Dosing of antibiotics in obesity

Brett Janson\textsuperscript{a} and Karin Thursky\textsuperscript{b,c}

Purpose of review
Obesity is becoming a major burden on healthcare systems worldwide. The management of infections is problematic due to both an increased risk of morbidity and mortality, as well as a lack of information about dosing of antibiotics in the obese population. Recommendations in this patient group are severely lacking, so clinicians need to consider pharmacokinetic/pharmacodynamic parameters and the relative risks of overdosing and underdosing.

Recent findings
Since 2011, articles on a number of antibiotics have been published, including cefazolin/cephazolin, cefepime, cefotixin, clindamycin, cotrimoxazole, daptomycin, ertapenem, levofloxacin, linezolid, meropenem, moxifloxacin, piperacillin/tazobactam and vancomycin.

Summary
Obesity causes a number of changes, including an increase in volume of distribution and changes in hepatic metabolism and renal excretion. Several antibiotics have sufficient data to be able to make recommendations, whereas other antibiotics may need to make use of doses at the upper end of the recommended range, or utilize other dose modifications based on pharmacokinetic/pharmacodynamic parameters, in an attempt to reach adequate levels and achieve similar efficacy.

Keywords
antibiotics, dosing, obesity, pharmacokinetic/pharmacodynamic

INTRODUCTION
The increasing worldwide incidence of obesity will become a major burden on healthcare systems both from a patient safety and financial perspective [1,2]. Obesity is a risk factor for many comorbid conditions and is associated with increased morbidity and mortality in patients with bacteremia [3], nosocomial infections [4], surgical site infections (SSIs) [4–7], periodontal infections [4] and skin infections [4]. It has also been linked to impaired immune function [8,9], with reports of increased mortality risk during the H1N1 pandemic [10,11] and decreased immune response to vaccines [12–14] in humans.

The management of infections poses a particular problem in the obese population as there remains a paucity of published data on the dosing and pharmacodynamics of drugs, especially antibiotics, in obesity (as described by Erstad [15] as ‘as much an art as a science given the lack of published investigation’). Even when recommendations exist for higher dosing of antibiotics, these are often not followed [16]. There have been several published reviews on drug dosing [17–22] and pharmacokinetic changes in obesity [15,23,24\textsuperscript{*},27\textsuperscript{*},28].

The goal of all antibiotic therapy is to balance serum antibiotic concentrations, which vary over time, to optimize bacterial eradication while minimizing toxicity and side effects [29]. An understanding of pharmacokinetic and pharmacodynamic principles is essential in order to predict likely changes in the obese population.

MEASURES USED IN DESCRIPTIONS OF OBESITY AND DRUG CALCULATIONS
Obesity measurement can be performed using direct measurement (e.g. DEXA scan, skin fold measurements, underwater weighing) and indirect measurements (e.g. BMI, ideal body weight (IBW) and so on), which are calculated using readily available patient characteristics (see [30] for an excellent review). The

\textsuperscript{*}Pharmacy Department, \textsuperscript{\textasteriskcentered}Department of Infectious Diseases, Peter MacCallum Cancer Centre, East Melbourne, Victoria and \textsuperscript{\textasteriskcentered}Victorian Infectious Diseases Service, Royal Melbourne Hospital, Parkville, Melbourne, Australia

Correspondence to Brett Janson, Pharmacy Department, Peter MacCallum Cancer Centre, Locked Bag 1, A’Beckett Street, East Melbourne, VIC 8006, Australia. E-mail: brett.janson@petermac.org

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common formulas used to calculate values are presented in Table 1.

Classification of obesity is most commonly based on the BMI [31]. It is calculated by dividing the weight in kilograms of a person with the square of the height in metres to give a value in kg/m² (see Table 2 for terminologies used). BMI has a number of limitations as it does not consider sex, race [40] or extremes of musculature (a fact often commented on by bodybuilders looking for insurance [41]).

Total body weight (TBW) refers to the actual weight of the patient (sometimes called actual body weight). To differentiate between actual and adjusted body weight (ABW; see below), TBW will be used in this article.

IBW is based on actuarial data from the Metropolitan Life Insurance Company in 1943 (revised 1959) and essentially describes what weight a person should be in order to have the lowest mortality [42]; it was not developed as a pharmacokinetic measure. IBW is sometimes further subdivided according to body-frame [light framed (−10%), medium and heavy framed (+10%)] [42], which is related to elbow breadth or wrist circumference. Initially in tabular form, this parameter is now calculated, most commonly using the Devine formula [32]. %IBW is also used as a measure of obesity. Excess body weight (EBW) is the difference between TBW and IBW.

Lean body weight (LBW) and fat-free mass (FFM) are measurements not dissimilar from IBW [42]: LBW describes body weight devoid of adipose tissue, whereas FFM refers to certain body tissues (muscle, bone, organs and extracellular fluid), usually measured by bioelectric impedance analysis or estimated by equation. LBW is the more commonly used, with the formulas developed by Janmahasatian et al. [34] becoming the most used.

An ABW comprises IBW plus a proportion of the difference between TBW and IBW. This proportion is based on the observation that part of the excess weight will be ‘active’, whether metabolically or as a site of drug distribution. This proportion, sometimes referred to as a Dosing Weight Correction Factor (DWCF), is used where drugs are known to distribute to the excess adipose tissue, and varies between different drugs (e.g. aminoglycosides have a suggested DWCF of 0.38–0.58). A similar measure – predicted normal weight (PNW) [37],

<table>
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<tr>
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<tr>
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</tr>
<tr>
<td>IBW [Devine]</td>
<td>( \text{IBW} = 45.4 + [0.89 \times ([\text{Ht(cm)}] - 152.4)] ) (±4.5 if male)</td>
<td>[32]</td>
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<td></td>
</tr>
<tr>
<td>LBW [Janmahasatian]</td>
<td>Males: ( \text{LBW} = \frac{[9270 \times \text{TBW}]}{[6680 + (216 \times \text{BMI})]} )</td>
<td>[33,34]</td>
</tr>
<tr>
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<td>Female: ( \text{LBW} = \frac{[9270 \times \text{TBW}]}{[8780 + (244 \times \text{BMI})]} )</td>
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<td>FFM</td>
<td>Males: ( \text{FFM} = \frac{\text{TBW}}{[0.285]} + [12.1 \times \text{Ht(m)}^2] )</td>
<td>[35]</td>
</tr>
<tr>
<td></td>
<td>Females: ( \text{FFM} = \frac{\text{TBW}}{[0.287]} + [9.74 \times \text{Ht(m)}^2] )</td>
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</tr>
<tr>
<td>BSA Dubois and Dubois</td>
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<td>[36,38,39]</td>
</tr>
<tr>
<td>BSA Mosteller</td>
<td>( \text{BSA} = \sqrt{[\text{Ht(cm)} \times \text{Wt}]/3600} )</td>
<td>[39]</td>
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ABW, adjusted body weight; DWCF, dosing weight correction factor; EBW, excess body weight; FFM, fat-free mass; Ht(cm), height [in centimetres]; Ht(m), height (in metres); IBW, ideal body weight; LBW, lean body weight; PNW, predicted normal weight; TBW, total body weight; Wt, weight.

KEY POINTS

- There is a lack of data for most antibiotics regarding dosing in obese and morbidly obese patients.
- Knowledge of pharmacokinetics and pharmacodynamics of different antibiotics will assist with dosing.
- Some antibiotics may require higher doses at the same frequency, whereas others may require more frequent dosing.
- Extrapolation of results from one patient population to another needs to be performed with due consideration.
- Regulatory agencies may need to impose mandatory requirements regarding dosing of antibiotics in the obese population prior to registration.

Dosing of antibiotics in obesity Janson and Thursky

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which uses LBW instead of IBW as the basis of calculations – is not in common use.

Body surface area [38] is most commonly used for calculating anticancer chemotherapy doses; it is an occasional descriptor used in antibiotic dosing. The original formula by Dubois and Dubois is still in common use; however, others (in particular Mosteller [39]) are often used, due to their accuracy and ease of use.

**PHARMACOKINETIC CHANGES IN OBESITY**

Numerous physiological changes occur in the obese patient that may affect serum levels, including the following.

**Absorption**

Little data exists on changes in absorption in obesity. Obese patients have been shown to have delayed gastric emptying [43,44], possibly as a result of higher fat diet or gastric distension, which may result in a lower \( C_{\text{max}} \) or reduced absorption. With an oral antimicrobial where the absorption is increased by taking with a fatty meal, it could be inferred that absorption will be higher due to a presumptive higher intake of fatty foods. Intramuscular injections may inadvertently be administered deep subcutaneously but it is unknown if this will have an impact on absorption or efficacy.

**Distribution**

Distribution is measured using volume of distribution, a theoretical value calculated by dividing the dose given by the plasma concentration. A high volume of distribution implies that the drug is distributed extensively to tissue, whereas a low volume of distribution implies the drug is concentrated in the plasma [45]. The degree of drug distribution into tissue varies considerably depending on a number of physicochemical characteristics, which may include the hydrophilicity/lipophilicity, plasma protein binding and molecular weight of the antimicrobial. As EBW is approximately 30% water [45], this will necessarily lead to a higher volume of distribution in obesity.

The volume of distribution is also partially dependent on the lipophilicity of the drug. In general, lipophilic medications are associated with higher volumes of distribution, which usually require TBW dosing [45]. In contrast, hydrophilic medications are associated with lower volumes of distribution, which usually require IBW or ABW dosing; however, this has not been shown in all drugs [46]. Tissue distribution is particularly important in surgical prophylaxis where high tissue concentrations for the duration of surgery are required. Most antibiotic classes demonstrate an increased volume of distribution in obesity, although the changes are not easily quantifiable in relation to any particular parameters, especially for lipophilic drugs. The effect of obesity on plasma protein binding of drugs is also largely unknown; however, any changes in plasma proteins could be expected to affect free concentrations (\( f \)) of drugs. Other factors include an increased blood volume and cardiac output [26*], and poorer peripheral perfusion [25*].

**Excretion**

The effect of obesity on renal function is bidirectional – obesity results in a baseline general increase in renal clearance (although not proportional to the increase in weight), but the higher incidence of

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<th>Classification (various terminologies)</th>
<th>BMI (kg/m²)</th>
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<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5 to &lt;25</td>
</tr>
<tr>
<td>Overweight</td>
<td>≥25</td>
</tr>
<tr>
<td>Pre-obese</td>
<td>25 to &lt;30</td>
</tr>
<tr>
<td>Obese</td>
<td>≥30</td>
</tr>
<tr>
<td>Obese (obesity class I)</td>
<td>30 to &lt;35</td>
</tr>
<tr>
<td>Severely obese (obesity class II)</td>
<td>35 to &lt;40</td>
</tr>
<tr>
<td>Morbidly obese (obesity class III)</td>
<td>≥40</td>
</tr>
<tr>
<td>Super obese</td>
<td>≥50</td>
</tr>
<tr>
<td>Super-super obese</td>
<td>≥60</td>
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</tbody>
</table>

Table 2. Terminologies used to describe different BMI categories
renal dysfunction (usually hypertension- or diabetes-induced) results in decreased renal function. Commonly used creatinine clearance (CrCl) calculations (Cockcroft–Gault [48]), and automatically-generated results using the Modification of Diet in Renal Disease (MDRD4) equation [49] may not accurately reflect renal function. In particular, the MDRD4 was based on patients with chronic renal disease so estimations in patients without renal disease may be inaccurate. However, it has been reported to be the more accurate of the two in obese patients [50,51]. A recent study [52] compared measured versus calculated renal clearance in 164 potential kidney donors, including 49 with a BMI 30–35 kg/m$^2$ and 32 with BMI more than 35 kg/m$^2$. The authors found that different equations (Cockcroft–Gault, MDRD4, CKD-EPI [53]) can either overestimate or underestimate glomerular filtration rate (GFR) variously depending on the BMI of the patient. Demirovic et al. [54] suggested the use of LBW or FFM in the Cockcroft–Gault equation, as these provided comparable estimates of CrCl, whereas TBW and ABW, and the Salazar–Corcoran equation [55], all overestimated CrCl [54]. A more accurate (and more expensive) measure of renal function in obese patients involves either a 24-h urine collection or preferably a nuclear GFR [56].

**PHARMACOLOGICAL INDICES FOR DOSSING OF ANTIBIOTICS**

The major goal of pharmacodynamics is to establish which pharmacokinetic/pharmacodynamic (PK/PD) target is required for effective antibiotic therapy [29,57,58,59]. The PK/PD indices $T>MIC$, $C_{\text{max}}/MIC$ and $AUC/MIC$ (defined below) are used to predict in-vivo antimicrobial activity. $T>MIC$ is used to predict the efficacy of time-dependent antibiotics (e.g., β-lactams, glycopeptides, macrolides, clindamycin and oxazolidinones). Drugs that belong to these classes show no or little enhancement of the effect with an increase in antibiotic concentration. The optimal concentration is mostly the two-fold to four-fold minimum inhibitory concentration (MIC) of the pathogen [59]. For antibiotics in which $T>MIC$ (percentage of time the drug concentration is above the MIC for the organism being treated) is important, it follows that increasing doses or frequency, or even using continuous infusions, will improve the pharmacodynamics (see Fig. 1 [29] and Fig. 2 [60]).

The $C_{\text{max}}/MIC$ is the peak level ($C_{\text{max}}$) divided by the MIC, and is used to predict the efficacy of concentration-dependent antibiotics (aminoglycosides and fluoroquinolones). The $C_{\text{max}}$ will be dependent on the unit dose and inversely related to the volume of distribution. The $AUC_{24h}/MIC$ is defined as the area under the concentration–time curve over 24h divided by the MIC, and is also used for concentration-dependent antibiotics. The $AUC_{24h}/MIC$ can be optimized by adapting the total daily dosage.

The important parameters for each antibiotic class (where known) are shown in Table 3. The magnitude of the PK/PD ratio is related to in-vivo efficacy (e.g., bacteriostasis, one or two log

![FIGURE 1. Main pharmacokinetic–pharmacodynamic (PK–PD) parameters. AUC, $C_{\text{max}}$, $C_{\text{min}}$, MIC, $T>MIC$ are values that are often expressed using the more relevant free concentration (f) of the drug e.g. $fT>MIC$, referring to the time the free concentration of the drug is above the MIC, $fAUC/MIC$ and $fC_{\text{max}}/MIC$ ratios etc. AUC, area under curve; $C_{\text{max}}$, maximum concentration (peak); $C_{\text{min}}$, minimum concentration (trough); $Ht(m)$, height (in metres); $Ht(cm)$, height (in centimetres); MIC, minimum inhibitory concentration; $T>MIC$, time the concentration is above the MIC. Reproduced with permission from [29].](image-url)
kill). For example, AUC$_{24h}$/MIC and C$_{max}$/MIC are important indices for the efficacy of aminoglycosides. In serious Gram-negative infections, an AUC$_{24h}$/MIC ratio more than 110 and C$_{max}$/MIC ratio more than 8–10 are required for more than 90% efficacy against Gram-negative bacilli [115,116]. AUC$_{24h}$/MIC is the PK/PD index correlating best with in-vivo antimicrobial efficacy of glycopeptides. An AUC$_{24h}$/MIC ratio of more than 400 was associated with significantly more rapid microbiological cure in lower respiratory tract infections with Staphylococcus aureus treated with vancomycin [117]. The probability of reaching an AUC$_{24h}$/MIC ratio more than 400 will decrease with increased MIC [118]. Other effects that may be important for particular antibiotics include trough levels (C$_{min}$) (e.g. for teicoplanin, a C$_{min}$ target of 13 mg/l and an AUC$_{0-24}$ target of 750 mg h/l were associated with 90% eradication of methicillin-resistant S. aureus [119]), peak levels (C$_{max}$) and post-antibiotic effects (PAE), as these may also relate to toxicity and efficacy.

It also follows that with the emergence of antibiotic resistance and higher MICs, dosing decisions become increasingly important. Recommendations for the most commonly used agents are shown in Table 3.

**Surgical prophylaxis**

Antibiotic prophylaxis before surgery is a standard of care and a critical factor in the prevention of surgical site infection (SSI). The goal of prophylaxis is to ensure that therapeutic drug concentrations are achieved at the surgical site during the period of the procedure, that is from the time of incision to closure. Timing of administration is critical and it is recommended to be 30–60 min (or 120 min for vancomycin) prior to incision. Obesity is an independent risk factor for SSI and this risk factor persists despite antibiotic prophylaxis [120–122]. Patients undergoing colorectal surgery are at 2.5–5 times higher risk of SSI if obese [123]. The mechanism of increased SSI in obesity is likely to be related to altered drug pharmacokinetics and disposition. Reduced tissue penetration of antibiotics leading to subtherapeutic tissue antibiotic concentrations had been associated with increased rate of SSI [80,81].

**PHARMACODYNAMICS OF SELECTED ANTIMICROBIALS IN OBESITY**

Only a few antibiotics (aminoglycosides, vancomycin, daptomycin and linezolid) have been substantially studied in the obese population. Many of the
### Table 3. List of relevant pharmacokinetic/pharmacodynamic properties of antibiotics and recommendations for dosing of antibiotics in obese patients

<table>
<thead>
<tr>
<th>Antibiotic class [17]</th>
<th>Antibiotic</th>
<th>Clinically important parameters</th>
<th>Weight used for dosing</th>
<th>Suggested dosage in obese patients or highest dose in product information (not a recommended dose for this population)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides (hydrophilic)</td>
<td>Gentamicin; amikacin; tobramycin</td>
<td>$C_{\text{max}}$/MIC [takes preference over $\text{AUC}_{24\ h}$/MIC due to toxicity concerns], PAE</td>
<td>IBW</td>
<td>Gentamicin, tobramycin: 5–7 mg/kg IBW with appropriate reduction for renal impairment and/or age. Consider capping at 480–640 mg. Amikacin: 20–28 mg/kg IBW with appropriate reduction for renal impairment and/or age. Consider capping at 2–2.5 g. Higher dose for severe infections.</td>
<td>[11,36,61–63]</td>
</tr>
<tr>
<td>Glycopeptides (hydrophilic)</td>
<td>Vancomycin</td>
<td>$T_{\text{&gt;MIC}}$, PAE</td>
<td>TBW for initial doses.</td>
<td>Loading dose 15–20 mg/kg $^b$ TBW, maintenance dose reduced appropriately based on renal function. Check levels prior to third dose. May need to shorten interval to maintain increased trough level (e.g. q12h to q8h dosing). Patients ≥101 kg and/or with doses ≥4 g/day have been associated with increased risk of developing nephrotoxicity; $^b$Higher dose for severe infections.</td>
<td>[64–70,71*]</td>
</tr>
<tr>
<td></td>
<td>Teicoplanin</td>
<td>$C_{\text{max}}$/MIC; $T_{\text{&gt;MIC}}$</td>
<td>Unknown</td>
<td>No data on dosing in obesity. Maximum doses in literature suggest 12 mg/kg q12h for 3 doses followed by 6–12 mg/kg q24h thereafter; higher doses (15 mg/kg) have also been suggested for deep seated infections in which higher trough levels are needed, and 30 mg/kg has been used in one trial for staphylococcal endocarditis in IV drug users. Suggest TDM [where available].</td>
<td>[72–74]</td>
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<td>β-Lactams–penicillins (hydrophilic)</td>
<td>Piperacillin/tazobactam</td>
<td>T&gt;MIC</td>
<td>TBW</td>
<td>Suggest higher doses [4.5 g q6h] or consider continuous infusions for isolates with higher MIC. Maximum dose of piperacillin (not piperacillin/tazobactam) reported as 24 g/day.</td>
<td>[75–79]</td>
</tr>
<tr>
<td></td>
<td>Other penicillins*</td>
<td>T&gt;MIC</td>
<td>TBW</td>
<td>Consider dosing at upper end of recommended doses or use more frequent dosing.</td>
<td>[15]</td>
</tr>
<tr>
<td>β-Lactams–cephalosporins (hydrophilic)</td>
<td>Cephazolin (Cefazolin)</td>
<td>T&gt;MIC</td>
<td>TBW</td>
<td>Single 2 g dose effective in obesity in surgery &lt;5 h. Repeated doses suggested every 4–5 h intraoperatively. Higher doses may be required for morbidly obese patients; for nonperioperative dosing: consider dosing at maximum recommended doses. Doses up to 12 g/day (2 g q4h) have been used for severe infections.</td>
<td>[80,81,82*,83]</td>
</tr>
<tr>
<td></td>
<td>Cefepime</td>
<td>T&gt;MIC</td>
<td></td>
<td>Dose of 2 g q8h required postoperatively in surgical patients (equivalent to usual dose used to treat severe or life-threatening conditions).</td>
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<td></td>
<td>Other cephalosporins*</td>
<td>T&gt;MIC</td>
<td>TBW</td>
<td>Consider higher stat doses for perioperative use, or dosing at upper end of recommended doses. See individual product information.</td>
<td>[15]</td>
</tr>
<tr>
<td>β-Lactams–carbapenems (hydrophilic)</td>
<td>Ertapenem</td>
<td>T&gt;MIC</td>
<td>Unknown</td>
<td>A higher dose of ertapenem should be considered in obese patients who are infected with organisms having MICs greater than 0.25–0.5 mg/ml because the standard 1g dose may not provide an adequate duration of exposure for concentrations above the MIC; however, no dose recommendation is possible with available information.</td>
<td>[85–87]</td>
</tr>
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<td>Antibiotic Class</td>
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<tr>
<td>β-Lactams–monobactam (hydrophilic)</td>
<td>Aztreonam</td>
<td>T&gt;/MIC</td>
<td>Unknown</td>
<td>Consider dosing at upper end of recommended dose range. Maximum dose in product information is 2 g q6h. [91,92]</td>
<td></td>
</tr>
<tr>
<td>Lipopeptides</td>
<td>Daptomycin</td>
<td>AUC_{24h}/MIC; C_{max}/MIC</td>
<td>TBW</td>
<td>Exposure increased by 25–30% when dose based on TBW, but still safe and tolerated in individuals ranging from 56–147 kg. [93]</td>
<td></td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Linezolid</td>
<td>T&gt;/MIC; AUC_{24h}/MIC; moderate PAE</td>
<td>Standard dosing</td>
<td>Consideration for a dose increase may be prudent in patients with isolates exhibiting an MIC of 4 mg/ml for example, 600 mg q8h; continuous infusions have also been tried. [94]</td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones (lipophilic)</td>
<td>Ciprofloxacin</td>
<td>AUC_{24h}/MIC; C_{max}/MIC; PAE</td>
<td>ABW</td>
<td>Suggested dose increase based on ABW using DWCF of 0.45; Doses of 800 mg IV q12h in severe morbid obesity (based on total dose = 400 mg + (3 × 0.45 × EBW) have been used. [95,96]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Levofloxacin</td>
<td>AUC_{24h}/MIC; C_{max}/MIC</td>
<td>Unknown</td>
<td>Maximum used dose is 750 mg daily. Limited evidence suggests no dose increase is needed. [97]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>AUC_{24h}/MIC; C_{max}/MIC</td>
<td>Unknown</td>
<td>In patients up to 166 kg, moxifloxacin pharmacokinetics were similar to controls. [98,99]</td>
<td></td>
</tr>
</tbody>
</table>

[Continued]
Table 3 (Continued)

<table>
<thead>
<tr>
<th>Antibiotic class [17]</th>
<th>Antibiotic</th>
<th>Clinically important parameters</th>
<th>Weight used for dosing</th>
<th>Suggested dosage in obese patients or highest dose in product information (not a recommended dose for this population)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrolides (lipophilic)</td>
<td>Erythromycin</td>
<td>T&gt;MIC; AUC&lt;sub&gt;24h&lt;/sub&gt;/MIC</td>
<td>Unknown</td>
<td>Maximum used doses are 1 g four times daily (maximum 4g/day) of erythromycin (independent of formulation) for severe pneumonia, diphtheria and Legionnaires. Up to 6g/day has been reported. Caution QT prolongation and interactions.</td>
<td>[100,101]</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>T&gt;MIC and AUC&lt;sub&gt;24h&lt;/sub&gt;/MIC</td>
<td>Unknown</td>
<td>Maximum dose found was clarithromycin 500 mg q8h for dual-therapy Helicobacter pylori eradication or 1000–2000 mg q12h for resistant mycobacterial infections (2000 mg dose was not as well tolerated).</td>
<td>[102,103]</td>
<td></td>
</tr>
<tr>
<td>Tetracyclines (Lipophilic)</td>
<td>Doxycycline</td>
<td>T&gt;MIC</td>
<td>Unknown</td>
<td>Maximum dose found was 300 mg IV daily or 300 mg oral daily in divided doses for ≥10 days for treatment of primary or secondary syphilis.</td>
<td>[104,105]</td>
</tr>
<tr>
<td>Glycylcyclines (Lipophilic)</td>
<td>Tigecycline</td>
<td>T&gt;MIC</td>
<td>Unknown</td>
<td>Whilst single doses up to 300 mg have been investigated in healthy volunteers, no doses above the standard 100 mg load followed by 50 mg q12h could be found.</td>
<td>[106–108]</td>
</tr>
<tr>
<td>Nitroimidazoles</td>
<td>Metronidazole</td>
<td>AUC&lt;sub&gt;24h&lt;/sub&gt;/MIC; C&lt;sub&gt;max&lt;/sub&gt;/MIC</td>
<td>Unknown</td>
<td>Single doses up to 2 g are used for treatment of trichomoniasis. Doses of 7.5 mg/kg (up to a maximum 1 g) q6h can be used for treatment of anaerobic bacterial infections.</td>
<td>[109,110]</td>
</tr>
</tbody>
</table>
published studies are several years (or even decades) old; as such, recommendations from these articles may no longer be relevant. The important parameters and conclusions are summarized in Table 3.

### Aminoglycosides

ABW using a dosing correction factor has previously been recommended for aminoglycoside dosing in the obese patient. Leader et al. [124] compared actual gentamicin pharmacokinetics to CrCl estimations using both the Cockcroft–Gault equation (using TBW, IBW and ABW using a DWCF of 0.4) as well as the Salazar–Corcoran equation in 100 obese and 100 non-obese patients, and recommended the use of ABW to calculate initial gentamicin doses in the obese population; others have made similar recommendations for gentamicin [36,62,63], amikacin [36,125] and tobramycin [36,62,126]. Ortega et al. [127] found that the best predictor of gentamicin volume of distribution was ABW in a diverse population of 198 solid tumour patients. A study by Blouin et al. [128] in 13 patients (including five morbidly obese) receiving perioperative doses of amikacin showed significantly increased total body clearance in the morbidly obese population, and recommends larger doses be given to achieve effective levels; doses used were lower than those used currently (7.5 mg/kg non-obese, 1200 mg obese). Duffull et al. [37] found that substituting PNW into the Cockcroft–Gault equation was more accurate than TBW for estimating clearance of gentamicin in obese patients. Despite the information suggesting ABW, current recommendations suggest dosing on LBW [61], with appropriate monitoring with the first dose.

### Vancomycin

Early studies in the obese population demonstrated much higher clearance of vancomycin, particularly in young adult morbidly obese patients necessitating much higher doses to obtain adequate trough concentrations [64,129]. Various groups developed formulas for the estimation of volume of distribution [65] but vancomycin dosing nomograms and standard dosing practices (1 g twice daily) performed poorly in the morbidly obese weight range [130,131]. Leong et al. [67] compared equations from two previous studies [132,133] and showed that using ABW (using a DWCF of 0.4) in the Leonard and Boro [132] vancomycin clearance calculation (vancomycin clearance = 0.9 × CrCl, with ABW used in the Cockcroft–Gault equation) was a more accurate way to estimate vancomycin clearance in the obese population. Most recently, Reynolds et al. [134] compared a standard dosing...
Antimicrobial agents

regimen (15–20 mg/kg q8–12 h) versus a reduced dose regimen (10 mg/kg q12 h or 15 mg/kg q24 h) and found patients with the reduced regimen had lower incidence of excessive trough levels (aim 10–20 mg/l). Of note, two articles by Lodise et al. [69,70] have found that patients with weight of at least 101 kg or with doses of at least 4 g/day were associated with a higher risk of developing nephrotoxicity. Current guidelines at our institution base loading doses of vancomycin on the TBW of the patient and maintenance doses on the calculated CrCl of the patient (as a substitute for vancomycin clearance). This approach appears to be gaining support [135] and would be a reasonable approach in the obese population; however, deciding whether to base CrCl calculations on ABW, IBW or another measure is still to be determined. A recent review [71*] discusses the issues with dosing of vancomycin in the obese and morbidly obese.

Penicillins

Despite their widespread use, there is very little information regarding dosing of penicillin antibiotics in obese patients. Some resources [15] suggest that penicillins (as well as cephalosporins, meropenem and aztreonam) should be dosed at the upper end of the suggested dosage ranges due to their relatively low rates of serious side effects. A case report by Newman et al. [76] followed a 167 kg morbidly obese male dosed with piperacillin–tazobactam at 3.375 g q4 h, and showed significantly lower Cmax, although levels remained above MIC (8 mg/l) at all times (T>MIC = 100%). However, with higher MICs a lower percentage T>MIC could be expected in obesity, which may reduce efficacy. A recent study [77] showed that piperacillin–tazobactam dosed at 3.375 g q6 h had a tendency towards worse cure rates in patients with BMI 30 or more (75 vs. 83%; not significant) in surgical patients with complicated intra-abdominal infections. A PK/PD study of piperacillin–tazobactam using 4.5 g q6 h dosing in a morbidly obese patient [75] found that appropriate PK/PD parameters were achieved; however, it suggested that extended infusions of piperacillin–tazobactam may improve PK/PD performance.

Cephalosporins

As a general rule, obese and morbidly obese patients require higher doses of cephalosporins to achieve similar outcomes; however, there are few absolute dosing recommendations that can be made. Obese patients receiving the same dose of cefotetan preoperatively as non-obese patients have higher rates of SSI [86], whereas obese patients receiving higher doses of cefazolin (2 vs. 1 g) had lower rates of perioperative wound infection (5.6 vs. 16.5%) [81]. A dose of 2 g cefazolin should provide adequate levels for at least 4 h even in super-morbid obesity [82*]. Administering a higher dose may not always be successful due to impaired tissue penetration or more rapid clearance: decreased tissue concentrations were found in obese patients given 2 g cefoxitin compared to normal-weight patients given 1 g [121], whereas inadequate soft tissue interstitial concentrations were found in six morbidly obese women given 1.5 g cefuroxime [136]; higher volume of distribution and clearance of cefotaxime in obese patients has also been reported [137]; and higher doses of cephepime (2 g q8 h, aiming at T>MIC 60%) were found to be needed in morbidly obese patients undergoing elective weight loss surgery [84*]. Mann and Buchwald [138] recommended that doses of cefamandole should be dosed on TBW for morbidly obese patients in the perioperative period: the regimen used at their institution was 2 g q3 h intraoperatively followed by 2 g q6 h postoperatively. Lower perioperative levels may result in concentrations inadequate to provide cover against Gram-negative organisms, which is of particular concern during abdominal surgery [136]. Lastly, Pezzer et al. [139] assessed cephalozolin concentrations in adipose tissue in 29 patients scheduled for caesarean, and found that obese and extremely obese pregnant patients had significantly lower levels, below the MIC for some common organisms.

Carbapenems

Ertapenem 1 g has been shown to achieve lower concentrations in obese and morbidly obese volunteers [85], with obese individuals attaining suitable bacteriostatic effects only for bacteria with MIC 0.25 µg/ml or less (compared with ≤0.5 µg/ml for normal volunteers). Obese patients have shown higher rates of SSI compared to non-obese patients (26.7 vs. 12.7%) [86]. Conversely, Zakrison et al. [77] showed ertapenem 1 g/day had nearly identical cure rates in surgical patients with complicated intra-abdominal infections with BMI less than 30 and at least 30 (80 vs. 81%). Two recent case studies [88,90] reported successful outcomes with high-dose meropenem (3 g q6 h via 3 h infusion) and continuous infusion meropenem (500 mg q4 h via continuous infusion). No data could be found for imipenem/cilastatin.

Aztreonam

A study investigating aztreonam pharmacokinetics [92] found that the one obese patient studied had a much lower AUC and much higher volume of distribution and clearance compared to the rest of the
patients and was the only patient not to obtain adequate drug levels.

**Daptomycin**
Daptomycin is predominantly renally cleared, with efficacy most closely correlating with AUC/MIC and \( C_{\text{max}}/\text{MIC} \) [140]. Despite a higher \( C_{\text{max}} \) and AUC in the obese population, TBW-based dosing achieves adequate therapeutic levels [102,103]. A study of 29 oncology patients with febrile neutropenia (11 of whom were obese) recommended a 6 mg/kg dose as being well tolerated and effective but without any specific recommendations in the obese subpopulation [141]. Lastly, a number of case reports [88,142] have outlined successful treatment of obese patients with severe infections using a variety of dosing strategies, including using the clearance of vancomycin to predict daptomycin pharmacokinetics.

**Linezolid**
A study by Stein et al. [143] looking at seven obese patients (TBW >150% of IBW) found that despite overall lower serum concentrations of linezolid (12.3 vs. 16.3–24 \( \mu \text{g/ml} \)), inhibitory activity remained (although bactericidal activity was not observed for most isolates); no higher doses were recommended, however concern was expressed that if a strain with a higher MIC was isolated coverage may not be provided. Two case studies [144,145] also showed lower levels close to or below MIC90; however, both showed successful treatment outcomes.

**Fluoroquinolones**
Early recommendations for ciprofloxacin were based on a study by Allard et al. [96], which compared the pharmacokinetics of 400 mg intravenous (IV) ciprofloxacin in 17 obese male volunteers and 11 controls, and found that an ABW using a DWC of 0.45 should be used to normalize the volume of distribution and calculate doses. More recent cases reported using doses of 800 mg IV q12 h with microbiological success in severely morbidly obese patients [95,146]; the second case using a dosing regimen of total dose = 400 mg + 3 × 0.45 × EBW to estimate required dose. Hollenstein et al. [147] compared the pharmacokinetics of 2.85 mg/kg TBW IV ciprofloxacin in 12 obese and 12 non-obese volunteers and concluded that despite a significantly higher AUC based on the levels found in the plasma compartment, tissue concentrations were similar, hence dosing should be based on TBW rather than ABW or IBW. A case study by Luque et al. [97] in a 179 kg man found that dosing this patient at double the normal dose (750 mg twice daily vs. 750 mg daily) of levofloxacin resulted in an AUC approximately double that found in the non-obese healthy population, raising the question of whether levofloxacin needs to be dose increased in the obese population. Moxifloxacin pharmacokinetics in 12 morbidly obese patients were compared to historical controls [98]. Although plasma pharmacokinetics remained comparable, concentrations in subcutaneous fat were found to be significantly lower than plasma concentrations; the conclusion that moxifloxacin dose adjustment is not warranted in the morbidly obese population may depend on the location of the infection. Lastly, one study found that both obesity and fluoroquinolone use were risk factors for Achilles tendon rupture [148].

**Macrolides**
Very little information is available for this class of drugs. Abdullahi et al. [149] showed lower rates of *Helicobacter pylori* eradication using a flat dose of clarithromycin 250 mg and amoxicillin 1 g three times daily with pantoprazole 40 mg twice daily in a population of obese (55%) vs. non-obese patients (85%; \( P=0.0059 \)), and suggested that higher doses of antibiotics may be necessary in this group; longer durations also appear more effective [150].

**Tetracyclines and glycylcyclines**
Tigecycline has been used at standard doses (100 mg loading dose followed by 50 mg q12 h for up to 14 days) in patients up to 200 kg [151], however no comparisons of efficacy could be found. Diabetic patients (with average BMI 30.4 ± 6.2) showed excellent tissue penetration (99–100% of plasma levels) [152]. A study assessing the pharmacokinetics of tigecycline in morbidly obese individuals has recently finished [153]. No data could be found regarding tetracyclines.

**Cotrimoxazole, clindamycin**
Langebrake et al. [154], in providing recommendations for morbidity obese patients undergoing allo- genic haematopoietic stem cell transplantation, suggested that IBW be used due to the hydrophilic nature and high renal clearance of cotrimoxazole; however, this recommendation was not based on any patient data. Halilovic et al. [111] found morbidly obese patients with cellulitis±cutaneous abscess given inappropriately low doses of cotrimoxazole or clindamycin on discharge had significantly higher rates of treatment failure; the authors suggested dosing of these antibiotics be based on patient’s body mass (i.e. TBW).

**Metronidazole**
Mastrobattista et al. [110] performed a secondary analysis of two previous studies to assess the effect
of BMI of 738 pregnant women with bacterial vaginosis receiving 2 g metronidazole at 0 and 48 h, and found that BMI did not have an effect on rate of recurrence of bacterial vaginosis, implying that efficacy of metronidazole was similar among the different BMI categories.

Antituberculotic drugs

Very little information is available on the dosing of antituberculotic drugs in obesity, especially given the usual association between malnutrition and tuberculosis [155] and lower rates among obese and overweight individuals [156]. In summary, doses based on IBW have shown serum levels similar to the lean population [157,158], whereas side-effects appear more commonly when doses are based on TBW [159,160]; however, no dosing recommendations can be made from such small numbers.

DISCUSSION

Many potentially confounding factors were identified during the review of the literature. It is unknown whether results from healthy obese volunteers can be extrapolated to the sick obese inpatient population, or the critically ill postsurgical elderly obese patient with renal dysfunction, cancer and diabetes. Equally, whether results from an obese population can be extrapolated to a morbidly obese population, or whether results found in a nondiabetic patient can be extrapolated to a diabetic patient is unknown. Given the altered pharmacodynamics in obesity, it is likely that the type or location of infection may necessitate different dosing strategies. There is also little data available on whether inadequate dosing of antimicrobials in this patient population is contributing to the development of resistance, although this is likely to be an important issue [161].

CONCLUSION

In summary, there is insufficient data for most antibacterial agents to allow prescribers to dose their obese patients appropriately. Prescribers should carefully consider the important PK/PD indices for each antimicrobial and bacterial pathogen combination when estimating the dosing regimen. Although therapeutic drug monitoring is usually readily available for glycopeptides and aminoglycosides, concentration monitoring for other drugs remains difficult. Particular attention should be paid to single or loading doses (e.g. preoperative, emergency department, febrile neutropenia, peripheral infection) where appropriate early treatment may facilitate early recovery or significantly reduce complications. Given the incidence of obesity compared to the incidence of renal dysfunction, it has to be asked whether the relevant authorities (e.g. Food and Drug Administration in USA, European Medicines Agency in the European Union, Therapeutic Goods Administration in Australia) should consider imposing mandatory requirements regarding the dosing of drugs in the obese population in a similar manner to that imposed in patients with renal dysfunction.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

* of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 720).


Dosing of antibiotics in obesity Janson and Thursky

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