter/g)	44.29 ± 12.11	46.35 ± 10.14	43.88 ± 12.62	0.65
Observed T_{max} (min)	12.9 ± 4.6	11.6 ± 2.6	13.1 ± 4.9	0.34
$AUC_{0-\infty}$ (μg · h/ml)	266.92 ± 97.51	328.30 ± 34.03	254.64 ± 101.75	0.009
CL (ml/min)	349.02 ± 118.22	232.11 ± 48.28	372.40 ± 114.37	<0.001
CL/TBW (ml/min/kg)	2.80 ± 0.91	2.05 ± 0.28	2.94 ± 0.92	<0.001
CL/IBW (ml/min/kg)	6.04 ± 2.09	3.44 ± 0.37	6.56 ± 1.89	<0.001
CL/LBW2005 (ml/min/kg)	5.88 ± 1.99	3.65 ± 0.45	6.33 ± 1.88	<0.001
CL/AdjBW (ml/min/kg)	4.09 ± 1.33	2.70 ± 0.31	4.37 ± 1.28	<0.001
V (liters)	29.28 ± 9.83	21.34 ± 9.12	31.12 ± 9.44	0.08
V/TBW (liters/kg)	0.23 ± 0.07	0.19 ± 0.06	0.24 ± 0.07	0.25
V/IBW (liters/kg)	0.51 ± 0.19	0.32 ± 0.12	0.55 ± 0.18	0.01
V/LBW2005 (liters/kg)	0.49 ± 0.17	0.34 ± 0.14	0.53 ± 0.16	0.05
V/AdjBW (liters/kg)	0.34 ± 0.11	0.25 ± 0.09	0.36 ± 0.11	0.08
$t_{1/2}$ (h)	1.05 ± 0.54	1.06 ± 0.38	1.05 ± 0.58	0.96
k_{el} (h)	0.75 ± 0.20	0.71 ± 0.18	0.75 ± 0.21	0.33
Tissue pharmacokinetics				
Observed C_{max} (mg/liter)	12.62 ± 5.89	11.08 ± 2.35	12.93 ± 6.36	0.28
Observed T_{max} (min)	16.7 ± 5.9	16.8 ± 6.6	16.7 ± 6.0	0.97
$AUC_{0-\infty}$ (μg · h/ml)	15.35 ± 6.24	13.09 ± 3.58	15.80 ± 6.61	0.22
$t_{1/2}$ (h)	1.73 ± 0.73	1.66 ± 0.65	1.74 ± 0.75	0.81
k_{el} (h)	0.45 ± 0.15	0.49 ± 0.26	0.44 ± 0.13	0.70
Serum concns				
Surgical opening (mg/liter)	174.41 ± 38.07	168.48 ± 36.58	175.60 ± 38.98	0.71
60 min postinfusion (mg/liter)	93.13 ± 23.69	97.31 ± 31.80	92.30 ± 22.48	0.75
180 min postinfusion/surgical closure (mg/liter)	37.62 ± 24.34	50.73 ± 34.25	35.00 ± 21.84	0.38
Tissue concns				
Surgical opening (mg/liter)	12.62 ± 5.89	11.08 ± 2.35	12.93 ± 6.36	0.28
60 min postinfusion (mg/liter)	6.33 ± 2.01	6.97 ± 3.26	6.21 ± 1.74	0.64
180 min postinfusion/surgical closure (mg/liter)	4.26 ± 1.80	4.49 ± 2.21	4.22 ± 1.75	0.81
Tissue/serum concn ratios				
Surgical opening (mg/liter)	0.08 ± 0.05	0.07 ± 0.02	0.08 ± 0.05	0.37
60 min postinfusion (mg/liter)	0.07 ± 0.02	0.07 ± 0.01	0.07 ± 0.02	1.00
180 min postinfusion/surgical closure (mg/liter)	0.14 ± 0.07	0.10 ± 0.04	0.14 ± 0.07	0.09
Ratio of tissue/blood AUCs from surgical opening to closure	0.08 ± 0.03	0.07 ± 0.05	0.08 ± 0.04	0.28

[a] Values are means ± SDs.
[b] Comparison of patients with BMIs of <40 kg/m^2 and those with BMIs of ≥40 kg/m^2.

(83%) had BMIs of >40 kg/m^2 (global median, 44.46; [interquartile range [IQR], 41.03 to 49.31]), including 7 patients (23%) with BMIs of >50 kg/m^2. Table 1 also provides a comparison between patients with BMIs of <40 kg/m^2 and those with BMIs of ≥40 kg/m^2. Other than the expected differences in weight and BMI, characteristics of these two groups were otherwise generally similar except that those with BMIs of <40 kg/m^2 were significantly older and taller; these specific differences likely had minimal impact on cefoxitin pharmacokinetics. Serum and tissue samples were analyzed from all patients. The median initial i.v. cefoxitin dose administered was 5 g (IQR, 4.5 to 5.0 g; range, 4.0 to 7.5 g) infused over a median of 5 min. The end of the antibiotic infusions occurred an average of 1.2 min before surgical incision (range, 7 min before incision to 1 min after). Serum and tissue pharmacokinetic parameters are provided in Table 2. The mean serum maximum concentration (C_{max}) was 216.15 ± 41.8 mg/liter, and C_{max}/D was 44.29 ± 12.11 mg/liter/g. Calculated CL_s and V normalized to weight (in milliliters per minute per kilogram and liters per kilogram, respectively) varied over 2-fold when using TBW and IBW, with both LBWs and AdjBW estimates falling in between. The mean serum cefoxitin elimination half-life was 1.05 h. Those patients with BMIs of ≥40 kg/m^2 exhibited significantly

TABLE 3 MIC frequency distribution for *Escherichia coli*, *Bacteroides fragilis*, and *Staphylococcus aureus* isolates collected from the EUCAST database

Organism	No. of isolates	% of isolates with indicated cefoxitin MIC (mg/liter)[a]											
		<0.125	0.125	0.25	0.5	1	2	4	8	16	32	64	>64
E. coli	66,874	0	0	0.1	2.1	6.9	34.3	37.1	12.8	3.8	1.7	1.1	0.1
B. fragilis	1,898	0	0	0.8	0.1	0.2	2.2	27.5	34.4	17.4	8.8	3.6	5.1
S. aureus	856	0	0.1	1.0	7.8	32.4	27.8	19.5	3.4	1.6	1.9	0.8	3.6

[a] Current CLSI susceptibility MIC breakpoints are indicated by distribution percentages that are underlined.

greater cefoxitin CL_s, regardless of how this parameter was normalized for various weights, compared to patients with BMIs of <40 kg/m^2; there was also a strong trend toward an increased V and a significantly lower $AUC_{0-\infty}$ in the group of patients with greater BMIs. Despite observed differences in CL_s and V, no significant differences were seen in the calculated C_{max} or half-life between the two BMI groups.

Tissue mean C_{max} at surgical opening of the abdomen was 12.62 mg/liter measured at 16.7 min after antibiotic administration. Tissue cefoxitin elimination half-life was 1.73 h, with a mean 180-min (or surgical closure) concentration of 4.26 mg/liter. The ratio of tissue/blood concentrations at surgical opening, 60 min, and 180 min (or surgical closure) were 8%, 7%, and 14%, respectively. Tissue AUC from opening to closure was 15.35 h · mg/liter. The ratio of tissue/blood AUC from surgical opening to 180 min (or surgical closure) was 8.1 ± 3.3%. Cefoxitin tissue pharmacokinetics and tissue/blood concentration ratios were not significantly different between among patients with BMIs of <40 kg/m^2 compared to those with BMIs of ≥40 kg/m^2.

Monte Carlo simulation estimating the PTA based on pharmacodynamic targets of *f*T>MIC of 100% and 70% for 1 to 4 h based on the EUCAST MIC distributions (Table 3) are presented in Table 4 for both weight-based and non-weight-based dosing. In this population, a weight-based dosing regimen achieved ≥90% PTA up to 2 h postdose for *E. coli* and *S. aureus* for the target of serum *f*T>MIC of 100% and up to 3 h with *f*T>MIC of 70%. For *B. fragilis*, serum PTA ≥90% was realized after weight-based doses for 2 h for *f*T>MIC of 70% but only 1 h for *f*T>MIC of 100%. In contrast, simulation of a standard 2-g i.v. cefoxitin dose using the same PK parameters resulted in ≥90% PTA of only 1 h for *S. aureus* and less than 1 h for *E. coli* and *B. fragilis* when considering *f*T>MIC of 100%. When considering a target of *f*T>MIC of 70%, a ≥90% PTA was extended to 2 h for *S. aureus* and 1 h for *E. coli*, and PTA remained <90% for *B. fragilis* at all tested time points. Estimates of PTA in tissue after either 40 mg/kg or 2 g of i.v. cefoxitin were dismal for all three pathogens.

Monte Carlo simulations were also performed for patients with BMIs of <40 kg/m^2 and ≥40 kg/m^2 using pharmacokinetic parameters specific for these groups (Table 5). Simulations provided estimated PTAs which were not substantially different between these two BMI groups and which were overall similar to those for the entire group of patients as shown in Table 4.

The PTA of cefoxitin 40 mg/kg and 2 g according to specific pathogen MIC are presented in Table 6. The 40-mg/kg dose achieved ≥90% PTA at the *E. coli* and *S. aureus* susceptibility breakpoints (MIC = 8 mg/liter) at 1 h, and for MIC of 4 mg/liter at 2 h, at the target *f*T>MIC of 100% in serum. In contrast, the 2-g dose achieved favorable PTA at serum concentrations which were generally one MIC dilution lower than those achieved with the weight-based dosing; i.e., PTA ≥90% was achieved after 1 h at an MIC of 4 mg/liter and after 2 h at an MIC of 2 mg/liter. When considering MICs of 16 mg/liter (the cefoxitin susceptibility

TABLE 4 PTA of single-dose cefoxitin regimens in obese patients with BMIs of >30 kg/m^2 against *Escherichia coli*, *Bacteroides fragilis*, and *Staphylococcus aureus*

Compartment and pharmacodynamic target	Cefoxitin dose	PTA by pathogen (%)[a]											
		E. coli at indicated time after dose (h)				*B. fragilis* at indicated time after dose (h)				*S. aureus* at indicated time after dose (h)			
		1	2	3	4	1	2	3	4	1	2	3	4
Serum													
*f*T>MIC of 100%	40 mg/kg	**97**	**95**	76	46	**92**	79	47	18	**100**	**100**	78	36
	2 g	89	68	37	14	74	36	10	2	**100**	68	19	3
	2 g in nonobese patients (from reference 34)	**98**	35	12	4	69	13	3	0	**98**	35	12	4
*f*T>MIC of 70%	40 mg/kg	**98**	**95**	**91**	80	**94**	**90**	77	54	**100**	**100**	**99**	84
	2 g	**92**	84	66	42	82	60	32	13	**100**	**95**	62	26
Tissue													
*f*T>MIC of 100%	40 mg/kg	27	7	2	1	0	0	0	0	55	26	8	2
	2 g	4	1	0	0	0	0	0	0	17	3	1	0
*f*T>MIC of 70%	40 mg/kg	38	16	6	3	0	0	0	0	63	44	26	10
	2 g	6	2	0	0	0	0	0	0	25	10	3	0

[a] Values meeting the desired goal of PTA of ≥90% at each time point are in bold.

TABLE 5 PTA at *f*T>MIC of 100% of single-dose cefoxitin regimens in obese patients with BMIs of <40 kg/m^2 and ≥40 kg/m^2 against *Escherichia coli*, *Bacteroides fragilis*, and *Staphylococcus aureus* using EUCAST susceptibility data

Compartment and BMI	Cefoxitin dose	PTA by pathogen (%)[a]											
		E. coli at indicated time after dose (h)				*B. fragilis* at indicated time after dose (h)				*S. aureus* at indicated time after dose (h)			
		1	2	3	4	1	2	3	4	1	2	3	4
Serum													
BMI < 40 kg/m^2	40 mg/kg	**98**	**95**	88	68	85	75	53	28	**94**	**93**	**92**	82
BMI ≥ 40 kg/m^2	40 mg/kg	**97**	**94**	82	65	86	72	51	31	**94**	**93**	87	77
BMI < 40 kg/m^2	2 g	**95**	85	62	34	70	45	20	6	**92**	89	79	59
BMI ≥ 40 kg/m^2	2 g	**91**	76	50	31	61	34	16	7	**92**	86	69	50
Tissue													
BMI < 40 kg/m^2	40 mg/kg	37	13	0	0	4	1	0	0	63	39	16	0
BMI ≥ 40 kg/m^2	40 mg/kg	35	15	3	2	0	0	0	0	64	38	19	8
BMI < 40 kg/m^2	2 g	7	2	0	0	0	0	0	0	30	9	0	0
BMI ≥ 40 kg/m^2	2 g	5	1	0	0	0	0	0	0	19	7	0	0

[a] Values meeting the desired goal of PTA of ≥90% at each time point are in bold.

breakpoint for *B. fragilis*), a cefoxitin dose of 40 mg/kg achieved ≥90% PTA for *f*T>MIC of 100% at 1 h, while the PTA after the standard fixed 2-g dose was 9%. The cefoxitin 40-mg/kg dose was thus able to achieve desired PTA at MICs up to and including the susceptibility breakpoints for all target pathogens over a 1- to 2-h period, while the fixed 2-g dose was uniformly unable to achieve desired PTA against organisms even at MICs which would be defined as susceptible to the drug.

Using PK parameters determined in this study, Monte Carlo simulations estimated that a cefoxitin dose of 50 mg/kg is required to achieve a 92% PTA for *f*T>MIC of 100% in serum at 2 h at the *E. coli* and *S. aureus* MIC susceptibility breakpoint of 8 mg/liter. A cefoxitin dose of 60 mg/kg is required to achieve 88% and 93% PTA for *f*T>MICs of 100% and 70%, respectively, for *B. fragilis* at the MIC susceptibility breakpoint of 16 mg/liter. In our population, this relates to an average cefoxitin dose of 6.5 g (50 mg/kg) or 7.5 g (60 mg/kg) given over 5 min.

DISCUSSION

Obesity is a commonly encountered comorbidity, especially in the United States, yet pharmacokinetic changes associated with changes in body habitus have not been well studied for many antibiotics. Cefoxitin has long remained a standard perioperative antibiotic for a wide variety of surgical procedures. The most recent consensus surgical prophylaxis guidelines recommend a standard 2-g i.v. dose for adults, with a redosing interval at 2 h (6).

TABLE 6 PTA of single-dose cefoxitin surgical prophylaxis regimens according to pathogen MIC at different time points after dosing in obese patients with BMIs of >30 kg/m^2

*f*T>MIC and cefoxitin dose	Time (h)	PTA (%) at indicated MIC (mg/liter)[a]								
		0.5	1	2	4	8[b]	16[c]	32	64	128
*f*T>MIC of 100%										
40 mg/kg	1	**100**	**100**	**100**	**100**	**100**	**90**	25	0	
	2	**100**	**100**	**100**	**100**	82	25	1	0	
	3	**100**	**100**	**97**	75	30	2	0		
	4	**99**	**92**	71	34	5	0			
2 g	1	**100**	**100**	**100**	**100**	73	9	0		
	2	**100**	**100**	**97**	67	12	0			
	3	**100**	**93**	64	17	0				
	4	87	61	22	2	0				
*f*T>MIC of 70%										
40 mg/kg	1	**100**	**100**	**100**	**100**	**100**	**98**	45	1	0
	2	**100**	**100**	**100**	**100**	**99**	65	9	0	
	3	**100**	**100**	**100**	**99**	77	23	1	0	
	4	**100**	**100**	**99**	84	40	4	0		
2 g	1	**100**	**100**	**100**	**100**	**91**	22	0		
	2	**100**	**100**	**100**	**95**	41	2	0		
	3	**100**	**100**	**96**	60	10	0			
	4	**100**	**96**	72	25	1	0			

[a] Values meeting the desired goal of PTA of ≥90% at each time point are in bold.
[b] Current CLSI breakpoints = 8 mg/liter for *E. coli* and *S. aureus*.
[c] Current CLSI breakpoint = 16 mg/liter for *B. fragilis*.

Although these guidelines recognize obesity as a variable which may alter serum and tissue concentrations, no conclusive recommendations are offered regarding the use of weight-based or higher doses, as clinical data are lacking. A previously published pharmacokinetic evaluation of a 2-g i.v. cefoxitin dose suggested inadequate perioperative tissue concentrations in obese patients despite adequate serum concentrations due to decreased distribution into adipose tissue (24).

This study reports the pharmacokinetics of cefoxitin at 40 mg/kg i.v. in an obese population; a majority of the patients in this study were classified as morbidly obese, which is distinctly different from the case with previous investigations. The mean serum cefoxitin half-life observed in this study was similar to that previously reported for obese patients after a standard 2-g i.v. dose (24); this half-life is slightly prolonged compared to that previously reported for nonobese adults (35). Despite administration of substantially higher doses, the mean C_{max} observed in the present study was similar to concentrations previously reported for other populations, including nonobese adults receiving fixed cefoxitin doses (24, 33, 37). This decreased C_{max}/D ratio and the prolonged half-life are both consistent with a 2-fold-higher V observed in this study compared to that reported for nonobese individuals. Thus, substantially higher weight-based doses were needed in order to achieve drug exposures which are similar to those observed in previous studies with nonobese and obese subjects. As expected, normalizing pharmacokinetic variables to weight (TBW) or calculated weights (IBW, LBW2005, or AdjBW) resulted in a large variability in estimates. Normalization of both CL_s and V to AdjBW provide PK parameter estimates which are most similar to values observed for nonobese adults. However, it remains unclear which dosing weight is most appropriate for cefoxitin based on these data. Indeed, one may argue that due to inadequate tissue penetration in obesity, cefoxitin is not an ideal antibiotic for the prevention of SSI in the obese population. Given that caveat, weight-based dosing based on TBW appears to provide the most favorable serum concentrations in this population of obese and morbidly obese patients.

Despite the use of higher doses with increased systemic drug exposures, tissue concentrations remained poor, with an average tissue/serum ratio of only 8%. Mean tissue concentrations at incision and 60 min and 180 min (or at closure) postincision were below the CLSI breakpoint for anaerobes targeted by cefoxitin. Furthermore, mean 60-min tissue concentrations were below the susceptibility breakpoint for *S. aureus* and *E. coli*, suggesting inadequate coverage in the event of intraoperative contamination. It is known that subcutaneous adipose tissue blood flow decreases in morbid obesity; similarly, antibiotic penetration has been inversely correlated to BMI (17, 38–41). Our findings of an 8% cefoxitin penetration into pericolonic/perirectal adipose tissue are consistent with those of a previous study using 2-g i.v. doses, which achieved mean penetrations into subcutaneous fat of 11% and 5% in obese and morbidly obese patients, respectively (24). Although penetration may be greater in tissues which are more highly perfused than adipose, the results of this study suggest that simply using a weight-based dosing regimen of 40 mg/kg of cefoxitin to improve concentrations in blood does not necessarily overcome inadequate tissue concentrations and that alternative dosing strategies may be needed (42).

Monte Carlo simulations based on EUCAST MIC distributions and CLSI breakpoints suggest serum concentrations achieve PTA of >90% over at least 1 h for *B. fragilis* and for at least 2 h (a recommended redosing interval) for *S. aureus* and *E. coli*. However, PTA for *B. fragilis* falls below the targeted goal within 2 h after dosing. Although the weight-based dose performed better than a standard 2-g dose, it may still be inadequate for all targeted pathogens. Since the PD target for surgical prophylaxis is largely undefined and contamination may occur at any point during the procedure, fT>MIC of 100% may be the most ideal target for β-lactam antibiotics (34). Although this study also evaluated a more conservative fT>MIC, 70%, tissue concentrations failed to meet PTA of >90% at any time point regardless of the specified target. This further supports a potential need for alternative dosing strategies or agents for antimicrobial surgical prophylaxis in obese and morbidly obese patients.

As previously presented, we estimated doses required to achieve desired serum PD targets using PK parameters observed in our study population. In these patients, an average cefoxitin dose of 6.5 g (50 mg/kg) or 7.5 g (60 mg/kg) given over 5 min would be necessary to achieve desired PK/PD targets for all pathogens of interest. An alternative strategy of cefoxitin loading, followed by an extended or continuous infusion, should be studied to assess the potential for improving PK/PD indices while requiring lower cefoxitin doses (42).

Perioperative cephalosporin dosing in obese, morbidly obese, and superobese populations has been previously studied. Most investigations utilized cefazolin (17, 35, 43) and suggest that although total serum concentrations remain above an MIC breakpoint of 8 mg/liter, adipose tissue concentrations typically fail to achieve this concentration throughout the duration of the surgical procedures (43). Cefazolin at 2 g i.v. was associated with lower rates of wound infections in morbidly obese patients than obtained with a 1-g dose (17). Further, cefazolin at 3 g i.v. has been suggested as a reasonable dose for those weighing >120 kg (2, 6). Conversely, a small pharmacokinetic evaluation of cefuroxime plasma, skeletal muscle, and subcutaneous adipose tissue concentrations using microdialysis catheter techniques in morbidly obese patients suggests a higher ratio of tissue/blood AUC, 0.63. It should, however, be noted that there was high variability in this estimate (44). Nevertheless, these data suggest that alternative agents with potentially greater *in vitro* potency and better tissue penetration should be investigated in special populations. For example, ertapenem has been previously shown to have favorable pharmacokinetics and achieve excellent PTAs against relevant bacteria across a wide range of body weights, including morbid obesity (45). These properties may be associated with reduced SSIs compared to those obtained with other pharmacodynamically less potent antibiotics, which may be more adversely effected by extremes of body weights (46–48). Appropriate antibiotic selection and appropriate dosing are both important for achieving optimal outcomes related to surgical prophylaxis (49, 50); currently recommended cefoxitin regimens may not be optimal in either respect.

There are a number of strengths to this study. First, an adequate sample of patients with BMIs ranging from 35.0 to 76.7 kg/m^2 were enrolled and analyzed. Adverse events were also assessed and none were noted, suggesting that weight-based regimens utilizing comparatively large doses are safe in this population. Next, multiple blood samples were obtained, which allowed for patient-specific PK analysis and assessment of tissue penetration at three different, defined time intervals. In addition, al-

though tissue penetration is often difficult to accurately assess, results of the present study are similar to those previously reported in studies using fixed dosing regimens; this lends validity to the observed results of this study. Finally, the robust PD assessment resulted in hypothesis-generating data and usable clinical information, which may serve as a possible partial explanation to the observed link between obesity and higher SSI rates.

We also acknowledge potential limitations of our study. First, for purposes of making comparisons, we applied PK parameters calculated from a 40-mg/kg dose to simulate (rather than directly measure) values which would have been achieved after 2-g fixed doses. However, these simulations of 2-g doses resulted in serum PTA estimates similar to those previously published (34). Similarly, the observed tissue penetration of 8% was similar to previously reported tissue penetration estimates (24). Therefore, we believe that the extrapolated model is valid. In addition, one may argue that $fT>MIC$ of 100% was not an appropriate or valid goal for assessing target attainment. However, there are few prospective or retrospective clinical studies which have firmly validated antimicrobial PK/PD goals specifically in the setting of perioperative prophylaxis. Since bacterial contamination of surgical sites may potentially occur at any time during the procedure, and since maintaining adequate drug concentrations throughout the duration of the procedure until surgical closure is a reasonable goal of perioperative prophylaxis (36), $fT>MIC$ of 100% should appropriately be targeted over the expected duration of the surgical procedure when β-lactam antibiotics are used. Although the study by Zelenitsky et al. (36) specifically identified end-of-procedure aminoglycoside concentrations as being strongly associated with surgical site infections, the need for adequate drug concentrations up until the time of surgical wound closure is likely applicable to other classes of antibiotics as well. Recognizing that this goal of $fT>MIC$ of 100% is not universally accepted, the present study also analyzed and presented results achieved using the more traditional conservative cephalosporin target of $fT>MIC$ of 70%. A related limitation is that although no SSIs were reported for this study population, the sample size of 30 patients was likely not adequate to evaluate for such clinical outcomes. Finally, while the results of this study suggest that a weight-based dosing regimen is more appropriate than fixed doses in this population, we are unable to definitively recommend an optimal dose of cefoxitin due to the inadequacy of even 40 mg/kg (based on TBW) for certain key pathogens. The additional analyses presented in this study suggest that 50 to 60 mg/kg (based on TBW) may be necessary, but the adequacy and safety of these doses have not been clinically evaluated.

Conclusion. Perioperative weight-based dosing of cefoxitin, with associated pharmacokinetic parameters and pharmacodynamics target attainment, was investigated in obese and morbidly obese patients and proven to have minimal tissue penetration. Serum PTA following a 40-mg/kg i.v. dose (based on TBW) of cefoxitin was adequate for *E. coli* and *S. aureus* over 2 h; however, this was not the case for *B. fragilis*. Furthermore, tissue penetration was not adequate at 1 h postdose for any of the targeted bacteria. Although the weight-based cefoxitin dose performed better than a simulated 2-g dose, alternative dosing regimens and agents should be explored in order to obtain adequate PK/PD parameters for perioperative surgical prophylaxis in morbidly obese patients.

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REFERENCES

1. **Kirkland KB, Briggs JP, Trivette SL, Wilkinson WE, Sexton DJ.** 1999. The impact of surgical-site infections in the 1990s: attributable mortality, excess length of hospitalization, and extra costs. Infect Control Hosp Epidemiol **20:**725–730. http://dx.doi.org/10.1086/501572.
2. **Bratzler DW, Houck PM, Surgical Infection Prevention Guideline Writers Workgroup.** 2005. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Am J Surg **189:**395–404. http://dx.doi.org/10.1016/j.amjsurg.2005.01.015.
3. **Stratchounski LS, Taylor EW, Dellinger EP, Pechere JC.** 2005. Antibiotic policies in surgery: a consensus paper. Int J Antimicrob Agents **26:**312–322. http://dx.doi.org/10.1016/j.ijantimicag.2005.07.002.
4. **Rovera F, Diurni M, Dionigi G, Boni L, Ferrari A, Carcano G, Dionigi R.** 2005. Antibiotic prophylaxis in colorectal surgery. Expert Rev Anti Infect Ther **3:**787–795. http://dx.doi.org/10.1586/14787210.3.5.787.
5. **Nelson RL, Glenny AM, Song F.** 2009. Antimicrobial prophylaxis for colorectal surgery. Cochrane Database Syst Rev **21:**CD001181.
6. **Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA.** 2013. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm **70:**195–283. http://dx.doi.org/10.2146/ajhp120568.
7. **Dellinger EP, Gross PA, Barrett TL, Krause PJ, Martone WJ, McGowan JE, Jr, Sweet RL, Wenzel RP.** 1994. Quality standard for antimicrobial prophylaxis in surgical procedures. Clin Infect Dis **18:**422–427. http://dx.doi.org/10.1093/clinids/18.3.422.
8. **Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR.** 1999. Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. Am J Infect Control **27:**97–132.
9. **Bratzler DW, Hunt DR.** 2006. The Surgical Infection Prevention and Surgical Care Improvement Projects: national initiatives to improve outcomes for patients having surgery. Clin Infect Dis **43:**322–330. http://dx.doi.org/10.1086/505220.
10. **Dellinger EP.** 2007. Prophylactic antibiotics: administration and timing before operation are more important than administration after operation. Clin Infect Dis **44:**928–930. http://dx.doi.org/10.1086/512198.
11. **Dellinger EP.** 2008. What is the ideal time for administration of antimicrobial prophylaxis for a surgical procedure? Ann Surg **247:**927–928. http://dx.doi.org/10.1097/SLA.0b013e31817586c8.
12. **Ogden CL, Carroll MD, Kit BK, Flegal KM.** 2014. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA **311:**806–814. http://dx.doi.org/10.1001/jama.2014.732.
13. **Thomas EJ, Goldman L, Mangione CM, Marcantonio ER, Cook EF, Ludwig L, Sugarbaker D, Poss R, Donaldson M, Lee TH.** 1997. Body mass index as a correlate of postoperative complications and resource utilization. Am J Med **102:**277–283. http://dx.doi.org/10.1016/S0002-9343(96)00451-2.
14. **Dindo D, Muller MK, Weber M, Clavien PA.** 2003. Obesity in general elective surgery. Lancet **361:**2032–2035. http://dx.doi.org/10.1016/S0140-6736(03)13640-9.
15. **House MG, Fong Y, Arnaoutakis DJ, Sharma R, Winston CB, Protic M, Gonen M, Olson SH, Kurtz RC, Brennan MF, Allen PJ.** 2008. Preoperative predictors for complications after pancreaticoduodenectomy: impact of BMI and body fat distribution. J Gastrointest Surg **12:**270–278. http://dx.doi.org/10.1007/s11605-007-0421-7.
16. **Mullen JT, Davenport DL, Hutter MM, Hosokawa PW, Henderson WG, Khuri SF, Moorman DW.** 2008. Impact of body mass index on perioperative outcomes in patients undergoing major intra-abdominal cancer surgery. Ann Surg Oncol **15:**2164–2172. http://dx.doi.org/10.1245/s10434-008-9990-2.
17. **Forse RA, Karam B, MacLean LD, Christou NV.** 1989. Antibiotic prophylaxis for surgery in morbidly obese patients. Surgery **106:**750–756.
18. **Cheymol G.** 2000. Effects of obesity on pharmacokinetics. Implications for drug therapy. Clin Pharmacokinet **39:**215–231.
19. **Bearden DT, Rodvold KA.** 2000. Dosage adjustments for antibacterials in

obese patients. Applying clinical pharmacokinetics. Clin Pharmacokinet **38:**415–426.
20. **Pai MP, Bearden DT.** 2007. Antimicrobial dosing considerations in obese adult patients. Insights from the Society of Infectious Diseases Pharmacists. Pharmacotherapy **27:**1081–1091.
21. **Janson B, Thursky K.** 2012. Dosing of antibiotics in obesity. Curr Opin Infect Dis **25:**634–649. http://dx.doi.org/10.1097/QCO.0b013e328359a4c1.
22. **Falagas ME, Karageorgopoulos DE.** 2010. Adjustment of dosing of antimicrobial agents for body weight in adults. Lancet **375:**248–251. http://dx.doi.org/10.1016/S0140-6736(09)60743-1.
23. **Han PY, Duffull SB, Kirkpatrick CMJ, Green B.** 2007. Dosing in obesity: a simple solution to a big problem. Clin Pharmacol Ther **82:**505–508. http://dx.doi.org/10.1038/sj.clpt.6100381.
24. **Toma O, Suntruo P, Stefanescu A, London A, Mutch M, Kharasch E.** 2011. Pharmacokinetics and tissue penetration of cefoxitin in obesity: implications for risk of surgical site infection. Anesth Analg **113:**730–737. http://dx.doi.org/10.1213/ANE.0b013e31821fff74.
25. **Cockcroft DW, Gault MH.** 1976. Prediction of creatinine clearance from serum creatinine. Nephron **16:**31–41. http://dx.doi.org/10.1159/000180580.
26. **Lawson EH, Hall BL, Ko CY.** 2013. Risk factors for superficial vs deep/organ-space surgical site infections: implications for quality improvement initiatives. JAMA Surg **148:**849–858. http://dx.doi.org/10.1001/jamasurg.2013.2925.
27. **Fry DE.** 2002. The economic costs of surgical site infection. Surg Infect **3**(Suppl 1):S37–S43.
28. **Devine BJ.** 1974. Gentamicin therapy. Drug Intell Clin Pharm **8:**650–655.
29. **Hume R.** 1966. Prediction of lean body mass from height and weight. J Clin Pathol **19:**389–391. http://dx.doi.org/10.1136/jcp.19.4.389.
30. **Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B.** 2005. Quantification of lean bodyweight. Clin Pharmacokinet **44:**1051–1065. http://dx.doi.org/10.2165/00003088-200544100-00004.
31. **Clinical and Laboratory Standards Institute.** 2016. Performance standards for antimicrobial susceptibility testing; 26th ed. Document M100 S26:2016. CLSI, Wayne, PA.
32. **Craig WA.** 1998. Pharmacokinetic/pharmacodynamic parameters: rationale for antimicrobial dosing for mice and men. Clin Infect Dis **26:**1–10. http://dx.doi.org/10.1086/516284.
33. **Isla A, Troconiz IF, de Tejada IL, Vazquez S, Canut A, Lopez JM, Solinis MA, Rodriguez Gascon A.** 2012. Population pharmacokinetics of prophylactic cefoxitin in patients undergoing colorectal surgery. Eur J Clin Pharmacol **68:**735–745. http://dx.doi.org/10.1007/s00228-011-1206-1.
34. **Moine P, Fish DN.** 2013. Pharmacodynamic modeling of intravenous antibiotic prophylaxis in elective colorectal surgery. Int J Antimicrob Agents **41:**167–173. http://dx.doi.org/10.1016/j.ijantimicag.2012.09.017.
35. **Ho VP, Nicolau DP, Dakin GF, Pomp A, Rish BS, Towe CW, Barie PS.** 2012. Cefazolin dosing for surgical prophylaxis in morbidly obese patients. Surg Infect **13:**33–37. http://dx.doi.org/10.1089/sur.2010.097.
36. **Zelenitsky SA, Ariano RE, Harding GK, Silverman RE.** 2002. Antibiotic pharmacodynamics in surgical prophylaxis: an association between intraoperative antibiotic concentrations and efficacy. Antimicrob Agents Chemother **46:**3026–3030. http://dx.doi.org/10.1128/AAC.46.9.3026-3030.2002.
37. **Ko H, Cathcart S, Griffith DL, Peters GR, Adams WJ.** 1989. Pharmacokinetics of intravenously administered cefmetazole and cefoxitin and effects of probenecid on cefmetazole elimination. Antimicrob Agents Chemother **33:**356–361. http://dx.doi.org/10.1128/AAC.33.3.356.
38. **Jansson PA, Larsson A, Smith U, Lonnroth P.** 1992. Glycerol production in subcutaneous adipose tissue in lean and obese humans. J Clin Invest **89:**1610–1617. http://dx.doi.org/10.1172/JCI115756.
39. **Jansson PA, Larson A, Smith U, Lonnroth P.** 1994. Lactate release from the subcutaneous tissue in lean and obese men. J Clin Invest **93:**24024–24026.
40. **Bolinder J, Kerckhoffs DA, Moberg E, Hagstrom-Toft E, Arner P.** 2000. Rates of skeletal muscle and adipose tissue glycerol release in nonobese and obese subjects. Diabetes **45:**797–802.
41. **Edmiston CE, Krepel C, Kelly H, Larson J, Andris D, Hennen C, Nakeeb A, Wallace JR.** 2004. Perioperative antibiotic prophylaxis in the gastric bypass patient: do we achieve therapeutic levels? Surgery **136:**738–747. http://dx.doi.org/10.1016/j.surg.2004.06.022.
42. **Roberts JA, Lipman J, Blot S, Rello J.** 2008. Better outcomes through continuous infusion of time-dependent antibiotics to critically ill patients? Curr Opin Crit Care **14:**390–396. http://dx.doi.org/10.1097/MCC.0b013e3283021b3a.
43. **Pevzner L, Swank M, Krepel C, Wing DA, Chan K, Edmiston CE.** 2011. Effects of maternal obesity on tissue concentrations of prophylactic cefazolin during cesarean delivery. Obstret Gynecol **117:**877–882. http://dx.doi.org/10.1097/AOG.0b013e31820b95e4.
44. **Barbour A, Schmidt S, Rout WR, Ben-David K, Burkfardt O, Derendorf H.** 2009. Soft tissue penetration of cefuroxime determined by clinical microdialysis in morbidly obese patients undergoing abdominal surgery. Int J Antimicrob Agents **34:**231–235. http://dx.doi.org/10.1016/j.ijantimicag.2009.03.019.
45. **Chen M, Nafziger AN, Drusano GL, Ma L, Bertino JS.** 2006. Comparative pharmacokinetics and pharmacodynamic target attainment of ertapenem in normal-weight, obese, and extremely obese adults. Antimicrob Agents Chemother **50:**1222–1227. http://dx.doi.org/10.1128/AAC.50.4.1222-1227.2006.
46. **Itani KM, Wilson SE, Awad SS, Jensen EH, Finn TS, Abramson MA.** 2006. Ertapenem versus cefotetan prophylaxis in elective colorectal surgery. N Engl J Med **355:**2640–2651. http://dx.doi.org/10.1056/NEJMoa054408.
47. **Moine P, Asehnoune K.** 2007. Antibiotic prophylaxis in colorectal surgery. N Engl J Med **356:**1684. http://dx.doi.org/10.1056/NEJMc070105.
48. **Mahajan SN, Ariza-Heredia EJ, Rolston KV, Graviss LS, Feig BW, Aloia TA, Chemaly RF.** 2014. Perioperative antimicrobial prophylaxis for intra-abdominal surgery in patient with cancer: a retrospective study comparing ertapenem and nonertapenem antibiotics. Ann Surg Oncol **21:**513–519. http://dx.doi.org/10.1245/s10434-013-3294-x.
49. **Eagye KJ, Nicolau DP.** 2011. Selection of prophylactic antimicrobial agent may affect incidence of infection in small bowel and colorectal surgery. Surg Infect **12:**451–457. http://dx.doi.org/10.1089/sur.2010.108.
50. **Deierhoi RJ, Dawes LG, Vick C, Itani KMF, Hawn MT.** 2013. Choice of intravenous antibiotic prophylaxis for colorectal surgery does matter. J Am Coll Surg **217:**763–769. http://dx.doi.org/10.1016/j.jamcollsurg.2013.07.003.