Antimicrobial Dosing in Obese Patients

Rebecca Wurtz, Gail Itokazu, and Keith Rodvold

Although the dose of some drugs is commonly adjusted for weight, weight-related dosage adjustments are rarely made for most antimicrobials. We reviewed the English-language literature on antimicrobial pharmacokinetics and dosing in obesity. Although there are many potential pharmacokinetic consequences of obesity, the actual effect on the pharmacokinetics and clinical efficacy of most antimicrobials is unknown. Since ~30% of adipose is water, an empirical approach is use of the Devine formula to calculate ideal body weight (IBW), to which is added a dosing weight correction factor (DWCF) of 0.3 times the difference between actual body weight (ABW) and IBW (IBW + 0.3 × [ABW-IBW]) to arrive at a weight on which to base dosage of hydrophilic antibiotics. No studies confirm this approach for β-lactam drugs. Clinical studies suggest a DWCF of ~0.40 for aminoglycosides and 0.45 for quinolones. Final dosage adjustments for antimicrobials with a narrow toxic-therapeutic window should be based on serum concentrations.

Ideal Body Weight, Obesity, Body Surface Area, and Body Mass Index

Equations to calculate IBWs for men and women are given in table 2 (curiously, the equations mix metric and standard measures) [10–12]. The commonly used Devine formula [10] defines IBW for men as 50 kg plus 2.3 times the height in inches over 60 inches; for women, a base weight of 45 kg is used instead. While there are only a handful of definitions of IBW [10–13], there are many definitions of obesity [8, 14]; one frequently used definition is body fat contents of 25% and ≥30% of ABW for men and women, respectively [8]. A common definition of morbid or extreme obesity is weight exceeding 200% of IBW [8].

Body surface area (BSA) is used as the basis for calculating cancer chemotherapy doses, and some researchers have advocated the use of BSA to calculate antimicrobial dose [15–17]. One study showed that the standard formula for calculating BSA in lean subjects [18] still applies for extremely obese subjects [19]. However, with the exception of calculating acyclovir doses for children, BSA is not used in antimicrobial dosing, and no studies have demonstrated that use of BSA optimally predicts serum antimicrobial levels in obese subjects [20].

Body mass index, the weight in kilograms divided by height in meters squared, has also been advocated as a basis for calculating drug dosage, but a study by Traynor et al. [21] demonstrated that using IBW as the basis for calculating aminoglycoside dosing was as accurate as using body mass index. Abernethy and Greenblatt have shown that body mass index and percentage of IBW correlate well [2]. For clinical purposes, calculating IBW on the basis of the widely used Devine formula [10] is most convenient. In most of the pharmacokinetic studies...
Table 1. Obesity-associated physiological changes with potential consequences for antimicrobial pharmacokinetics.

- Increased body mass, including both lean body mass and adipose tissue
- Increased cardiac output and blood volume
- Increased renal clearance
- Hepatic metabolic changes
- Changes in serum protein levels

Table 2. Equations for ideal body weight (IBW) or mass.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>[10]</td>
<td>IBW (kg) for men = 50 + (2.3 × height in inches over 60&quot;)</td>
</tr>
<tr>
<td>[11]</td>
<td>IBW (kg) for women = 45 + (2.3 × height in inches over 60&quot;)</td>
</tr>
<tr>
<td>[12]</td>
<td>Ideal body mass (kg) for children = 2.596 e^{0.0023 × height in cm}</td>
</tr>
</tbody>
</table>
Histopathologic changes in the liver (fibrosis, cirrhosis, fatty infiltration) and alterations in cytochrome activity may result from obesity and could affect hepatic drug metabolism [8, 45–49]. However, there have been no studies evaluating the consequences of obesity-associated hepatic changes specifically for antimicrobials. Phase I hepatic metabolic reactions (oxidation, reduction, hydrolysis) are substrate-dependent and are usually increased or unchanged in obesity [8]. Metronidazole, clindamycin, erythromycin, and clarithromycin are metabolized by phase I reactions [50, 51]. In contrast, metabolism of drugs by some phase II reactions (conjugation by sulfation or glucuronidation) is consistently increased in obesity [8, 52]. Zidovudine is metabolized by glucuronidation [53].

Compared with lean controls, obese patients have a higher creatinine clearance (CrCl) [24, 54]. The exact cause of the increased clearance in obese humans is unknown, although possible reasons include an increase in the number or size of nephrons [55] and an increase in blood flow (due to increased blood volume and cardiac output) to the kidney [56].

Equations used in clinical practice to estimate CrCl do not accurately predict the higher CrCl observed in obese humans [24]. In a group of 43 morbidly obese men and women, CrCl estimates that included weight as a variable were inaccurate when compared with estimates from methods using a 24-hour urine collection and serum creatinine determinations. When ABW was used, the CrCl was overestimated, and when IBW was used, the CrCl was underestimated [54]. Thus, Salazar and Corcoran proposed alternative formulas (based on animal models) for CrCl in obese subjects, to more accurately predict the elimination of drugs primarily excreted by glomerular filtration [24]. These equations require clinical confirmation.

Pharmacokinetics may be different in the extremely or morbidly obese (an ABW of \( \geq 200\% \) of IBW) than in the mildly or moderately obese [8], but no comparative studies have been performed with regard to antibiotics.

In sum, although there are many potential pharmacokinetic consequences of obesity, the actual consequences for the pharmacokinetics and clinical efficacy of antimicrobials in humans are largely unknown.

**Individual Antibiotics (Table 3)**

- **β-Lactam drugs.** In general, β-lactam drugs are protein-bound and hydrophilic and do not diffuse well into adipose. The pharmacokinetics of β-lactam drugs in obesity have not been studied systematically; most of the data reviewed here are derived from small studies or single case reports. Although an empirical DWCF of 0.30 can be suggested on the basis of the water composition of adipose, there are no clinical study data to confirm this approach. While β-lactam drugs are not associated with concentration-dependent killing, a serum or tissue concentration below an MIC might lead to antibiotic failure.

### Table 3. Reported adjustments of antimicrobial dosing in obesity.

<table>
<thead>
<tr>
<th>Type of antimicrobial</th>
<th>Weight for calculating dose</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Lactam drug</td>
<td>Empirical: IBW + 0.3(ABW-IBW)</td>
<td>...*</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>Gentamicin: IBW + 0.43(ABW-IBW)</td>
<td>[21]</td>
</tr>
<tr>
<td></td>
<td>Tobramycin: IBW + 0.58(ABW-IBW)</td>
<td>[57]</td>
</tr>
<tr>
<td></td>
<td>For children: IBW + 0.40(ABW-IBW)</td>
<td>[58]</td>
</tr>
<tr>
<td></td>
<td>Amikacin: IBW + 0.38(ABW-IBW)</td>
<td>[59]</td>
</tr>
<tr>
<td></td>
<td>Vancomycin: IBW</td>
<td>[60]</td>
</tr>
<tr>
<td></td>
<td>Sulfonamide: IBW (^1)</td>
<td>[61]</td>
</tr>
<tr>
<td>Quinolone</td>
<td>Ciprofloxacin: IBW + 0.45(ABW-IBW)</td>
<td>[62, 63]</td>
</tr>
<tr>
<td></td>
<td>Macrolide: IBW</td>
<td>[64]</td>
</tr>
<tr>
<td></td>
<td>Mycobacterial: IBW</td>
<td>[65] (single case report)</td>
</tr>
<tr>
<td>Antifungal</td>
<td>Amphotericin: Empirical: ABW</td>
<td>...*</td>
</tr>
<tr>
<td></td>
<td>Fluconazole: 6 mg/kg qd</td>
<td>[67]</td>
</tr>
<tr>
<td></td>
<td>Antiviral: Acyclovir: IBW</td>
<td>[68]</td>
</tr>
<tr>
<td></td>
<td>Zidovudine: ABW</td>
<td>[69] (2 case reports of pregnant women)</td>
</tr>
</tbody>
</table>

* No clinical studies confirm this approach.

\(^1\) May vary for different sulfonamides.

Miskowiak and colleagues looked at the absorption of oral penicillin before and after gastroplasty for morbid obesity in patients initially weighing an average of 117 kg [70]. They found that absorption was not altered by obesity or by gastropasty; serum levels were the same before and after the surgery and were within the recommended therapeutic range for penicillin [70].

Kampmann and colleagues studied the pharmacokinetics of iv and oral ampicillin in patients who weighed an average of 131 kg before gastric bypass [71]. They found that the volume of distribution was 0.60 L/kg before surgery, compared with 0.41 L/kg in the same patients 1 year later, when the average weight was 87 kg. This suggests that ampicillin is distributed in adipose tissue to some extent. They did not report the serum concentrations.

Yuk et al. measured nafcillin serum levels in a patient with endocarditis who weighed 162 kg and concluded that there was a significant increase in the volume of distribution [72]. They suggested that a modified dosing regimen, such as 3 g every 6 hours, was needed to achieve the same drug concentration as observed in nonobese patients receiving 2 g every 4 hours.

Pories et al. [73] studied the tissue levels of cefazolin following perioperative administration of prophylactic cefazolin in obese patients weighing an average of 129 kg. They concluded that 1 g given iv 2 hours before surgery and again at induction...
of anesthesia and 500 mg given every 6 hours for eight doses yielded adequate tissue levels [73]. However, Forse and colleagues [74] found that a 1-g infusion in patients weighing an average of 127.3 kg yielded serum levels below the MICs for many surgically relevant bacteria. This study was the only one that looked at the clinical outcome of adjusting the dose upward for obese patients. Surgical wound infection rates dropped from 16.5% to 5.6% when the prophylactic dose of cefazolin was increased from 1 g to 2 g for obese patients.

Mann and Buchwald studied the distribution and elimination of cefamandole during and after gastric bypass surgery in individuals weighing a mean of 230% of IBW [16]. They found that in their subjects the volume of distribution and clearance of cefamandole were higher, and they concluded that the surgical-prophylaxis dosage of cefamandole should be 2 g at induction of anesthesia and every 3 hours thereafter during prolonged procedures.

Chiba et al. [17] studied the pharmacokinetics of cefotiam in sumo wrestlers weighing 130%–220% of IBW. They found that the volume of distribution was twice that for people weighing 100% of IBW. When kinetic parameters were adjusted on the basis of BSA, the differences in volume of distribution and clearance were not significant. They concluded that the dose of cefotiam should be calculated on the basis of BSA for morbidly obese athletes.

Yost and Derendorf found that the volume of distribution of cefotaxime, a very hydrophilic drug, increased by 50% and its clearance increased by 25% in patients weighing 190%–210% of IBW [15]. Despite these changes, the authors did not believe that it was necessary to adjust the dose of cefotaxime. Brown and Sands concluded that ceftriaxone should not be given in a dosage of 1 g every 24 hours to morbidly obese patients, but they did not state the basis for this opinion [75].

**Aminoglycosides.** Determining the daily dose of an aminoglycoside with use of ABW may result in higher than desirable serum concentrations, while doses based on IBW may lead to subtherapeutic serum concentrations [76]. These findings are consistent with the fact that aminoglycosides are primarily distributed into extracellular fluid.

Several small studies have determined DWCFs for aminoglycosides ranging from 0.38 to 0.58 [21, 57, 59, 76–78], although Bauer et al. [76] found a wide range in DWCFs between individual patients. In these studies, obese patients weighed 125%–200% of IBW; were infected, presumed to be infected [21, 63], or uninfected [57, 59, 77–80]; and were given a single dose [78] or multiple doses of gentamicin [21, 76], tobramycin [21, 76], or amikacin [77]. Traynor et al. studied 1,708 patients (weighing an average of 150% of IBW) and calculated a DWCF of 0.43 [21]. However, given the broad range of DWCFs for individual patients [76], final dosage adjustments should be based on serum concentrations.

Although the clearance of aminoglycosides in obese humans is significantly higher than in lean controls [76], the larger volume of distribution in obese subjects (which prolongs elimination half-life) cancels out the effect of increased clearance, resulting in an elimination half-life that is similar for both obese and lean subjects. As a consequence, alteration in dosage interval is not necessary for obese individuals.

Human and animal data indicate that nephrotoxicity associated with aminoglycoside use is more common in obese subjects, perhaps because of an increased concentration of aminoglycoside in the kidneys [26, 60]. In one report, an increase was noted in the incidence of nephrotoxicity (as measured by a doubling of serum creatinine level) in mildly obese patients (with body mass indices of 27–29 kg/m²), as compared with the incidence in control patients (whose body mass indices were 19–24 kg/m²) [60]. More nephrotoxicity was observed in obese subjects despite the fact that their total aminoglycoside doses and duration of therapy were similar to those of the control subjects. Serum concentrations were maintained within the recommended ranges. One confounding factor, however, was the greater likelihood of obese patients to have received furosemide.

**Vancomycin.** Although two studies [55, 81] concluded that vancomycin doses for obese patients should be based on ABW, only one of these studies analyzed patients receiving vancomycin for therapeutic purposes [81]. Blouin et al. [55] studied six morbidly obese subjects and concluded that ABW should be used to determine vancomycin doses. Vance-Bryan and colleagues [81] studied vancomycin pharmacokinetics in 107 patients weighing 20% or more over their IBWs and also concluded that using empirical dosage regimens such as 1 g every 12 hours would produce suboptimal peak and trough vancomycin concentrations in the serum of obese patients. They recommended basing the dose on ABW and giving 20–30 mg/kg·d [81]. Nonstandard doses should be checked by measuring troughs and perhaps peaks.

**Sulfonamides.** Kaul and Ritschel demonstrated increased numbers of free fatty acids and decreased protein binding of sulfonamides in genetically obese Zucker rats [28, 29]. In their studies, however, the volume of distribution for various sulfonamide antibiotics depended on many factors, not simply protein binding [28]. In a study of three patients before and after intestinal bypass surgery for morbid obesity, Garrett and colleagues [61] showed that the volume of distribution for iv and oral sulfisoxazole and its N⁴-acetylsulfisoxazole metabolite did not change despite weight loss of as much as 44% of total body weight. Renal clearance of sulfisoxazole was essentially constant, but that of the N⁴-acetylsulfisoxazole metabolite decreased as total weight decreased. The investigators concluded that the sulfisoxazole dose should not be determined on the basis of weight.

**Quinolones.** Ciprofloxacin is distributed less to adipose than to other tissues [62], a circumstance suggesting that calculating a dose on the basis of ABW would overestimate the dose. Allard and colleagues studied the volume of distribution for ciprofloxacin and found that it was 23% greater in obese subjects weighing an average of 160% of their IBW than in
nonobese controls [62]. They also determined that ciprofloxacin clearance was increased. They found that maximum ciprofloxacin plasma concentrations were lower in obese subjects than in nonobese ones after a 400-mg iv infusion, but the concentrations were still within the recommended therapeutic range. Allard et al. [62] concluded that the ciprofloxacin dose should be based on IBW plus a DWCF of 0.45.

Caldwell and Nilsen [63] described a patient weighing 250 kg who had an infection requiring iv ciprofloxacin. They used the formula of Allard et al. [62] and measured peak serum ciprofloxacin level 20 minutes after completion of a 60-minute infusion on day 4 of therapy; the level was 4.2 mg/L, within the recommended therapeutic range of 0.5–5.0 mg/L.

**Macrolides.** Little has been written about macrolide dosing in obesity. Prince and colleagues administered 250 mg of oral erythromycin base to seven obese adults, weighing an average of 157.7 kg, prior to bariatric surgery [64]. This dose resulted in a mean peak concentration of 1.04 \( \mu \text{g/mL}, \) a peak concentration similar to that in nonobese adults [82].

**Mycobacterial antibiotics.** In a single case report of a subject weighing 190% of his IBW, Geiselser et al. noted that dosing rifampin, streptomycin, ethambutol, and pyrazinamide on the basis of IBW yielded levels in the therapeutic range [65]. Isoniazid levels were not measured.

**Antifungals.** Amphotericin is a highly lipophilic drug and has traditionally been dosed on a weight basis, with doses ranging from 0.5 to 1.5 mg/kg, depending on the severity of the infection. There is a single case report of an obese patient with nonmeningeal cryptococcal infection successfully treated with amphotericin B plus fluconazole, followed by oral fluconazole [66]. The dose of amphotericin was based on ABW; levels were not determined. The dose of fluconazole was based on IBW, and serum levels were maintained within the desired therapeutic range, without hematologic toxicity.

Koldin and colleagues [30], using a rabbit model made hypercholesterolemic by diet, found that there was no difference in the level of amphotericin B toxicity in comparison with that in normal rabbits. When amphotericin B was given in a mixture with human low-density lipoproteins, it was more toxic than when given without the lipoproteins, but this level of toxicity was not compared with that in rabbits given human lipoproteins alone.

Vadiei et al. [27] found that volume of distribution and clearance of amphotericin B were markedly decreased and renal toxicity increased in obese Zucker rats with hyperlipoproteinemia as compared with those in lean litter mates; they attributed this to lipoprotein binding of amphotericin B in the vascular space. Chavanan et al. found that an increase in serum triglycerides—but not cholesterol in very-low-density and low-density lipoproteins—resulted in decreased renal toxicity in a mouse model [44]. The net clinical consequence of these observations is unclear.

There is less experience with the pharmacokinetics of azoles. In a recent article comparing amphotericin and fluconazole for the treatment of candidemia, Rex et al. specified that patients being treated with fluconazole and weighing >90 kg received 6 mg/kg [67]. No rationale was given for that dose.

**Antivirals.** A study in which a single dose of acyclovir was administered to seven uninfected subjects weighing an average of 203% of IBW demonstrated that pharmacokinetic parameters were not significantly different from those in a normal-weight control group; the authors concluded that doses should be based on IBW [68]. Acosta and colleagues [69] found that “standard doses” of zidovudine (200 mg and 100 mg, respectively) yielded lower-than-expected plasma concentrations in two women weighing 142.5 kg and 128 kg; the conclusion with regard to dosing in obesity is complicated by the fact that the women were pregnant.

**Children**

Antibiotic dosage is routinely calculated on the basis of weight for children, although some authors believe that BSA is more appropriate [20]. Should IBW (table 2) [12] or ABW be used for obese children? For children, the difference between IBW and ABW is usually relatively small [83]. Dudley concluded that IBW is probably appropriate for most situations [83].

Koshida et al. studied the volume of distribution for tobramycin and cefazolin in a group of children with an average ABW of 161% of IBW, and they concluded that the loading dose of cefazolin should be calculated on the basis of ABW, while the initial tobramycin dose should be calculated on the basis of the IBW plus a DWCF of 0.40(ABW–IBW) [58].

**Surgical Prophylaxis**

Numerous studies have identified obesity as a factor in post-operative wound infections; this is usually attributed to mechanical complications, but it is possible that antibiotics do not achieve effective levels in obese patients [16, 74]. Pories et al. [73] concluded that 1 g of prophylactic cefazolin given 2 hours preoperatively and again at induction of anesthesia to morbidly obese patients before gastric bypass surgery yielded adequate antibiotic concentrations in tissue, but Forse et al. [74] suggested a dose of 2 g iv (instead of 1 g iv or im) at induction of anesthesia [73].

Mann and Buchwald studied cefamandole levels in serum, adipose tissue, and wound drainage during and after surgery in morbidly obese patients and concluded that the surgical-prophylaxis dose of cefamandole should be 2 g at induction of anesthesia and every 3 hours thereafter during prolonged procedures [16].

**Conclusions**

With the exception of the aminoglycosides, the net effect of the pharmacokinetic consequences of obesity has not been
rigorously studied with regard to antimicrobials. Approximately 30% of adipose is water, and an empirical approach uses the Devine formula [10] to calculate IBW and then adds a DWCF of 0.3 times the difference between ABW and IBW (IBW + 0.3 × [ABW−IBW]) to arrive at a weight on which to base dosage for hydrophilic antibiotics such as β-lactam drugs. No clinical studies have confirmed this approach.

Clinical studies suggest a DWCF of ~0.40 for aminoglycosides and ~0.45 for quinolones. Given the broad range of levels for individual patients, final dosage adjustments for antimicrobials with a narrow toxic-therapeutic window should be based on serum concentrations.

References