

## “Weighing In” on Antibiotic Dosing in Obese Patients

by Dana Siu, Pharm.D.

Obesity is a growing problem that increases the risk of many diseases and contributes to other health-related problems. For healthcare providers involved in choosing appropriate dosage regimens for therapy, the management of obese patients can be a challenge. Obesity results in physiologic changes that affect the pharmacokinetic parameters of many drugs. Particularly, with antibiotics, an allowance for these alterations may be necessary to obtain desirable serum concentrations in obese patients. The limited availability of data regarding the pharmacokinetic differences of antibiotics in obese patients, relative to patients of “normal” weight, affords an opportunity for the provider to review key pharmacokinetic principles and apply this knowledge to the treatment of this growing population.

Obesity can be defined based on the percentage above ideal body weight (% IBW) or based on the body mass index (see Table I). Although several equations have been formulated, the Devine formulas<sup>1</sup> (see Equations 1 and 2) are most frequently used to calculate IBW.<sup>2,3</sup>

Table I: Defining Obesity<sup>4,5</sup>

Classification	% IBW	Body Mass Index (BMI)
Normal	80 - 125% IBW	18.5 - 24.9 kg/m <sup>2</sup>
Obese	126 - 190% IBW	30.0 - 39.9 kg/m <sup>2</sup>
Morbidly obese	>190% IBW	≥40 kg/m <sup>2</sup>

**Equation 1:**  $IBW_{(male)} = 50kg + 2.3kg \times (\text{inches over } 5ft \text{ tall})$

**Equation 2:**  $IBW_{(female)} = 45.5kg + 2.3kg \times (\text{inches over } 5ft \text{ tall})$

Since obesity can impact the distribution and clearance of drugs, changes to the volume of distribution (Vd) and total body clearance (CL) are the key pharmacokinetic parameters that must be considered in calculating the dose of antibiotic necessary to achieve desired serum concentrations. The Vd is physiologically determined by the volume of blood, the volume of body tissues and organs, and the binding of the drug in the tissues relative to the blood.<sup>6</sup> The Vd in obese patients, therefore, depends on the drug’s affinity for and quantity of adipose tissue; a greater affinity for adipose tissue affords a greater volume for drug accumulation. In addition to physiologic determinants, the Vd of antibiotics can be influenced by the drug’s solubility in body water relative to adipose tissue. Most antibiotics are hydrophilic and will distribute into body water better than into adipose tissue (e.g., acyclovir). For these antibiotics, Vd correlates better with lean body mass, or IBW.<sup>7</sup> However, since lean body mass tends to increase along with adipose tissue in obesity, the Vd for some hydrophilic drugs (e.g., aminoglycosides) correlates better with adjusted body weight (ABW).<sup>4</sup> On the other hand, lipophilic compounds (e.g., amphotericin B), may have an expanded Vd in obese patients, and thus correlate better with total body weight (TBW).<sup>7</sup> Finally, it should be noted that TBW is also recommended as the basis for dosing certain obese patient populations with hydrophilic antibiotics when (a) the safety of this approach has been demonstrated (e.g., daptomycin), or when (b) clinically significant differences in Vd and CL have not been detected in comparative studies (e.g., dalfopristin-quinupristin).

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Due to the physiological and pharmacokinetic alterations associated with obesity, using conventional doses of antibiotics may not be adequate to achieve minimal effective concentrations.<sup>6</sup> In addition, weight-based formulas that fail to adequately correct for drug distribution into excess adipose tissue may lead to an underestimation of drug clearance in obese patients.<sup>17</sup>

Calculating the Vd (see Equation 3)<sup>8</sup> can help to determine an appropriate loading dose for obese patients.<sup>4</sup> For this calculation, the Vd determined for a drug in a non-obese population is simply multiplied by a factor that takes into account the excess body weight and corrects for additional distribution of the drug into adipose tissue. A generic correction factor of 0.4 for hydrophilic drugs is an average of factors (0.37-0.58) validated in pharmacokinetic studies of aminoglycosides,<sup>4,9-13</sup> but different correction factors are recommended for beta-lactams (0.3)<sup>2</sup> and ciprofloxacin (0.45).<sup>14</sup> Although the generic correction factor of 0.4 is inferred from theoretical data on aminoglycosides, it provides the best current alternative for estimating the parameter for other hydrophilic antibiotics when clinical studies in obese patients are lacking.

$$\text{Equation 3: } Vd_{(obese)} = Vd_{(non-obese)} \times \text{Adjusted Body Weight} \\ \text{Adjusted Body Weight} = IBW + [(*C) \times (TBW - IBW)]$$

\*C = correction factor (see explanation in text above and Table III below)

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Table III: Literature-Based Antibacterial Dosing Recommendations for Obese Patients

Antibacterial Agent & Reference (*drug manufacturer)	Primary Considerations	Adult, non-obese, normal renal function		Recommendation(s) (for explanation see text and references cited)
		Vd (L/kg)	t <sub>1/2</sub> (h)	
<b>Aminoglycosides</b>				
Amikacin <sup>19</sup>	- Aminoglycosides are primarily distributed into extracellular fluids (ECF). - Higher CL, but greater Vd cancels out effect; alteration in dosage interval not necessary.	0.26	2	- Initial doses should be based on Vd using ABW with correction factor of 0.4 (ABW=IBW+0.4[TBW-IBW]). - Final dosage adjustments should be based on serum concentrations.
Gentamicin <sup>11,13</sup>		0.25	1.5-4	
Tobramycin <sup>11,13</sup>		0.26	1.6-3	
<b>β-Lactams / Penicillins</b>				
Ampicillin <sup>20</sup>	- Distributed in adipose tissue to some extent, but serum concentration not reported.	0.27-0.29	1-1.9	- No dose adjustment recommended.
Ampicillin-Sulbactam*	- No data available.	A: 0.27-0.29 S: 0.34	A: 1-1.9 S: 1-1.3	- No information on obesity dosing available. Base dose on Vd using ABW with correction factor for H <sub>2</sub> O composition of adipose tissue (ABW=IBW + 0.3 [TBW-IBW]). <sup>2</sup>
Nafcillin <sup>21</sup>	- Significant increase in Vd (almost double that of non-obese parameter). - CL unaffected.	0.57-1.55	0.5-1	- Increase non-obese dose of 2G IV q 4h to 3G IV q 6h in obese individuals.
Penicillin G <sup>22</sup>	- Drug absorption and serum levels not altered by obesity.	0.47	0.3-0.8	- No dose adjustment recommended.
Piperacillin-Tazobactam*	- Not evaluated in obese patients; multi-center trials studied patients with mean TBW of 73.3 kg. - CL and Vd not affected by changes in TBW.	0.14-0.23	0.9	- Base dose on diagnosis and CLcr.
Ticarcillin-Clavulanate*	- No data available.	T: 0.15 C: 0.29	T: 1 C: 1-1.5	- Base dose on CLcr.
<b>β-Lactams / Cephalosporins</b>				
Cefazolin <sup>23,24</sup>	- In surgical prophylaxis, lower mean serum and adipose tissue concentrations in obese patients. - Higher prophylactic doses needed to achieve serum and tissue concentrations similar to those in non-obese patients.	0.13-0.22	1.5-2.5	- Use 2G for surgical prophylaxis. - Pories et al. suggest 1G IV, 2h before surgery and at induction of anesthesia, followed by 500mg IV q 6h x 8 doses.
Cefepime*	- Hydrophilic drug. - No data available.	0.2-0.29	2	- No information on obesity dosing available. Base dose on Vd using ABW with correction factor for H <sub>2</sub> O composition of adipose tissue (ABW=IBW + 0.3 [TBW-IBW]). <sup>2</sup>
Cefotaxime <sup>25</sup>	- Hydrophilic drug, Vd and CL increased 50% and 25%, respectively in patients ranging from 190% to 210% of IBW.	0.46-0.53	0.8-1.4	- Base dose on Vd using ABW with correction factor for H <sub>2</sub> O composition of adipose tissue (ABW=IBW + 0.3 [TBW-IBW]). <sup>2</sup>
Cefotetan <sup>*26</sup>	- Clinical efficacy for prophylaxis in cesarean section patients weighing 106-305 pounds was 93%.	0.11-0.2	3-4.6	- No dose adjustment recommended.
Ceftazidime*	- No data available.	0.28-9.4	1.6-2	- Base dose on CLcr.
Ceftriaxone*	- No data available.	0.08-0.19	5.8-8.7	- No information on obesity dosing available. Base dose on Vd using ABW with correction factor for H <sub>2</sub> O composition of adipose tissue (ABW=IBW + 0.3 [TBW-IBW]). <sup>2</sup>
Cefuroxime*	- No data available.	0.17-0.31	1.1-1.9	- Base dose on CLcr.

Literature on obesity dosing is available for only 18 of the antibiotics on the UW Medicine Drug Formulary.

There is debate in the literature regarding whether the ↑ in CLcr in obese patients is due to an ↑ in the number of nephrons. The Salazar-Corcoran equations (see Equations 4-5) are thought to provide the best estimate of CLcr in obese patients.<sup>18</sup>

In addition to Vd, alterations in total body clearance (CL) should also be considered in determining a maintenance dose and dosing interval necessary to achieve desired steady-state concentrations in obese patients. The Cockcroft and Gault equation<sup>15</sup> (see Table II on next page), is most commonly used in clinical practice to estimate drug clearance, but the accuracy of this method is limited to normal-weight patients. Although obesity generally is associated with an increase in creatinine clearance (CLcr), the original Cockcroft and Gault equation tends to overestimate the parameter,<sup>16</sup> prompting several modifications to the original (see Table II).<sup>15,17</sup> Even with these modifications, however, the Cockcroft and Gault equations are not thought to provide an accurate enough estimate for CLcr in obese patients.<sup>17</sup> Rather, the Salazar-Corcoran equations<sup>18</sup> (see Equations 4 and 5) have been shown to result in more accurate predictions of CLcr for obese patients. While other non-renal changes in CL occur in obesity, data regarding the implications for drug dosing are limited.<sup>4</sup>

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Table III: Literature-Based Antibacterial Dosing Recommendations for Obese Patients (continued)

Antibacterial Agent & Reference (*drug manufacturer)	Primary Considerations	Adult, non-obese, normal renal function		Recommendation(s) (for explanation see text and references cited)
		Vd (L/kg)	t <sub>1/2</sub> (h)	
<b>β-Lactams / Carbapenems</b>				
Ertapenem <sup>27,28</sup>	- AUC was significantly decreased in obese and morbidly obese patients; however, no dosing adjustment was recommended.	0.11	4	- Use standard dose of 1G/day.
Meropenem <sup>29</sup>	- Increased CL, Vd, and T <sub>1/2</sub> . - Percentage of time the dose was above the MIC during an 8h dosing interval was not significantly different.	0.33-0.43	1	- No dose adjustment recommended.
Imipenem-Cilastatin*	- No data available.	0.14-0.33	1	- Base dose on CLcr.
<b>Fluoroquinolones</b>				
Ciprofloxacin <sup>14,30</sup>	- Less distributed to adipose tissue, Vd increased by 23%, increased CL, and lower C <sub>max</sub> ; however, concentrations still within recommended therapeutic range.	1.2-2.7	3-6 (Extended-release: 6-7)	- Dose should be based on Vd using ABW with correction factor of 0.45 (ABW = IBW + 0.45[TBW-IBW]).
Levofloxacin*	- Drug is lipophilic, and widely distributed into body tissues.	1.25	6-8	- No information on obesity dosing available. - Base dose on CLcr.
Moxifloxacin*	- No data available.	1.7-2.7	14.8	- Use standard dose of 400mg IV/PO daily.
<b>Macrolides</b>				
Azithromycin*	- No data available.	23-31	11-68	- No information on obesity dosing available.
Erythromycin <sup>31</sup>	- Peak concentrations similar in obese and non-obese adults.	0.57	1-1.5	- Base dose on IBW.
<b>Miscellaneous</b>				
Acyclovir <sup>32</sup>	- Pharmacokinetics not significantly different in obese and non-obese groups. - Half-life depends on renal function.	0.8	2.2-20	- Base dose on IBW.
Amphotericin B <sup>33</sup>	- Drug is lipophilic. - Zucker rats with hyperlipoproteinemia: ↓Vd, ↓CL, ↑ renal toxicity.	4	360	- Use traditional dosing of 0.5-1.5mg/kg based on TBW.
Aztreonam* <sup>34</sup>	- Drug is lipophilic.	0.1-0.2	1.5-3	- Use dose at upper end of range for treating serious infections in morbidly obese adults.
Clindamycin*	- No data available.	0.6-1.2	1.5-5	- No information on obesity dosing available.
Dalfopristin-Quinupristin*	- Terminal phase Vd was similar between obese and non-obese subjects. - Distributes more into lean body mass than into fat tissue.	D: 0.24 Q: 0.45 (dose-dependent)	1.3-1.5	- Use traditional q 8h or q 12h dosing of 7.5mg/kg based on TBW.
Daptomycin <sup>35</sup>	- Increased Vd and CL in obese vs. non-obese subjects. - Large molecular mass with high polarity, low lipid solubility, and high plasma protein binding. - Exposure increased by 25-30% when dose based on TBW, but still safe and tolerated in subjects ranging from 56-147kg.	0.12	7-11	- Base dose on TBW.
Doxycycline*	- Drug is lipophilic.	0.75	15-24	- No information on obesity dosing available.
Fluconazole <sup>36</sup>	- Hydrophilic agent, eliminated by kidney.	0.56-0.82	30	- A higher dose is recommended (e.g., 1200mg/day for candida fungaemia in necrotizing fasciitis).
Linezolid <sup>37</sup>	- Prolonged inhibitory activity observed despite ↓serum concentrations.	0.57-0.86	5	- Use standard dose of 600mg IV/PO q 12h.
Metronidazole*	- No data available.	0.25-0.85	6-14	- No information on obesity dosing available.
Sulfamethoxazole-Trimethoprim*	- No data available.	S: 0.360 T: 2	S: 8-11 T: 6-17	- No information on obesity dosing available.
Tigecycline*	- Study subjects weighed 39-200kg.	7-9	42	- Use traditional dose of 100mg IV followed by 50mg IV q 12h.
Vancomycin <sup>38-40</sup>	- Increased Vd and CL in obese patients correlates better with TBW.	0.7	7-9	- Base dose on TBW, giving 20-30mg/kg/day. - If necessary, shorten administration interval to maintain serum trough >5mg/L.

There is evidence that cytochrome P450 activity may be altered in obesity and blood flow to the liver is generally increased.

The only antibiotic class to have outcomes correlated with serum concentrations in obese patients is the aminoglycosides.<sup>13</sup> Without clinical studies in obese patients, recommendations for other drugs are largely theoretical.

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References available upon request.

Table II: Cockcroft and Gault Estimations of Creatinine Clearance<sup>15</sup>

Method	Equation
Original	$(140 - \text{Age}) \times \text{TBW} / (\text{SCr} \times 72)$
Modified	$(140 - \text{Age}) \times \text{IBW} / (\text{SCr} \times 72)$
Modified with correction factor	$(140 - \text{Age}) \times [\text{IBW} + 0.4 \times (\text{TBW} - \text{IBW})] / (\text{SCr} \times 72)$

**Equation 4:**  $CLCr_{(males)} = (137 - \text{age}) \times [(0.285 \times \text{TBW}) + (12.1 \times \text{Ht}^2)] / (51 \times \text{Scr})$

**Equation 5:**  $CLCr_{(females)} = (146 - \text{age}) \times [(0.287 \times \text{TBW}) + (9.74 \times \text{Ht}^2)] / (60 \times \text{Scr})$

Estimating the Vd and CL in an obese patient allows for easy calculation of a drug's half-life ( $t_{1/2}$ ; see Equation 6),<sup>8</sup> the time to reach steady state conditions (3-5 half-lives) and the time for all of the administered drug to be eliminated (5 half-lives). Calculating an appropriate antibiotic regimen to achieve optimal drug concentrations, however, requires the use of a more complicated set of equations.<sup>8</sup> Literature-based recommendations for commonly used intravenous antibiotics have been compiled in Table III (see pages 10-11). Contact a clinical pharmacist for advice regarding individualizing the dosing regimen of other anti-infectives.

**Equation 6:**  $t_{1/2} = (0.693 \times \text{Vd}) / \text{CL}$

In summary, data regarding the dosing of antibiotics in obese patients is limited to mainly a handful of small pharmacokinetic studies and a few case reports. With the exception of aminoglycosides and vancomycin, the pharmacokinetics of most other antibiotic agents have not been extensively investigated in the obese population. Just the same, it may be necessary to make allowances for the physiological changes associated with obesity in order to obtain desired serum concentrations and achieve positive clinical and microbiological outcomes. While a clinical pharmacist can assist in the selection of a rational dosing regimen based on sound pharmacokinetic principles, the fine-tuning of dosage regimens must continue to be based on clinical and laboratory evidence of response.

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