PHARMACOTHERAPY

Comprehensive Guidance for Antibiotic Dosing in Obese Adults

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Physiologic alterations seen in obesity commonly impact the pharmacokinetics (PK) and pharmacodynamics (PD) of antibiotics and may result in suboptimal dosing in this expanding but understudied population. Much of the published clinical and PK evidence to date consists of small patient populations and are retrospective with, not infrequently, heterogeneous results that in some cases are contradictory. In the last 10 years, additional antimicrobial PK/PD and clinical data encompassing prolonged infusion strategies and examination of critically ill populations have emerged to inform antimicrobial dosing in obesity. In this narrative review, we critically review literature on dosing, PK, and possible dosing strategies in obese adults. We searched PubMed, Scopus, and the Cochrane Library using Medical Subject Headings including *anti-infectives*, specific antimicrobial names, *obese*, *pharmacokinetics,* and others. We reviewed articles, cross-referenced select cited references, and when applicable, referenced drug databases and package inserts to develop dosing recommendations. We provide an overall critical review of the available data regarding PK and dosing issues including dosing recommendations in both critically ill and noncritically ill patients with significant obesity. We developed dosing recommendations for 34 antimicrobials based on 121 articles of the 2336 identified by the search strategy. Although 11 of these do not appear to require dose adjustment, obesity-specific dosing guidance is provided for the remaining 23 antimicrobials. Additional studies are needed to better understand and resolve discrepant published results regarding the PK of antibiotics to establish optimal dosing strategies in obese adults. Alternative dosing strategies, such as extended infusions, should be considered for time-dependent antibiotics (e.g., β-lactams) in obese patients to achieve PD targets reliably. Therapeutic drug monitoring across the spectrum of antimicrobials is of increasing importance in this and other populations to ensure optimized dosing.

KEY WORDS antibiotic, antimicrobial, critically ill, dosing, obesity, pharmacokinetics.

(**Pharmacotherapy 2017;37(11):1415–1431) doi: 10.1002/phar.2023**

The obesity epidemic has innumerable health consequences for individuals including an increased risk of several types of infection.[1] At the same time, however, the altered physiology of obesity may have significant effects on the pharmacokinetics (PK) of antimicrobials sufficient to require altered dosing regimens.

Obesity is most often classified using body mass index (BMI) (Table 1) and total body weight (TBW) as a percentage of ideal body weight (IBW).[2, 3] But BMI does not scale proportionally to adipose tissue and lean muscle mass. Alternative size descriptors of body composition include lean body weight (LBW), adjusted body weight (ABW; commonly with correction factors of 0.3 or 0.4, $ABW_{0.3}$ and

Conflicts of interest: The authors have no conflicts of interest or financial relationships relevant to this article to disclose.

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Table 1. Body Mass Index Classification[1]

BMI, kg/m^2	WHO classification
< 18.50	Underweight
18.50–24.99	Normal weight
25.00–29.99	Overweight
30.00–34.99	Obese class I
35.00–39.99	Obese class II
≥ 40.00	Obese class III (alternative terms: morbidly obese, extremely obese)

BMI = body mass index; WHO = World Health Organization.

$ABW_{0.4}$, respectively), IBW, and body surface area (BSA) (Table 2).[2]

The volume of distribution (Vd) relates the total amount of drug in the body to plasma concentration and is the principal determinant of a loading dose. Distribution into tissues is influenced by a drug's physiochemical characteristics and determined by drug delivery from blood to tissues, ability to cross tissue membranes (e.g., permeability, drug molecular size, degree of ionization, lipid solubility), binding within blood and tissues (e.g., protein binding), and partitioning into fat.[2, 4]

In obese patients, increases in Vd are generally observed as a result of increased adipose and lean muscle mass.[1] Vd may be overestimated if based on TBW if the drug does not enter adipose tissue well (e.g., hydrophilic drugs). Thus in these cases, ABW may be more appropriate when calculating a weight-based loading dose. Conversely, if absolute Vd is increased, but weight-normalized Vd (Vd/TBW) is similar between obese versus nonobese patients, it would suggest high drug distribution into excess body weight (mostly adipose tissue) and that TBW is more appropriate for calculations.[2]

Factors other than lipophilicity and Vd affect dosing in obesity (Figure 1). For example, maintenance doses are mostly driven by total body clearance (Cl), which is the sum of the clearances by each of the eliminating organs (primarily the liver and kidneys), and increased organ mass in obesity may influence Cl.[4] Increased renal clearance was attributed to increased kidney mass and renal blood flow in obesity, and it may affect the elimination rate (k).[1, 5] In addition, Cl estimations are influenced by the definition of weight used, with weight-normalized Cl often correlating better with modified body weights such as LBW instead of TBW.[5]

Elimination half-life ($t_{1/2}$) is related to Vd and Cl through two equations: $k = Cl/Vd$ and $t_{1/2} = 0.693/k$.[4] Because Vd and Cl may be altered to different extents in obesity, half-life can be prolonged or shortened. Furthermore, many of the factors altered by obesity are also altered in acute illness and the critically ill (Figure 1). Although Cl may be decreased in acute kidney injury, it has also been increased in critically ill patients with augmented renal clearance defined as creatinine clearance (Cl_{cr}) of 130 ml/minute/1.73 m^2 or higher.[1]

Renal drug dosing is commonly based on the Cockcroft-Gault equation (using IBW), a surrogate of glomerular filtration rate (GFR).[1] However, in obese adults, $ABW_{0.4}$ may be the most appropriate and practical dosing weight descriptor. A study of 45 morbidly obese patients found that fat-free weight (FFW) or LBW in the Cockcroft-Gault equation resulted in a more unbiased, precise, and accurate estimate of Cl_{cr} compared with other methods including Cockcroft-Gault using IBW, TBW, $ABW_{0.3}$, $ABW_{0.4}$,

Table 2. Equations for Body Weight Descriptors and GFR Estimates[2, 3]

Body weight descriptor or GFR estimate	Equation
IBW, kg	Male: 50.0 + 2.3 × (number of inches over 5 ft) Female: 45.5 + 2.3 × (number of inches over 5 ft)
ABW, kg	IBW + C × (TBW − IBW) where C = either 0.3 or 0.4
LBW or LBW_{2005}, kg	Male: 9270 × TBW/6680 + 216 × BMI Female: 9270 × TBW/8780 + 244 × BMI
FFW, kg	Male: 0.00139 × (height in centimeters)^2 − 0.0801 × R + 0.187 × TBW + 39.83 Female: 0.00151 × (height in centimeters)^2− 0.0344 × R + 0.140 × TBW − (0.158 × age) + 20.387 *R* = resistance
MDRD-4, ml/min/1.73 m^2	$186 \times Scr^{-1.154} \times age^{-0.203}$ × (0.742 if female) × (1.210 if black)
Salazar-Corcoran, ml/min	Male: (137 − age) × ([0.285 × TBW] + [12.1 × height in meters]^2)/51 × S_{cr} Female: (146 − age) × ([0.287 × TBW] + [9.74 × height in meters]^2)/60 × S_{cr}

ABW = adjusted body weight; FFW = fat-free weight; GFR = glomerular filtration rate; IBW = ideal body weight; LBW = lean body weight; MDRD-4 = four-parameter Modification of Diet in Renal Disease; S_{cr} = serum creatinine; TBW = total body weight.

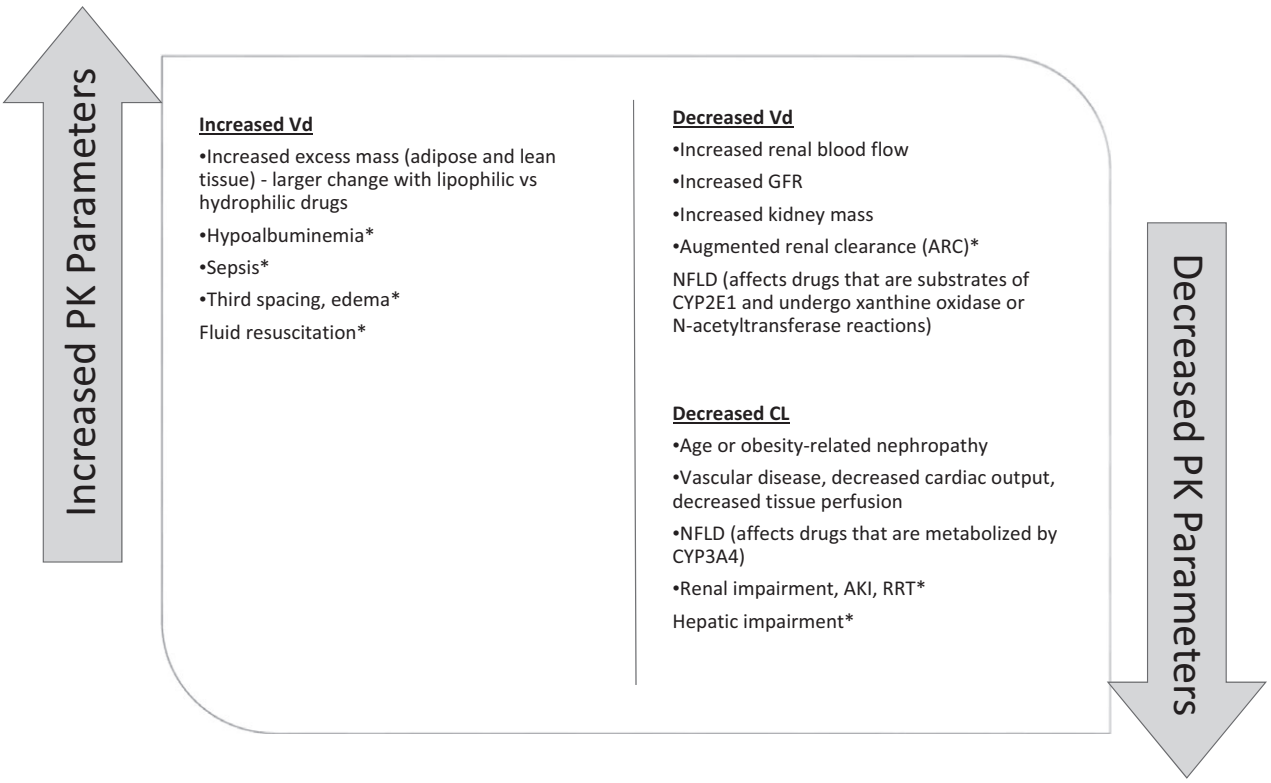

Figure 1. Changes in antimicrobial pharmacokinetics based on physiologic alterations in noncritically ill and critically ill obese patients.[1–5] *Additional factors as commonly described in a critically ill population. AKI = acute kidney injury; CL = drug clearance; NFLD = nonalcoholic fatty liver disease; RRT = renal replacement therapy; Vd = volume of distribution.

Salazar-Corcoran, and four-parameter Modification of Diet in Renal Disease equations.[6] However, a study of 2065 obese patients showed that the use of $ABW_{0.4}$ in the Cockcroft-Gault equation is the most accurate and least biased way to calculate Cl_{cr} compared with TBW, LBW, $ABW_{0.3}$, and IBW.[7] Direct measurement of Cl_{cr} via 24-hour urine collection is more accurate, and this time-consuming process may be reserved for use in certain obese subpopulations, such as critically ill obese patients who show large errors in Cl_{cr} estimates. In addition, the use of serum creatinine (S_{cr}) in the Cockcroft-Gault equation may be affected by age, sex, or muscle mass, possibly leading to inaccurate Cl_{cr} and antibiotic renal dosing estimates in obese patients. Compared with S_{cr}, cystatin C is a biomarker unaffected by these factors and may more accurately estimate GFR in the obese population but is not readily available for clinical use at most centers.[8, 9]

In this narrative review, current data are reviewed, and their implications for antibacterial use in obese individuals including those with critical illness is discussed. Antifungals, antiretrovirals, antiparasitic, and antituberculosis agents are excluded. For a review of antifungal dosing in obesity, interested readers should refer to a review referenced at the end of this article.[10]

Methods

We searched PubMed, Scopus, and the Cochrane Library to identify articles in the English-language literature from 1966 through May 2017, using subject headings containing *anti-infectives*, specific antimicrobial names, *obese*, *pharmacokinetics,* and other Medical Subject Headings (Table S1 describes the search strategies).

Results

We screened 2336 articles including 121 articles, drug databases, and package inserts to develop dosing recommendations for 35 antimicrobials (Tables 3 and 4). We recommend no dose adjustments for 11 of the 35 antimicrobials. Table S2 provides complete references and a companion summary of critically evaluated studies. Physiochemical properties and the PK

profile of select antimicrobials were reviewed and are summarized in Table S3.[15–24]

Review of Specific Antimicrobial Agents

β-Lactams

Piperacillin/Tazobactam

Among the penicillins, the PK of piperacillin/tazobactam has been the most extensively studied in obese patients with critical illness. These evaluations have generally found that piperacillin Vd is increased in obesity, and some also report an increase in its clearance.[25–29] However, in one report, PK parameters of broad-spectrum β-lactams did not differ in obesity, although this study was limited by heterogeneity in patient populations and the variable use of renal replacement therapy.[30] In addition, in a study of 23 critically ill septic patients, piperacillin levels were highly variable.[29]

An indirect but important way of evaluating the effects of obesity on PK is to estimate pharmacodynamic target attainment (PTA) after administration in the clinical setting. In a retrospective analysis of 919 patients from three intensive care units (ICUs), obesity itself did not hinder achievement of adequate piperacillin PTA, although unbound plasma concentrations were significantly lower in obese versus nonobese patients, except in simulations using a pharmacodynamics (PD) target of 100% $fT > 4 \times$ minimum inhibitory concentration (MIC).[31] However, more than half of the patients received continuous infusions of piperacillin/tazobactam, and PK data were sampled sparsely.

Estimated PTAs are often inadequate with intermittent infusion of piperacillin/tazobactam in obese patients. In 31 obese noncritically ill patients, simulations of piperacillin/tazobactam 4.5 g every 6 hours intermittent infusion predicted suboptimal (68–84%) PTA.[30] Simulations using PK data from morbidly obese critically ill patients predicted only 58–69% PTA.[28] Perhaps Cl_{cr} is more important than BMI in achieving target piperacillin PD exposure in obese patients, regardless of whether they are critically ill. Higher Cl_{cr} better correlated with lower PD achievement than did BMI in three studies.[27, 28, 31]

High-dose prolonged infusion regimens may be advantageous in overcoming PD shortcomings while decreasing risks of toxicity. Piperacillin/tazobactam 4.5 g every 8 hours, but not 3.375 g every 8 hours, both administered via extended infusion, achieved piperacillin PTA greater than 90% in 14 obese patients from mixed ICU and medicine ward populations.[26] Simulations of continuous infusion of piperacillin/tazobactam 12 g/24 hours in 23 critically ill obese and nonobese patients showed adequate PTA at a MIC of 16 and 32 mg/L, but at a MIC of 64 mg/L, the obese group was unable to achieve adequate PTA despite increasing to 16 g/24 hours dosing.[29] Their simulations showed that if doses were increased to 20 g/24 hours, 18% of obese patients would experience potentially toxic (greater than 150 mg/L) concentrations.

Summary

Data suggest that the Vd of piperacillin and clearance of piperacillin is increased in obese patients.[25–28, 30, 31] Intermittent infusion of piperacillin/tazobactam predicted suboptimal PTA in several studies.[28, 30] In the absence of therapeutic drug monitoring (TDM), prolonged infusion dosing strategies may help decrease variability in PD achievement, especially in critically ill populations with fluctuating renal function and unpredictable plasma levels. Although data are lacking, it may be reasonable to apply these principles to other penicillins with similar PK profiles.

Cephalosporins

Cephalosporins are hydrophilic and often have high degrees of protein binding, characteristics that limit their penetration into adipose tissues including at subcutaneous sites, which may affect their efficacy for both treatment of skin and soft tissue infections and surgical prophylaxis. Cefazolin, given as prophylaxis for bariatric surgery, has shown relatively high (greater than 75%) but saturable protein binding, good correlation of Vd with TBW and LBW, and decreased subcutaneous tissue penetration with increasing body weight (Table S2). Various studies of 2–4 g cefazolin administered to obese patients before cesarean section also found inadequate concentrations in myometrium and subcutaneous adipose tissue, despite adequate plasma concentrations in most patients (Table S2).

Studies of other cephalosporins in surgical prophylaxis have similarly demonstrated that adequate plasma levels may not indicate that tissue levels are similarly adequate. Adipose tissue penetration of cefoxitin in obese patients undergoing abdominal and pelvic surgery was only

Table 3. Recommended Antimicrobial Dosing in Obesity

Drug	Maximum dose[a]	Study type[b]			Comments
		Case studies	PK/PD studies	Clinical outcomes	
β-lactams					
Penicillins					
Amoxicillin	No data				• Consider upper limit of normal dosing in severe infections[c] (e.g., up to 1 g PO q8h)
Ampicillin	Insufficient data	●			• Consider upper limit of normal dosing in severe infections[c] (e.g., up to 2 g q4h) • Single study with 6 patients: higher Vd but decreased Vd/kg_{TBW}, Cl unchanged
Nafcillin	Insufficient data	●			• Single case report in critically ill obese patient: consider upper end of normal dosing in severe infections[c] (e.g., up to 2 g q4h)
Piperacillin-tazobactam	Up to 4.5 g q8h (prolonged infused over 4 hrs) or 4.5 g q6h (30-min infusion)	●	●	●	• Prolonged infusions preferred for critically ill obese patients • High-dose prolonged infusion if critically ill, obese, with Cl_{cr} > 100 ml/min
Cephalosporins					
Cefazolin	Insufficient data	●	●		• Consider upper limit of normal dosing in severe infections (e.g., up to 2 g q8h [option for continuous infusion],[11] or 1.5–2 g q6h intermittent dosing) • In posttrauma critically ill patients, data suggest 2 g q6h if Cl_{cr} > 215 ml/min[12]
Cephalexin	No data				• Consider upper end of normal dosing in severe infections[c] (e.g., 500–1000 mg q6h)
Cefepime, ceftazidime	Up to 2 g q8h prolonged infusion	●			
Ceftazidime/avibactam	No change		●		
Ceftolozane/tazobactam	No change		●		
Carbapenems					
Doripenem	No change		●		• Consider extended infusion if targeting a higher PD end point of 100% *f*T > MIC or with less susceptible pathogens (i.e., MIC > 2)
Ertapenem	No change		●	●	
Imipenem	No data				• Use caution in renal impairment and with high doses (1 g q6h): increased risk of seizures
Meropenem	Same dose: consider prolonged infusion for critically ill patients	●	●		• Prolonged infusion if critically ill, obese with Cl_{cr} > 100 ml/min, if targeting a higher PD end point of 100% *f*T > MIC, or infections with less susceptible pathogens (i.e., MIC > 2)

(continued)

Table 3 (continued)

Drug	Maximum dose[a]	Study type[b]			Comments
		Case studies	PK/PD studies	Clinical outcomes	
Monobactam					
Aztreonam	Insufficient data	●			• Single case report suggests higher dosing needed • Consider upper end of normal dosing in severe infections[c] (e.g., 2 g q6–8h)
Fluoroquinolones					
Ciprofloxacin	In critically ill septic patients on CRRT with organisms with MICs > 0.5 mg/L (e.g., *Pseudomonas aeruginosa, Acinetobacter baumannii*): > 90 kg: 400 mg IV q8h	●	●		• Insufficient data except as noted in critically ill septic patients on CRRT • Consider upper end of normal dosing in severe infections[c] (e.g., up to 400 mg IV q8h or 750 mg PO q12h)
Levofloxacin	750 mg q24h	●	●		• PK reportedly unaltered by obesity; however, serum levels may be sensitive to Cl_{cr}: 1000 mg q24h has been suggested for Cl_{crIBW} > 110 ml/min to target gram-negative pathogens
Moxifloxacin	No change		●		
Aminoglycosides					
Amikacin	Use $ABW_{0.4}$ for initial dose		●		• Adjust by TDM
Gentamicin	Use $ABW_{0.4}$ for initial dose		●		• Adjust by TDM
Tobramycin	Use $ABW_{0.4}$ for initial dose		●		• Adjust by TDM
Polymyxins					
Colistin methanesulfonate	Use IBW		●		• Maximum dose of 360 mg/day to limit the risk of nephrotoxicity
Polymyxin B	Limited data. Consider $ABW_{0.4}$, especially in upper end of dosing range		●		• Consider maximum dose 200 mg or 2 million units/day to limit risk of toxicity
Anti-MRSA agents					
Ceftaroline	No change		●	●	• Consider q8h if targeting 50% *f*T > MIC for MRSA
Clindamycin	IV: 600 mg q6h or 900 mg q8h PO: 450–600 mg q6h or 600–900 mg q8h		●	●	• Studies from prosthetic joint infection and SSTI suggest increased doses warranted • Manufacturer maximum: 2700 mg/day in severe infections; 4800 mg/day given by intermittent or continuous infusion for life-threatening infections[13]
Dalbavancin	No change		●	●	
Daptomycin	Same weight-based dose but use $ABW_{0.4}$	●	●	●	• Caution in renal insufficiency, dialysis. Monitor CKs and signs of myopathy
Linezolid	No change	●	●	●	
Oritavancin	No change		●		

(continued)

Table 3 (continued)

Drug	Maximum dose[a]	Study type[b]			Comments
		Case studies	PK/PD studies	Clinical outcomes	
Sulfamethoxazole/ trimethoprim	SSTI or severe/complicated UTI: up to 320 mgTMP PO q12h or 8–10 mgTMP/kg_{ABW}/day in divided doses		●	●	• Limited data to guide optimal dosing weight • Consider $ABW_{0.4}$ when using high doses (e.g., > 8 mg/kg/day)
Tedizolid	No change		●		
Telavancin	Same dose; consider a maximum of 1000 mg/dose		●	●	• Increased systemic exposure may be related to acute kidney injury • These are tentative dosing recommendations pending results of an ongoing phase I trial (NCT02753855)
Tigecycline	No change		●	●	
Vancomycin	Load: 20–25 mg/kg_{TBW} (consider a maximum of 2.5 g) Maintenance: 10–15 mg/kg_{TBW} q12h* initially (consider a maximum of 2 g/dose), then adjust by TDM Consider 10–12.5 mg/kg_{TBW} q12h* if BMI ≥ 40 kg/m^2 **May convert to q8h regimen based on adequate renal function (e.g., Cl_{cr} > 120 ml/min) and age* Consider an initial maximum daily dose of 4.5 g (including load)	●	●		• Alternative approach using $ABW_{0.4}$: loading dose 25–30 mg/kg_{ABW}, initial maintenance dose ~15 mg/kg_{ABW} q12h* • Loading doses commonly ranged from none to 3 g; daily doses commonly ranged 2–4 g or 20–30 mg/kg_{TBW}/day (Table S2) • Adjust doses by TDM (peak and trough) using software utilizing Bayesian methods and AUC targets. – If calculating without software, see reference for equations[14] – If only measuring troughs, more cautious and frequent initial monitoring of levels may be warranted

ABW = adjusted body weight; $ABW_{0.4}$ = adjusted body weight using a correction factor of 0.4; AUC = area under concentration; BMI = body mass index; CK = creatinine phosphokinase; Cl_{cr} = creatinine clearance; CRRT = continuous renal replacement therapy; IBW = ideal body weight; IV = intravenous; MIC = minimum inhibitory concentration (mg/L); MRSA = methicillin-resistant *Staphylococcus aureus*; PD = pharmacodynamic; PK = pharmacokinetic; PO = oral; SSTI = skin and soft tissue infections; T > MIC = duration of a dosing interval for which the antibiotic concentration remains above the MIC of the known or suspected pathogen; TBW = total body weight; TDM = therapeutic drug monitoring; TMP = trimethoprim; UTI = urinary tract infection; Vd = volume of distribution.

[a]Does not include dose adjustments for renal and/or hepatic impairment. Doses listed are within usual safety margins. Lower doses may be sufficient in mild infections (e.g., UTI). Dosages are based on the provided references and/or the authors' opinion, and should not replace clinical judgment. Cl_{cr} assumes calculation using $ABW_{0.4}$ unless specified in table.

[b]Dots represent types of studies available and not quantity. Table S2 summarizes the studies used in developing dosing guidance.

[c]Dosing recommendations are for severe or deep-seated infections based on similarities in PK profile (Table S3) and dosing recommendations with other antibiotics of the same class when data are insufficient or lacking in obese patients.

Table 4. Summary of Antibiotic Dosing Adjustments in Obese Patients

Antibiotics	Comments
Ceftaroline, ceftolozane/tazobactam, ceftazidime/avibactam, doripenem, ertapenem, imipenem, meropenem, moxifloxacin, linezolid, tedizolid, dalbavancin, oritavancin, and tigecycline	• Do not appear to require dose adjustments based on obesity alone • Extended infusions may be considered for meropenem and doripenem in certain scenarios as described in Table 3
Gentamicin, tobramycin and amikacin, polymyxin B, trimethoprim-sulfamethoxazole, and daptomycin	• Consider $ABW_{0.4}$ as the dosing weight scalar to limit risks of toxicity
Colistin methanesulfonate	• Consider IBW as the dosing weight scalar to limit risks of toxicity
Vancomycin	• Doses do not appear to scale linearly with body weight; require decreases in weight-based doses • Two point measurements (peak and trough) would increase accuracy of AUC estimates, as would single levels if using software capable of Bayesian analysis
Telavancin	• May warrant dosing adjustments (e.g., fixed dose and a dose cap at 1000 mg). These are tentative recommendations that should be reassessed after completion of an ongoing phase I trial (NCT02753855)
Amoxicillin, nafcillin, piperacillin/tazobactam, cefazolin, cephalexin, ceftazidime, cefepime, ciprofloxacin, levofloxacin, clindamycin	• Data are inadequate and/or conflicting; dosing in the upper end of the normal dosing range would be reasonable in severe and/or deep-seated infections
Imipenem/cilastatin	• No data: increased risk of seizures in renal impairment and with high doses 4 g/day
β-lactams	• Alternative dosing strategies (e.g., prolonged or continuous infusions) should be considered, particularly in severe deep-seated infections or for patients with fluctuating renal function
Various antimicrobials (e.g., β-lactams, fluoroquinolones)	• The role of TDM of is increasing importance in guiding antimicrobial dosing in obese, critically ill, and other special populations

ABW = adjusted body weight; AUC = area under the curve; IBW = ideal body weight; TDM = therapeutic drug monitoring.

22% that of nonobese patients, despite doubling the dose in the obese group, and did not correspond to a proportional increase in plasma exposure, described as area under the curve (AUC), ($AUC_{0-\infty} = Dose/Vd \times k$).[32] In addition to inadequate tissue concentrations, standard unadjusted doses in some instances may also fail to achieve adequate plasma concentrations.

These data are consistent with national guideline recommendations to use increased doses of cephalosporins based on body weight for surgical prophylaxis and also have potential implications for their therapeutic use. However, one retrospective review suggested that increased doses of cefazolin do not lead to lower surgical site infection rates.[33] Future data will clarify the clinical impact of weight-based dosing of cephalosporins used for surgical prophylaxis.

Ceftazidime and Cefepime

As stated earlier, perioperative prophylaxis data can inform therapeutic dosing strategies. Single-dose cefepime in morbidly obese patients before bariatric surgery yielded an elevated Vd and Cl. Using this data in simulations, one study found low PTA with 2 g IV every 12 hour dosing, leading the authors to recommend 2 g every 8 hour dosing in morbidly obese patients (Table S2).

Two small sparsely sampled PK studies of ceftazidime and cefepime in obese critically ill and noncritically ill patients showed subtherapeutic concentrations, elevated Vd, increased Cl, and suboptimal PTA at the resistant breakpoint (MIC 16 mg/L or lower) for *Pseudomonas aeruginosa* with 2 g every 8 hour dosing.[28, 30] In noncritically ill obese patients, higher Cl_{cr} was a risk factor for failure.[28] In critically ill patients, the investigators did not detect significant differences in Vd and Cl between obese and nonobese patients, probably due to a small sample size and imbalanced patient groups.[30]

Ceftazidime/Avibactam

Ceftazidime/avibactam was successful in treating two obese patients with *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* bacteremia and renal impairment.[34] Both patients had ceftazidime Vd 1.4–2.8 times that

of the package insert. Avibactam PK was explored in an early drug development program and showed significant increases in AUC by up to 20% and Vd up to 56% in normal/overweight patients compared with those in obese class III, although changes are not expected to impact the concentration-time profile or dosing regimen.[35]

Ceftolozane

No dose adjustment for ceftolozane is expected in obesity based on a population PK meta-analysis from phase I and II studies that showed increases in Vd and minimal changes in Cl that did not result in any clinically relevant change in exposure.[36] Too few obese patients were included in phase III studies to draw conclusions on the effectiveness of standard doses in these patients.

Ceftaroline

A phase I PK study of ceftaroline 600 mg every 12 hours showed that while Vd and Cl were significantly increased in those with a BMI higher than 40 mg/m^2, Monte Carlo simulations predicted excellent stasis target exposure (30% $fT \geq$ MIC) with MIC of 1 mg/L or lower that would be adequate concerning most clinical isolates of *Staphylococcus aureus, Streptococcus pneumoniae*, and non–extended-spectrum β-lactamase–producing *Escherichia coli* or *Klebsiella* spp.[37] They concluded that higher doses (e.g., every 8 hours) may be considered if targeting 50% $fT \geq$ MIC for methicillin-resistant *S. aureus* (MRSA), but this warrants further studies. These results are in line with clinical success reported from retrospective registry data of ceftaroline 600 mg every 12 hours dosing in diabetic foot infections or skin and skin structure infections that included obese patients.[38, 39]

Summary

Several studies with cephalosporins used for surgical prophylaxis have signaled concerns showing inadequate tissue penetration and subtherapeutic levels in obese patients. This finding may be further exacerbated by high Cl_{cr} or high protein binding. Enhanced exposure may provide optimized PD for treatment as well as surgical prophylaxis. For the former, this may be achieved by use of higher doses, more frequent dosing, or extended/continuous infusions, whereas for the latter the only practical approach is the use of higher doses.

Carbapenems

Ertapenem

In contrast to early PK studies suggesting that ertapenem may be underdosed in obese patients, a more recent population PK study showed that hospitalized patients dosed 1 g every 24 hours achieved 90% PTA or higher for MICs of 1 mg/L or lower in plasma but only for MICs of 0.25 mg/L or lower and 0.5 mg/L in subcutaneous tissue and peritoneal fluid, respectively (Table S2). This study then simulated regimens (using 0.5 g every 12 hours and 1 g/day as a continuous infusion) and showed better coverage at higher MICs.

Clinical studies also indicated that in obese patients, ertapenem 1 g every 24 hours may be sufficient for the treatment of moderate to severe diabetic foot infections and complicated intraabdominal infections.[40] Cure rates were similar between obese and nonobese groups, and obesity was not a risk factor for treatment failure. Perioperative ertapenem 1 g in obese patients undergoing abdominal surgeries was also associated with fewer surgical site infections than comparator antibiotics.[41]

Meropenem

Obesity increased meropenem Vd and Cl in both critically ill and noncritically ill patients, but these differences did not hinder achievement of standard PD targets (Table S2). PTA was generally high (greater than 80%) and similar in obese and nonobese critically ill patients, and greater than 90% in other hospitalized populations at an MIC of 2 mg/L, the susceptibility breakpoint for *P. aeruginosa*.[1, 30, 42] One study showed high meropenem tissue penetration in five morbidly obese patients undergoing abdominal surgery (AUC ratio of 0.943 and 0.721 in peritoneal and subcutaneous tissue, respectively) (Table S2).

Altered renal function may impact target attainment in obese individuals. A subset analysis of critically ill patients showed that obesity did not impact the probability of achieving therapeutic targets at an MIC of 2 mg/L when they received continuous renal replacement therapy (CRRT); however, obese patients not receiving CRRT were more likely to miss targets compared with nonobese patients.[30] Prolonged infusion, increasing age, and Cl_{cr} of 100 ml/minute or lower were identified as factors associated with achieving PD

targets for meropenem and piperacillin in obese critically ill patients.[43] Simulations of various meropenem regimens up to 2 g every 8 hours given as prolonged infusions in morbidly obese critically ill patients showed better PD target attainment and increased coverage at higher MICs.[44]

In clinical practice, lower daily doses, given via continuous infusions, achieved PTA goals in obese patients. One institution's experience using meropenem continuous infusion dosed 750 mg to 5 g/day across Cl_{cr} 10–200 ml/minute with TDM found that 99.9% and 97.4% of steady-state values were at least 2 and 4 mg/L, respectively (Table S2).

Doripenem

Doripenem PK alterations are similar to those of meropenem and do not affect attainment of adequate PD targets (40% *f*T> MIC) at MICs of 2 mg/L or lower, the breakpoint for *P. aeruginosa* and *Enterobacteriaceae* (Table S2). Simulations of various extended-infusion regimens in critically ill patients showed improved PD attainment if targeting a higher PD end point (e.g., 100% *f*T > MIC) or pathogens of higher MICs.[45]

Imipenem

No PK data for imipenem in obesity were identified. High doses of imipenem (1 g every 6 hours) and renal impairment were identified as risk factors for seizures and should be weighed carefully when selecting doses.[46]

Summary

Overall, dose escalation for carbapenems may not be warranted based on obesity alone. Prolonged infusions of meropenem or doripenem may be considered for less susceptible pathogens, to target higher PD parameters, or in critically ill patients prone to fluctuating renal function and variable serum levels. As with other β-lactams, TDM is increasingly important in optimizing dosing in special populations.

Aminoglycosides

Gentamicin, Tobramycin, and Amikacin

Gentamicin, tobramycin, and amikacin each have a Vd of ~0.2–0.3 L/kg that is increased in obese patients when compared with normal-weight patients (Table S2). In addition to a higher total Vd, serum drug concentrations of gentamicin and tobramycin were also found to be 21% and 26% higher, respectively, in obese patients when dosed at 1 mg/kg TBW.[47] Although the total Vd is higher, obese patients had a lower Vd/TBW. This suggests that adipose tissue contributed less volume per kilogram than nonadipose tissue. However, when the Vd was normalized to IBW, Vd/IBW was significantly greater in obese patients than normal-weight patients. These two findings suggest that drug distribution does occur in adipose tissue but not to the same degree as in other tissues.

To normalize the Vd of obese patients to one closer to the normal-weight population, several studies have suggested correction factors ranging from 0.38–0.58, with the most commonly cited factor of 0.40 for the initial aminoglycoside dose with subsequent adjustments based on TDM (Table S2). The correction factor of 0.40 is thought to account for extracellular fluid contained in adipose tissue. The same correction factor has also been used with obese patients with once/day high-dose aminoglycosides without reports of treatment failure or added risk of toxicity.[48]

Summary

Aminoglycosides have increased Vd in obese subjects. Studies suggest that the initial dose of aminoglycoside for obese patients may be dosed based on ABW using this formula: ABW = IBW + 0.4(TBW − IBW). TDM should be used to guide subsequent dose adjustments.

Fluoroquinolones

Ciprofloxacin

One study showed that Vd and Cl were significantly increased in 17 healthy obese volunteers compared with nonobese patients. Because Vd/kg_{TBW} was significantly lower in obese versus nonobese patients, the authors concluded there was incomplete drug distribution into tissues and proposed that ABW be calculated as IBW + 45% × (TBW − IBW) in obese patients when estimating Vd. A dose of 800 mg intravenously (IV) every 12 hours was administered to two critically ill patients, one on CRRT, to target PD targets of AUC/MIC greater than 125 and C_{max}/MIC greater than 10 for gram-negative infections and led to a cure without toxicities (Table S2). Dosing in CRRT was

further studied in 11 critically ill septic patients: Monte Carlo simulations showed a decrease in PTA achievement with increasing body weights (50, 90, and 140 kg) and inadequate fractional target attainment (83%) with 400 mg IV every 8 hour dosing in those weighing more than 140 kg.[49]

Levofloxacin

The PKs of levofloxacin appear unaltered by obesity, although Cl and AUC results varied widely in a small study of 15 ambulatory and hospitalized obese patients.[50] Results from the largest PK study to date[51] suggests that dosing in morbidly obese patients depends on Cl_{crIBW} to a greater extent than it does on body weight. Monte Carlo simulations using TDM data from 68 morbidly obese patients (BMI of 40 or higher) with 394 levels (peaks and troughs) predicted doses of 750 mg/day for Cl_{crIBW} 60–110 ml/minute and doses exceeding 750 mg/day for Cl_{crIBW} over 110 ml/minute to target an AUC of 100 for gram-negative infections.[51] But they did not study outcomes or safety data for this nomogram-based dosing.

Doses exceeding 1000 mg/day have been rarely reported in the clinical setting. One study reported a case in which levofloxacin 4 mg/kg or 750 mg every 12 hours in a 179-kg patient with a BMI of 56 kg/m^2 and Cl_{cr} 78 ml/minute achieved clinical cure and no toxicities (Table S2). This dosing produced double the AUC_{0-24} and greater than double the Vd reported in healthy nonobese adults dosed 750 mg every 24 hours, which the authors considered excessive and led them to question whether dose adjustments are needed in morbidly obese patients.

Moxifloxacin

PK was not significantly altered by morbid obesity based on richly sampled PK data in 12 morbidly obese adults undergoing gastric bypass surgery.[52] Like ciprofloxacin, moxifloxacin Vd did not correlate well with TBW in morbidly obese patients.

Summary

Data are insufficient to guide ciprofloxacin dosing in obese populations, except in septic patients on CRRT with susceptible pathogens (e.g., *Pseudomonas aeruginosa* or *Acinetobacter baumannii*) with MICs between 0.5 and 1 mg/L; those weighing over 90 kg should receive 400 mg IV every 8 hours; those over 140 kg may not achieve target PD goals. Data suggest that obese patients with Cl_{crIBW} over 60 ml/minute should receive levofloxacin at least 750 mg/day when targeting gram-negative pathogens. Most preliminary data so far support no moxifloxacin dose adjustment in obesity.

Polymyxins

Colistin

Colistin methanesulfonate is the prodrug of colistin (polymyxin E). The package insert recommends use of IBW for dosing in obese patients.[53] Based on population PK studies performed in 214 critically ill patients up to 122 kg and with varied renal function (some requiring dialysis), one group developed dosing equations including a loading dose based on IBW ($C_{ss,avg}target \times 2 \times IBW$) and a maintenance dose $C_{ss,avg}target \times 10^{(0.0048 \times Cl_{cr}+1.825)}$ based on weight-independent Cl_{cr}.[54] The only significant covariate for Vd was body weight; thus it is not clear that IBW is the most appropriate weight definition to use in loading dose calculations in obese patients. A maximum dose of 360 mg was used based on a perceived threshold for colistin-associated nephrotoxicity, but this would not be expected to achieve PTA goals at MICs of 2 mg/L (the susceptibility breakpoint for *P. aeruginosa* and *A. baumannii*) in patients with Cl_{cr} of 80 ml/minute or greater.

In a nested case-control study of patients with BMI of 25 kg/m^2 or higher who received IV colistin methanesulfonate, the nephrotoxicity incidence was 48% (20/42 patients), with a median time to onset of 5 days.[55] Most cases of nephrotoxicity were attributed to excessive dosing because 64% were dosed by TBW. A multivariate analysis identified a BMI of 31.5 kg/m^2 or higher as a risk factor for nephrotoxicity (odds ratio 3.1; p=0.025); however, this analysis was limited by unbalanced cohort groups.

Polymyxin B

Polymyxin B is generally dosed using TBW, but caution should be used when applying this to obese patients given that PK data in obesity are limited to one case. In a population PK analysis of 24 critically ill patients with weights of 41–110 kg and only one 250kg patient (on

CRRT), Cl and Vd scaled linearly with TBW.[56] However, because Cl scaled slightly better with $TBW^{-0.75}$ (i.e., nonlinear), it was suggested that TBW is not the appropriate dosing scalar for weight-based dosing.[57] A calculated dose based on a TBW of 250 kg was expected to overdose the patient. $ABW_{0.4}$ was suggested as a more appropriate dosing weight scalar.[53]

Summary

To limit the risks of nephrotoxicity, colistin may be dosed using IBW with a limit of 360 mg/day. It may be reasonable to dose polymyxin B using $ABW_{0.4}$ in obese patients and to limit daily doses to 2 million units (200 mg).[53]

Vancomycin

Most studies in obese adults have reported increased vancomycin Vd and Cl relative to that in nonobese subjects, strong correlation of Cl_{cr} with Cl, and variable and conflicting correlation of Vd with TBW.[14, 58–60]

Increasing BMI was associated with a significantly higher proportion of obese patients reaching troughs less than 20 mg/L, even after controlling for dose, S_{cr}, and age.[61] Weight-normalized Vd (0.3–0.5 vs 0.7 L/kg_{TBW}) did not scale proportionally in a comparison of morbidly obese patients with obese patients, implying that lower loading doses would be an appropriate adjustment for patient groups with increasing BMIs (loading dose = $C_{max} \times Vd$).[14, 60] A large retrospective cohort of 334 patients estimated that patients with a BMI of 30–39 optimize target trough attainment with doses of 30 mg/kg_{TBW}/day.[62] Interestingly, they estimated that those with a BMI of 40 or greater require even lesser weight-based daily dosing (20–25 mg/kg_{TBW}/day), which is consistent with findings of the lack of scaling with increasing BMI.

Use of the dosing strategy recommended by the 2009 consensus panel (i.e., optional 25–30 mg/kg load followed by ~15 mg/kg_{TBW} every 8–12 hrs) in the obese population resulted in excessive trough concentrations (higher than 20 mg/L) in at least 50% of obese patients overall as well as in 79% of those requiring ICU care.[63] Using a revised obesity dosing protocol (20–25 mg/kg_{TBW} load followed by 10 mg/kg_{TBW} every 12 hrs), achievement of initial troughs of 10–20 mg/L numerically improved from 36 to 59% in 148 patients, with a significant improvement seen in the ICU subset (11 to 50%, p=0.032). In addition, 20% of patients received greater than 4 g/day (range 4–6 g/day) and did not experience nephrotoxicity. One group compared allometric dosing (dose = 1200 mg $\times[TBW(kg)/80]^{0.5}$, no loading dose) with consensus guideline dosing and found significant improvements in the achievement of initial troughs of 10–20 mg/L from 46 to 73% (p=0.03) in 74 obese patients.[64] A divided-load dosing protocol in 54 obese patients (1.5–2.5 g) utilized doses similar to those recommended for normal-weight patients (85% received 2 g in the initial 12 hrs corresponding to 3–4 g in the initial 24 hrs) and achieved goal troughs of 10–20 mg/L in 87% within 12 hours.[65] It is likely that their high success rate, however, was related to intense serum trough sampling because this allowed finer control of dose adjustments as early as 12 hours into therapy. These reported experiences consistently support nonlinear scaling of vancomycin dosing in obese populations. The common practice of substituting TBW with ABW as the dosing weight in consensus panel dosing in obese patients is also likely to improve dosing performance, although assessment of its relative accuracy has not been published.

It is difficult to assess the adequacy of loading doses on target trough attainment given its variable use in reported studies in obese patients. The contribution of cumulative daily doses may be more important than the loading dose strategy in optimizing initial target troughs. Studies commonly reported loading doses (if used at all) of 20–25 mg/kg_{TBW} (no dose cap mentioned except 3 g in one study), and mean daily doses of 2–4 g or 20–30 mg/kg/day were most frequently used and commonly associated with improved target trough attainment (Table S2).

PK alterations may lead to a net decrease in k ($k = Cl/Vd$, $t_{1/2} = 0.693/k$).[63] This is consistent with findings that vancomycin elimination decreased with increasing weights at similar BSA-normalized Cl_{cr} values in morbidly obese patients.[60] A decreased k may increase the likelihood of accumulation if the maintenance dose is not adjusted carefully. Thus frequent and careful TDM is especially important in the initial days of therapy, preferably performed using software capable of Bayesian analysis.

Bayesian analysis adjusts population PK model estimates using an individual's PK values derived from measured serum levels, thereby individualizing dosing predictions. Evidence indicates that use of trough concentrations alone is insufficient for accurate estimates of vancomycin exposure.

Results from a pilot study in 12 obese patients recently suggested that use of Bayesian software tools with peak and trough data provided more accurate AUC predictions than trough-only data.[66] If Bayesian tools are not available to perform dose revisions, use of two point measurements (peaks and troughs) should still be considered because it improves precision and lowers the bias of AUC estimates in obese adults.[14, 67]

Summary

A reasonable approach to initial vancomycin dosing in obese patients would be to reduce the loading dose (if indicated) to 20–25 mg/kg$_{TBW}$ and to reduce the starting maintenance dose, then adjust according to TDM. Software capable of Bayesian analysis should be used, if available, and/or peak and trough measurements (using Sawchuck and Zaske methods)[14] because it provides greater accuracy of AUC-guided dose revisions in obese patients.

Oxazolidinones

Linezolid

Previous data showed subtherapeutic linezolid levels, increased Cl and Vd, but variable AUC changes in obese patients compared with nonobese patients (Table S2). PK parameters are further altered in obese patients with critical illness; one study showed that C_{max} reduced by half, Cl nearly doubled, $t_{1/2}$ was shorter, and Vd was similar in comparison with healthy obese subjects (Table S2).

Alternative dosing strategies have been used in critically ill obese patients. One study reported two cases where high-dose linezolid (600 mg every 8 hrs) still did not achieve PD targets in this population (Table S2). Such dosing was associated with high rates of thrombocytopenia in up to 22.9% in obese populations.[68] Another report showed that two critically ill obese patients with ventilator-associated pneumonia (VAP) given continuous infusions had significantly better PTA of T > MIC but not AUC/MIC (the preferred efficacy parameter) at an MIC of 4 mg/L, and significantly higher epithelial lining fluid penetration compared with intermittent infusions (Table S2).

Despite these data, clinical studies have not found evidence of worse clinical outcomes in obese patients receiving standard doses of linezolid. Pooled data from two prospective phase IV studies compared linezolid (600 mg IV every 12 hrs) with vancomycin in 540 patients with confirmed MRSA infection who were stratified by weight into quartiles, including 82 patients with complicated skin and soft tissue infections (97–295 kg) and 54 patients with pneumonia (88–215 kg).[69] There was no difference in the rates of clinical success or adverse events among the quartiles treated with linezolid.

Tedizolid

Clinical data concerning tedizolid in obesity are limited. Pooled analyses of phase III studies showed a numerical, but nonsignificant, decrease in clinical response rates with increasing BMIs.[70] No dose adjustments for tedizolid are expected for obesity based on two analyses showing similar PK profiles (AUC, Vd, Cl, and C_{max}) in obese versus nonobese healthy adults and those with skin and skin structure infections.[70, 71]

Summary

Oxazolidinones do not appear to require dose adjustments in obesity. Data are insufficient at this time to recommend alternative linezolid dosing strategies (e.g., continuous infusions) in obese populations but should be studied in higher degrees of obesity (e.g., above 150 kg), for the treatment of VAP and those with concomitant critical illness.

Daptomycin

The manufacturer recommends the use of TBW in dosing daptomycin in obese patients based on 4 mg/kg single-dose PK data showing that obese subjects had significantly increased C_{max}, AUC, Vd, and Cl compared with matched nonobese controls, but that these values were within the range of safety and tolerability (Table S2). However, when Vd and Cl were normalized for TBW or IBW, these relative increases diminished, signaling incomplete distribution of drug into excess body tissues in obese patients. An ~60% increase was also found in both C_{max} and AUC_{24} in morbidly obese patients but nonstatistically significant increases were observed in Cl and Vd (~12% and 22%, respectively).[72] In examining the relationship of Vd to TBW, IBW, and FFW, defining Vd as a function of FFW yielded nearly identical results when comparing obese and nonobese subjects. Total Cl between

the two groups was similar, but morbidly obese patients had significantly lower Cl/kg compared with the control group, suggesting that daptomycin Cl in obese patients does not increase proportionately with increasing body weight.

Monte Carlo simulations of 6 mg/kg dosing based on $ABW_{0.4}$ produced AUC values closest to that of nonobese patients and those seen in bacteremia and endocarditis clinical trials.[73] In a retrospective analysis of patients with enterococcal and staphylococcal infections, no difference was reported in outcomes with dosing based on IBW or TBW, despite adjustment for age, sex, BMI, infection type, and organism type.[74] A more recent observational study showed that dosing by ABW provides similar clinical, microbiological, and safety outcomes compared with TBW in obese patients.[75]

Clinicians should be cognizant of daptomycin's dose-dependent musculoskeletal toxicity. A case series of long-term high-dose daptomycin (mean dose 8 mg/kg_{TBW} for at least 14 days) described 3 of 61 patients, 2 of whom were morbidly obese (class III) with musculoskeletal symptoms/creatine phosphokinase (CPK) elevations to over 1000 IU/L.[76] In a post hoc analysis, PK modeling demonstrated that daptomycin C_{min} of 24.3 mg/L or more was associated significantly with an increased probability of CPK elevation.[77] Of obese patients weighing at least 111 kg, 19.4% would be expected to reach this C_{min} threshold for an increased probability of CPK elevation compared with 6.5% in those weighing less than 111 kg. When daptomycin was administered as 6 mg/kg/day based on LBW rather than TBW in simulated patients weighing at least 111 kg, only 7.4% of patients would be expected to have a C_{min} of 24.3 mg/L or more. These findings are not unexpected considering obese patients have higher daptomycin AUC and C_{max} exposure compared with normal-weight patients and that its clearance does not proportionately increase. Clinical experience in the obese population also found a trend toward increasing rates of CPK elevations as BMI class increases (BMI class I [3.6%], BMI class II [10.3%], BMI class III [10.5%]; p=0.554), with therapy discontinuation due to adverse drug events having occurred in 8 (6.3%) patients and one developed rhabdomyolysis on day 9 of therapy.[78]

Summary

Obese patients when dosed by TBW experience higher daptomycin exposure compared with their nonobese counterparts.[73] Given the relatively wide therapeutic index of daptomycin and clinical experience of tolerability as well as data supporting the use of higher daptomycin doses (up to 10–12 mg/kg) for adequate PK/PD target attainment, dosing obese patients with $ABW_{0.4}$ is reasonable to ensure treatment efficacy while balancing the risk of muscle toxicity. Close monitoring is required because increasing BMI class is associated with increased risk of CPK elevation as well as therapy discontinuation due to toxicities.

Lipoglycopeptides

Telavancin

The package insert for telavancin recommends dosing 10 mg/kg_{TBW} every 24 hours for Cl_{cr} greater than 50 ml/minute calculated using IBW with no specific recommendations for obese patients.[79] Combined data from various phase 1, 2, and 3 studies showed that higher daily doses in obese patients up to 314 kg led to smaller nonlinear increases in AUC and Cl.[80] An interim analysis of a phase I trial (NCT02753855) in healthy obese adults showed more uniform PK exposure using fixed dosing of 500 mg for those weighing 50–74.9 kg, 750 mg for 75–99.9 kg, and 1000 mg for at least 100 kg.[81] A 1000-mg maximum dose should be considered because higher doses in obese patients may increase the risk of renal adverse events.[79] In a post hoc analysis of two phase III trials, renal events were 2.8 times greater in patients with a BMI of 35 kg/m^2 or greater versus a BMI lower than 35 kg/m^2.[82]

Dalbavancin

A population PK analysis of dalbavancin that included patients up to 320 kg and BSA 4.0 m^2 showed that BSA was a significant covariate for the Vd in the central compartment (linear relationship), and both BSA and Cl_{cr} were significant covariates of Cl.[83] The changes in Cl and plasma concentrations with increasing BSAs or body weights are considered small and not thought to impact clinical efficacy. Simulations of concentrations in individuals up to 3 times the normal weight showed similar concentrations at 24 hours and only a 33% decrease in AUC.[38] A phase III trial in skin and skin structure infection included approximately a third of study patients with a BMI higher than 30 kg/m^2 and reported overall clinical success of over 80%.[84]

Oritavancin

The PK profile of oritavancin was studied in patients up to 178 kg and a BMI of 67.4 kg/m^2.[38, 85] Oritavancin Cl was significantly associated with height, but not body weight, BMI, or BSA. Its Cl is predicted to increase by only 28% with heights between 55.1 and 78.7 inches, and $AUC_{0–72}$ is minimally changed.

Summary

A maximum telavancin dose of 1000 mg may be considered in obese patients. Results of an ongoing phase I study (NCT 02753855) will inform us whether further dose adjustments are indicated in obese patients. Based on limited data from retrospective registry studies and post hoc analyses, dose adjustments do not appear to be necessary for dalbavancin and oritavancin in obese patients.

Conclusions

Optimal dosing of antimicrobials in obesity is challenging given the limited amount of high-level evidence for many agents. Unresolved dilemmas in dosing antimicrobials in obesity include the lack of standardized estimation of Cl_{cr} (as a surrogate of GFR) and the variable use of dosing weights in weight-based dosing. Inclusion of obese patients in all phases of the Food and Drug Administration drug development process is needed to provide better guidance on dosing in this special population.

Acknowledgment

The authors would like to acknowledge Christopher Stave and Steven Dunlap for their help developing search strategies.

References

1. **Alobaid AS, Hites M, Lipman J, Taccone FS, Roberts JA.** Effect of obesity on the pharmacokinetics of antimicrobials in critically ill patients: a structured review. Int J Antimicrob Agents 2016;47:259–68.
2. **Hanley MJ, Abernethy DR, Greenblatt DJ.** Effect of obesity on the pharmacokinetics of drugs in humans. Clin Pharmacokinet 2010;49:71–87.
3. **Pai MP, Bearden DT.** Antimicrobial dosing considerations in obese adult patients. Pharmacotherapy 2007;27:1081–91.
4. **Rowland M, Tozer TN.** Clinical pharmacokinetics: concepts and applications. Baltimore, MD: Williams & Wilkins; 1995.
5. **Lemmens HJ, Ingrande J.** Pharmacology and obesity. Int Anesthesiol Clin 2013;51:52–66.
6. **Demirovic JA, Pai AB, Pai MP.** Estimation of creatinine clearance in morbidly obese patients. Am J Health Syst Pharm 2009;66:642–8.
7. **Winter MA, Guhr KN, Berg GM.** Impact of various body weights and serum creatinine concentrations on the bias and accuracy of the Cockcroft-Gault equation. Pharmacotherapy 2012;32:604–12.
8. **Pai MP.** Estimating the glomerular filtration rate in obese adult patients for drug dosing. Adv Chronic Kidney Dis 2010;17:e53–62.
9. **Mysliwiec P, Jasiewicz P, Hady HR, et al.** Creatinine or cystatin C—which is a better index of renal function in morbid obesity? Adv Med Sci 2013;58:376–81.
10. **Payne KD, Hall RG.** Dosing of antifungal agents in obese people. Expert Rev Anti Infect Ther 2016;14:257–67.
11. **Zeller V, Durand F, Kitzis MD, et al.** Continuous cefazolin infusion to treat bone and joint infections: clinical efficacy, feasibility, safety, and serum and bone concentrations. Antimicrob Agents Chemother 2009;53:883–7.
12. **Roberts JA, Udy AA, Jarrett P, et al.** Plasma and target-site subcutaneous tissue population pharmacokinetics and dosing simulations of cefazolin in post-trauma critically ill patients. J Antimicrob Chemother 2015;70:1495–502.
13. **Pfizer Inc.** Cleocin Phosphate (clindamycin) U.S. Prescribing Information. New York, NY; 2017.
14. **Hong J, Krop LC, Johns T, Pai MP.** Individualized vancomycin dosing in obese patients: a two-sample measurement approach improves target attainment. Pharmacotherapy 2015;35:455–63.
15. **Yuk J, Nightingale CH, Sweeney K, Levitz RE, Quintiliani R.** Pharmacokinetics of nafcillin in obesity. J Infect Dis 1988;157:1088–9.
16. **Kays MB, Fleming MR, Cheatham SC, Chung EK, Juenke JM.** Comparative pharmacokinetics and pharmacodynamics of doripenem and meropenem in obese patients. Ann Pharmacother 2014;48:178–86.
17. Micromedex healthcare series: DRUGDEX system—2017. Greenwood Village, CO: Thomson Micromedex, 2017.
18. **Heintz BH, Matzke GR, Dager WE.** Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. Pharmacotherapy 2009;29:562–77.
19. **Stass H, Dalhoff A, Kubitza D, Schuhly U.** Pharmacokinetics, safety, and tolerability of ascending single doses of moxifloxacin, a new 8-methoxy quinolone, administered to healthy subjects. Antimicrob Agents Chemother 1998;42:2060–5.
20. **Rybak JM, Marx K, Martin CA.** Early experience with tedizolid: clinical efficacy, pharmacodynamics, and resistance. Pharmacotherapy 2014;34:1198–208.
21. **Leighton A, Gottlieb AB, Dorr MB, et al.** Tolerability, pharmacokinetics, and serum bactericidal activity of intravenous dalbavancin in healthy volunteers. Antimicrob Agents Chemother 2004;48:940–5.
22. **Smith WJ, Drew RH.** Telavancin: a new lipoglycopeptide for gram-positive infections. Drugs of today (Barcelona, Spain: 1998) 2009;45:159–73.
23. **Karaiskos I, Friberg LE, Pontikis K, et al.** Colistin population pharmacokinetics after application of a loading dose of 9 mu colistin methanesulfonate in critically ill patients. Antimicrob Agents Chemother 2015;59:7240–8.
24. **Zavascki AP, Goldani LZ, Cao G, et al.** Pharmacokinetics of intravenous polymyxin B in critically ill patients. Clin Infect Dis 2008;47:1298–304.
25. **Chung EK, Cheatham SC, Fleming MR, Healy DP, Shea KM, Kays MB.** Population pharmacokinetics and pharmacodynamics of piperacillin and tazobactam administered by prolonged infusion in obese and nonobese patients. J Clin Pharmacol 2015;55:899–908.
26. **Cheatham SC, Fleming MR, Healy DP, et al.** Steady-state pharmacokinetics and pharmacodynamics of piperacillin and tazobactam administered by prolonged infusion in obese patients. Int J Antimicrob Agents 2013;41:52–6.
27. **Alobaid AS, Wallis SC, Jarrett P, et al.** Population pharmacokinetics of piperacillin in non-obese, obese and morbidly-obese critically ill patients. Antimicrob Agents Chemother 2017;61:e01276–16.

28. **Hites M, Taccone FS, Wolff F, et al.** Broad-spectrum β-lactams in obese non-critically ill patients. Nutr Diabetes 2014;4: e119.
29. **Jung B, Mahul M, Breilh D, et al.** Repeated piperacillin-tazobactam plasma concentration measurements in severely obese versus nonobese critically ill septic patients and the risk of under and overdosing. Crit Care Med 2017;45:e470–8.
30. **Hites M, Taccone FS, Wolff F, et al.** Case-control study of drug monitoring of beta-lactams in obese critically ill patients. Antimicrob Agents Chemother 2013;57:708–15.
31. **Alobaid AS, Brinkmann A, Frey OR, et al.** What is the effect of obesity on piperacillin and meropenem trough concentrations in critically ill patients? J Antimicrob Chemother 2016;71:696–702.
32. **Toma O, Suntrup P, Stefanescu A, London A, Mutch M, Kharasch E.** Pharmacokinetics and tissue penetration of cefoxitin in obesity: implications for risk of surgical site infection. Anest Analg 2011;113:730–7.
33. **Peppard WJ, Eberle DG, Kugler NW, Mabrey DM, Weigelt JA.** Association between pre-operative cefazolin dose and surgical site infection in obese patients. Surg Infect 2016;18:485–90.
34. **Veillette JJ, Truong J, Forland SC.** Pharmacokinetics of ceftazidime-avibactam in two patients with KPC-producing *Klebsiella pneumoniae* bacteremia and renal impairment. Pharmacotherapy 2016;36:e172–7.
35. Clinical Pharmacology And Biopharmaceutics Review: Ceftazidime-Avibactam, 2015. Available from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206494Orig1s000CllinPharmR.pdf. Accessed March 14, 2017.
36. **Ceftolozane/tazobactam.** Merck Global Medical Information; data on file. Merck & Co. Inc.
37. **Justo JA, Mayer SM, Pai MP, et al.** Pharmacokinetics of ceftaroline in normal body weight and obese (classes I, II, and III) healthy adult subjects. Antimicrob Agents Chemother 2015;59:3956–65.
38. **Pai MP.** Anti-infective dosing for obese adult patients: a focus on newer drugs to treat methicillin-resistant *Staphylococcus aureus* acute bacterial skin and skin structure infections. Clin Ther 2016;38:2032–44.
39. **Evans JD, Udeani G, Cole P, Friedland HD.** Ceftaroline fosamil for the treatment of acute bacterial skin and skin structure infections in obese patients. Postgrad Med 2014;126:128–34.
40. **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.
41. **de Werra C, Di Micco R, Pilone V, et al.** Serum in vivo and in vitro activity of single dose of ertapenem in surgical obese patients for prevention of SSIs. Obes Surg 2013;23:911–9.
42. **Chung EK, Cheatham SC, Fleming MR, Healy DP, Kays MB.** Population pharmacokinetics and pharmacodynamics of meropenem in nonobese, obese, and morbidly obese patients. J Clin Pharmacol 2017;57:356–68.
43. **Alobaid AS, Wallis SC, Jarrett P, et al.** Effect of obesity on the population pharmacokinetics of meropenem in critically ill patients. Antimicrob Agents Chemother 2016;60:4577–84.
44. **Cheatham SC, Fleming MR, Healy DP, et al.** Steady-state pharmacokinetics and pharmacodynamics of meropenem in morbidly obese patients hospitalized in an intensive care unit. J Clin Pharmacol 2014;54:324–30.
45. **Chung EK, Fleming MR, Cheatham SC, Kays MB.** Population pharmacokinetics and pharmacodynamics of doripenem in obese, hospitalized patients. Ann Pharmacother 2017;51:209–18.
46. **Zhanel GG, Wiebe R, Dilay L, et al.** Comparative review of the carbapenems. Drugs 2007;67:1027–52.
47. **Schwartz SN, Pazin GJ, Lyon JA, Ho M, Pasculle AW.** A controlled investigation of the pharmacokinetics of gentamicin and tobramycin in obese subjects. J Infect Dis 1978;138:499–505.
48. **Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R.** Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother 1995;39:650–5.
49. **Roger C, Wallis SC, Louart B, et al.** Comparison of equal doses of continuous venovenous haemofiltration and haemodiafiltration on ciprofloxacin population pharmacokinetics in critically ill patients. J Antimicrob Chemother 2016;71:1643–50.
50. **Cook AM, Martin C, Adams VR, Morehead RS.** Pharmacokinetics of intravenous levofloxacin administered at 750 milligrams in obese adults. Antimicrob Agents Chemother 2011;55:3240–3.
51. **Pai MP, Cojutti P, Pea F.** Levofloxacin dosing regimen in severely morbidly obese patients (BMI≥ 40 kg/m^2) should be guided by creatinine clearance estimates based on ideal body weight and optimized by therapeutic drug monitoring. Clin Pharmacokinet 2014;53:753–62.
52. **Kees MG, Weber S, Kees F, Horbach T.** Pharmacokinetics of moxifloxacin in plasma and tissue of morbidly obese patients. J Antimicrob Chemother 2011;66:2330–5.
53. **Kassamali Z, Jain R, Danziger LH.** An update on the arsenal for multidrug-resistant Acinetobacter infections: polymyxin antibiotics. Int J Infect Dis 2015;30:125–32.
54. **Nation RL, Garonzik SM, Thamlikitkul V, et al.** Dosing guidance for intravenous colistin in critically-ill patients. Clin Infect Dis 2016;64:565–71.
55. **Gauthier TP, Wolowich WR, Reddy A, Cano E, Abbo L, Smith LB.** Incidence and predictors of nephrotoxicity associated with intravenous colistin in overweight and obese patients. Antimicrob Agents Chemother 2012;56:2392–6.
56. **Sandri AM, Landersdorfer CB, Jacob J, et al.** Population pharmacokinetics of intravenous polymyxin B in critically ill patients: implications for selection of dosage regimens. Clin Infect Dis 2013;57:524–31.
57. **Pai MP.** Polymyxin B dosing in obese and underweight adults. Clin Infect Dis 2013;57:1785.
58. **Vance-Bryan K, Guay DR, Gilliland SS, Rodvold KA, Rotschafer JC.** Effect of obesity on vancomycin pharmacokinetic parameters as determined by using a Bayesian forecasting technique. Antimicrob Agents Chemother 1993;37:436–40.
59. **Bauer LA, Black DJ, Lill JS.** Vancomycin dosing in morbidly obese patients. Eur J Clin Pharmacol 1998;54:621–5.
60. **Adane ED, Herald M, Koura F.** Pharmacokinetics of vancomycin in extremely obese patients with suspected or confirmed *Staphylococcus aureus* infections. Pharmacotherapy 2015;35:127–39.
61. **Richardson J, Scheetz M, O'Donnell EP.** The association of elevated trough serum vancomycin concentrations with obesity. J Infect Chemother 2015;21:507–11.
62. **Morrill HJ, Caffrey AR, Noh E, LaPlante KL.** Vancomycin dosing considerations in a real-world cohort of obese and extremely obese patients. Pharmacotherapy 2015;35:869–75.
63. **Reynolds DC, White LH, Alexander DP, DeRyke CA.** Performance of a vancomycin dosage regimen developed for obese patients. Am J Health Syst Pharm 2012;69:944–50.
64. **Brown ML, Hutchison AM, McAtee AM, Gaillard PR, Childress DT.** Allometric versus consensus guideline dosing in achieving target vancomycin trough concentrations. Am J Health Syst Pharm 2017;74:1067–75. ajhp160260.
65. **Denetclaw TH, Yu MK, Moua M, Dowling TC, Steinke D.** Performance of a divided-load intravenous vancomycin dosing strategy for obese patients. Ann Pharmacother 2015;49:861–8.
66. **Carreno JJ, Lomaestro B, Tietjan J, Lodise TP.** Pilot study of a Bayesian approach to estimate vancomycin exposure in obese patients with limited pharmacokinetic sampling. Antimicrob Agents Chemother 2017;61:e02478-16.
67. **Pai MP, Hong J, Krop L.** Peak measurement for vancomycin AUC estimation in obese adults improves precision and lowers bias. Antimicrob Agents Chemother 2017;61:e02490–16.
68. **Fleming MR, Cheatham SC, Kays MB.** Evaluation of clinical outcomes and adverse events when administering alternative

doses of linezolid to obese patients [abstract]. Pharmacotherapy 2011;31(10):353e.
69. **Puzniak LA, Morrow LE, Huang DB, Barreto JN.** Impact of weight on treatment efficacy and safety in complicated skin and skin structure infections and nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus*. Clin Ther 2013;35:1557–70.
70. **Pai MP.** Pharmacokinetics of tedizolid in morbidly obese and covariate matched non-obese adults. Antimicrob Agents Chemother 2016;60:4585–9:AAC. 00682-16.
71. **Flanagan S, Minassian SL, Passarell JA, Fiedler-Kelly JB, Prokocimer P.** Tedizolid plasma pharmacokinetics are comparable in obese and nonobese patients and healthy subjects. 24th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 2014.
72. **Pai MP, Norenberg JP, Anderson T, et al.** Influence of morbid obesity on the single-dose pharmacokinetics of daptomycin. Antimicrob Agents Chemother 2007;51:2741–7.
73. **Farkas A, Sussman R.** Dosing of daptomycin in the morbidly obese: which body weight is it. IDWeek, San Diego, CA 2012;20.
74. **Ng JK, Schulz LT, Rose WE, et al.** Daptomycin dosing based on ideal body weight versus actual body weight: comparison of clinical outcomes. Antimicrob Agents Chemother 2014;58:88–93.
75. **Shemanski S, Bennett N, Boyd S, Woods M, Ploetz J, Kennedy K.** 698: Evaluation of clinical effectiveness utilizing adjusted body weight for daptomycin dosing. Crit Care Med 2016;44:251.
76. **Figueroa D, Mangini E, Amodio-Groton M, et al.** Safety of high-dose intravenous daptomycin treatment: three-year cumulative experience in a clinical program. Clin Infect Dis 2009;49:177–80.
77. **Bhavnani SM, Rubino CM, Ambrose PG, Drusano GL.** Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. Clin Infect Dis 2010;50:1568–74.
78. **Bookstaver PB, Bland CM, Qureshi ZP, et al.** Safety and effectiveness of daptomycin across a hospitalized obese population: results of a multicenter investigation in the southeastern United States. Pharmacotherapy 2013;33:1322–30.
79. **Pai MP.** Comment on: Acute renal insufficiency during telavancin therapy in clinical practice. J Antimicrob Chemother 2012;67:1300–1; author reply 1-2.
80. **Samara E, Shaw JP, Barriere SL, Wong SL, Worboys P.** Population pharmacokinetics of telavancin in healthy subjects and patients with infections. Antimicrob Agents Chemother 2012;56:2067–73.
81. **Bunnell K, Sikka M, Bleasdale SC.** Pharmacokinetics of fixed dose telavancin in obese and non-obese adult subjects. 27th European Congress of Clinical Microbiology and Infectious Disease. Vienna, Austria; 2017.
82. **Slover CM, Nkechi A, Barriere SL, Lu Q.** Telavancin for treatment of complicated skin and skin structure infections in obese patients [abstract L1-1491]. Fifty-first Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, American Society for Microbiology; 2011.
83. **Buckwalter M, Dowell JA.** Population pharmacokinetic analysis of dalbavancin, a novel lipoglycopeptide. J Clin Pharmacol 2005;45:1279–87.
84. **Dunne MW, Puttagunta S, Giordano P, Krievins D, Zelasky M, Baldassarre J.** A randomized clinical trial of single-dose versus weekly dalbavancin for treatment of acute bacterial skin and skin structure infection. Clin Infect Dis 2016;62:545–51.
85. **Rubino CM, Bhavnani SM, Moeck G, Bellibas SE, Ambrose PG.** Population pharmacokinetic analysis for a single 1,200-milligram dose of oritavancin using data from two pivotal phase 3 clinical trials. Antimicrob Agents Chemother 2015;59:3365–72.

Supporting Information

The following supporting information is available in the online version of this paper:

Table S1. Search strategies.

Table S2. Summary of Selected Published Studies Evaluating Antimicrobial Pharmacokinetics, Clinical Outcomes, or Dosing in Obese Adults.

Table S3. Typical Physiochemical Properties and Pharmacokinetic Profile of Antimicrobial Agents.[12, 15–24, 56, 80]