Dosing of antibiotics in obesity

Brett Janson[a] *and Karin Thursky*[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, cefoxitin, 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▪–27▪,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

[a]Pharmacy Department, [b]Department of Infectious Diseases, Peter MacCallum Cancer Centre, East Melbourne, Victoria and [c]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

Curr Opin Infect Dis 2012, 25:634–649
DOI:10.1097/QCO.0b013e328359a4c1

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.

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/m^2 (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 1. Common formulas used in obesity calculations

Measure	Formula	Source
BMI	$BMI = TBW/[Ht(m) \times Ht(m)]$	[31]
IBW (Devine)	$IBW = 45.4 + [0.89 \times (Ht(cm) - 152.4)]$ (+4.5 if male)	[32]
EBW	$EBW = TBW - IBW$	
LBW (Janmahasatian)	Males: $LBW = (9270 \times TBW) / [6680 + (216 \times BMI)]$ Female: $LBW = (9270 \times TBW) / [8780 + (244 \times BMI)]$	[33,34]
FFM	Males: $FFM = (TBW \times 0.285) + [12.1 \times Ht(m)^2]$ Females: $FFM = (TBW \times 0.287) + [9.74 \times Ht(m)^2]$	[35]
ABW	$ABW = IBW + [DWCF \times (TBW - IBW)]$ $ABW = IBW + (DWCF \times EBW)$	[36]
PNW	Males: $PNW = (TBW \times 1.57) - (TBW \times BMI \times 0.0183) - 10.5$ Females: $PNW = (TBW \times 1.75) - (TBW \times BMI \times 0.0242) - 12.6$	[37]
BSA Dubois and Dubois	$BSA = TBW^{0.425} \times Ht(cm)^{0.725} \times 0.007184$	[36,38,39]
BSA Mosteller	$BSA = \sqrt{[(Ht(cm) \times Wt)/3600]}$	[39]

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.

Table 2. Terminologies used to describe different BMI categories

Classification (various terminologies)	BMI (kg/m^2)
Underweight	<18.5
Normal weight	18.5 to <25
Overweight	≥25
Pre-obese	25 to <30
Obese	≥30
Obese (obesity class I)	30 to <35
Severely obese (obesity class II)	35 to <40
Morbidly obese (obesity class III)	≥40
Super obese	≥50
Super-super obese	≥60

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_{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▪].

Metabolism

Changes in hepatic metabolism associated with obesity are largely unknown. Hepatic volume does increase, but more likely due to fatty infiltration than an increase in metabolic capacity, with resulting risks of steatosis, hepatitis and fibrosis. Of the cytochrome P450 enzymes associated with phase I oxidative metabolism, CYP2E1 and possibly CYP1A2 and CYP2C9 have raised levels, and CYP3A4 has lower levels [27▪]; other CYP enzymes (CYP2C19 and CYP2D6) have no conclusive data [47]. There is limited information on increases in phase II conjugative metabolism involving glucuronidation and sulphation. Brill *et al.* [27▪] has an extensive section on both phase I and phase II metabolizing enzymes.

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

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–Gaul 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 DOSING 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_{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_{max}/MIC is the peak level (C_{max}) divided by the MIC, and is used to predict the efficacy of concentration-dependent antibiotics (aminoglycosides and fluoroquinolones). The C_{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

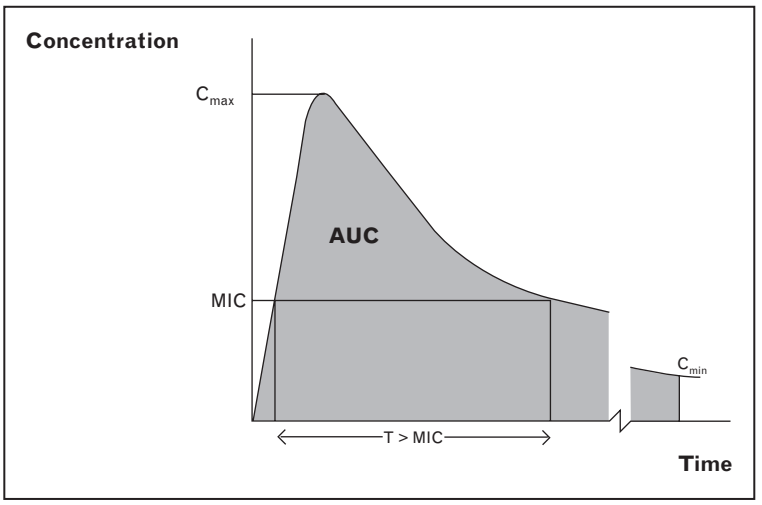

FIGURE 1. Main pharmacokinetic–pharmacodynamic (PK–PD) parameters. AUC, C_{max}, C_{min}, MIC, T>MIC are values that are often expressed using the more relevant free concentration (*f*) of the drug e.g. *f*T>MIC, referring to the time the free concentration of the drug is above the MIC, *f*AUC/MIC and *f*C_{max}/MIC ratios etc. AUC, area under curve; C_{max}, maximum concentration (peak); C_{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].

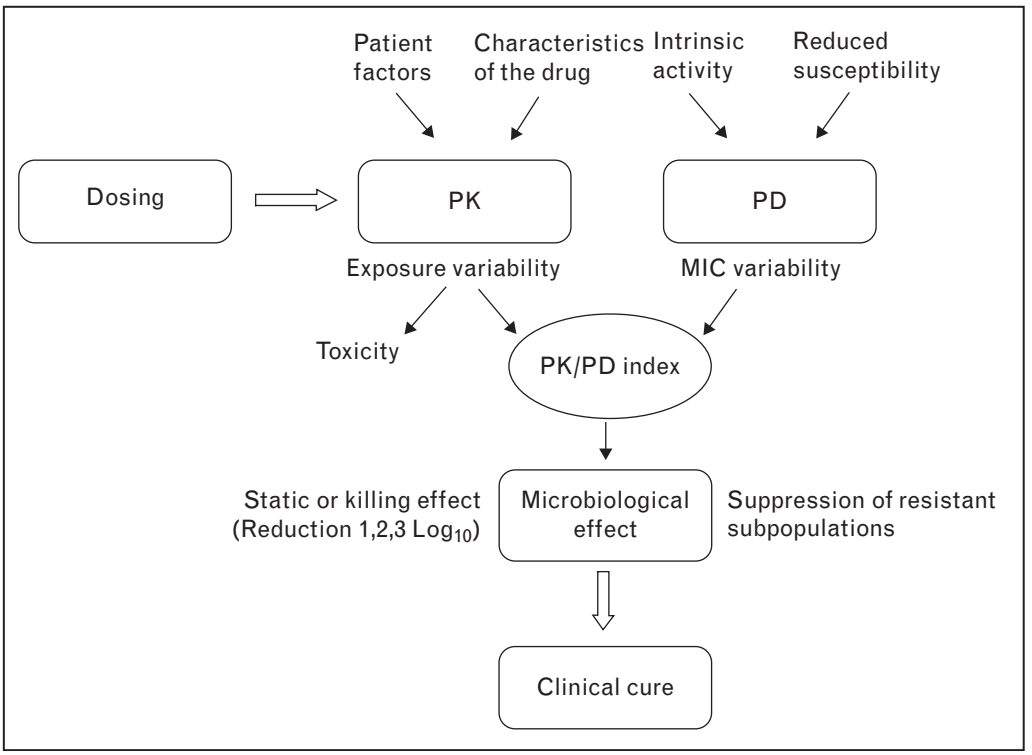

FIGURE 2. Variability and relationship between dosing, drug exposure [pharmacokinetics (PK)], minimum inhibitory concentration [(MIC), pharmacodynamics (PD)] and microbiological effect that predicts the probability of clinical cure. Reproduced with permission from [60].

kill). For example, AUC_{24h}/MIC and C_{max}/MIC are important indices for the efficacy of aminoglycosides. In serious Gram-negative infections, an $AUC_{24\,h}$/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]. $AUC_{24\,h}$/MIC is the PK/PD index correlating best with in-vivo antimicrobial efficacy of glycopeptides. An $AUC_{24\,h}$/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 $AUC_{24\,h}$/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

Antibiotic class [17]	Antibiotic	Clinically important parameters	Weight used for dosing	Suggested dosage in obese patients or highest dose in product information (not a recommended dose for this population)	References
Aminoglycosides (hydrophilic)	Gentamicin; amikacin; tobramycin	C_{max}/MIC (takes preference over $AUC_{24\,h}$/MIC due to toxicity concerns); PAE	IBW	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	[11,36,61–63]
Glycopeptides (hydrophilic)	Vancomycin	T>MIC; PAE	TBW for initial doses.	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	[64–70,71▪]
	Teicoplanin	C_{max}/MIC; T>MIC	Unknown	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).	[72–74]

(*Continued*)

Table 3 (*Continued*)

Antibiotic class [17]	Antibiotic	Clinically important parameters	Weight used for dosing	Suggested dosage in obese patients or highest dose in product information (not a recommended dose for this population)	References
β-Lactams–penicillins (hydrophilic)	Piperacillin/ tazobactam	T>MIC	TBW	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.	[75–79]
	Other penicillins[a]	T>MIC	TBW	Consider dosing at upper end of recommended doses or use more frequent dosing.	[15]
β-Lactams–cephalosporins (hydrophilic)	Cephazolin (Cefazolin)	T>MIC	TBW	Single 2 g dose effective in obesity in surgery <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.	[80,81,82▪,83]
	Cefepime	T>MIC		Dose of 2 g q8h required postoperatively in surgical patients (equivalent to usual dose used to treat severe or life-threatening conditions).	[84▪]
	Other cephalosporins[a]	T>MIC	TBW	Consider higher stat doses for perioperative use, or dosing at upper end of recommended doses. See individual product information.	[15]
β-Lactams–carbapenems (hydrophilic)	Ertapenem	T>MIC	Unknown	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.	[85–87]

	Meropenem	T>MIC	Unknown	No dosage adjustment required, however, consider dosing at upper end of recommended dose range (e.g. 2 g q8h). Higher doses have been used. Prolonged infusions have been used (caution with stability).	[88–90]
β-Lactams–monobactam (hydrophilic)	Aztreonam	T>MIC	Unknown	Consider dosing at upper end of recommended dose range. Maximum dose in product information is 2 g q6h.	[91,92]
Lipopeptides	Daptomycin	$AUC_{24\,h}$/MIC; C_{max}/MIC	TBW	Exposure increased by 25–30% when dose based on TBW, but still safe and tolerated in individuals ranging from 56–147 kg.	[93]
Oxazolidinones	Linezolid	T>MIC; $AUC_{24\,h}$/MIC; moderate PAE	Standard dosing	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]
Fluoroquinoliones (lipophilic)	Ciprofloxacin	$AUC_{24\,h}$/MIC; C_{max}/MIC; PAE	ABW	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]
	Levofloxacin	$AUC_{24\,h}$/MIC; C_{max}/MIC	Unknown	Maximum used dose is 750 mg daily. Limited evidence suggests no dose increase is needed.	[97]
	Moxifloxacin	$AUC_{24\,h}$/MIC; C_{max}/MIC	Unknown	In patients up to 166 kg, moxifloxacin pharmacokinetics were similar to controls.	[98,99]

(*Continued*)

Table 3 (*Continued*)

Antibiotic class [17]	Antibiotic	Clinically important parameters	Weight used for dosing	Suggested dosage in obese patients or highest dose in product information (not a recommended dose for this population)	References
Macrolides (lipophilic)	Erythromycin	T>MIC; $AUC_{24\,h}$/MIC	Unknown	Maximum used doses are 1 g four times daily (maximum 4 g/day) of erythromycin (independent of formulation) for severe pneumonia, diphtheria and Legionnaires. Up to 6 g/day has been reported. Caution QT prolongation and interactions.	[100,101]
	Clarithromycin	T>MIC and $AUC_{24\,h}$/MIC	Unknown	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).	[102,103]
Tetracyclines (Lipophilic)	Doxycycline	T>MIC C_{max}/MIC	Unknown	Maximum dose found was 300 mg IV daily or 300 mg oral daily in divided doses for $\geq$10 days for treatment of primary or secondary syphilis.	[104,105]
Glycylcyclines (Lipophilic)	Tigecycline	T>MIC	Unknown	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.	[106–108]
Nitroimidazoles	Metronidazole	$AUC_{24\,h}$/MIC; C_{max}/MIC	Unknown	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.	[109,110]

Cotrimoxazole (lipophilic)	Trimethoprim / sulphamethoxazole	Unknown	Unknown	Treatment of pneumocystis pneumonia uses dose of up to 20 mg/kg per 24 h trimethoprim and 100 mg/kg per 24 h sulphamethoxazole. Inadequate oral doses (<5 mg/kg per 24 h trimethoprim in divided doses) had worse outcomes in morbidly obese patients. It is unknown what dose should be used in the obese population.	[111▪,112,113]
Lincosamides (lipophilic)	Clindamycin	Unknown	Unknown	Doses up to 4800 mg (1200 mg q6h) have been used. Inadequate oral doses (<10 mg/kg per 24 h in divided doses) had worse outcomes in morbidly obese patients.	[111▪,114]

Where data does not exist for dosing in obese patients, the highest doses found in the US and/or Australian Product Information are included – these should not be interpreted as a recommendation. This table does not incorporate considerations such as renal or hepatic function, drug interactions, susceptibility, and so on. ABW, adjusted body weight; AUC, area under the curve; AUC/MIC, area under the curve to minimum inhibitory concentration ratio; Cl, clearance; C_{max}, maximum concentration; C_{max}/MIC, maximum concentration to minimum inhibitory concentration ratio; DWCF, dosing weight correction factor; ECF, extracellular fluid; IBW, ideal body weight; IV, intravenously; PAE, post-antibiotic effect; T>MIC, percentage of time where concentration of drug is greater than the minimum inhibitory concentration; $t_{1/2}$, half-life; Vd, volume of distribution.

[a]see Product Information for individual drugs.

[b]dose range 5–7mg per kg.

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 $= 0.9 \times$ 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

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 C_{max}, 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 cephazolin (2 vs. 1 g) had lower rates of perioperative wound infection (5.6 vs. 16.5%) [81]. A dose of 2 g cephazolin 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 cefepime (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, Pevzner *et al.* [139] assessed cephazolin 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_{max}/MIC [140]. Despite a higher C_{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 μg/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 DWCF 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 morbidly obese patients undergoing allogeneic 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).

1. Squires DA. Tracking trends in health system performance: issues in international health policy: explaining high healthcare spending in the United States: an international comparison of supply, utilization, prices, and quality. Issue Brief (Commonw Fund) 2012; 10:1–14.
2. Silber JH, Rosenbaum PR, Kelz RR, *et al.* Medical and financial risks associated with surgery in the elderly obese. Ann Surg 2012; 256:79–86.
3. Huttunen R, Laine J, Lumio J, *et al.* Obesity and smoking are factors associated with poor prognosis in patients with bacteraemia. BMC Infect Dis 2007; 7:13.
4. Huttunen R, Syrjanen J. Obesity and the risk and outcome of infection. Int J Obes (Lond) 2012. doi:10.1038/ijo.2012.62 [Epub ahead of print]
5. Harrop JS, Styliaras JC, Ooi YC, *et al.* Contributing factors to surgical site infections. J Am Acad Orthop Surg 2012; 20:94–101.
6. Wakefield H, Vaughan-Sarrazin M, Cullen JJ. Influence of obesity on complications and costs after intestinal surgery. Am J Surg 2012. [Epub ahead of print]
7. Schuster JM, Rechtine G, Norvell DC, Dettori JR. The influence of perioperative risk factors and therapeutic interventions on infection rates after spine surgery: a systematic review. Spine 2010; 35 (9 Suppl):S125–S137.
8. Marti A, Marcos A, Martinez JA. Obesity and immune function relationships. Obes Rev 2001; 2:131–140.
9. Milner JJ, Beck MA. The impact of obesity on the immune response to infection. Proc Nutr Soc 2012; 71:298–306.
10. Louie JK, Acosta M, Samuel MC, *et al.* A novel risk factor for a novel virus: obesity and 2009 pandemic influenza A (H1N1). Clin Infect Dis 2011; 52:301–312.
11. Van Kerkhove MD, Vandemaele KA, Shinde V, *et al.* Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. PLoS Med 2011; 8:e1001053.
12. Weber DJ, Rutala WA, Samsa GP, *et al.* Obesity as a predictor of poor antibody response to hepatitis B plasma vaccine. J Am Med Assoc 1985; 254:3187–3189.
13. Weber DJ, Rutala WA, Samsa GP, *et al.* Impaired immunogenicity of hepatitis B vaccine in obese persons. N Engl J Med 1986; 314:1393.
14. Eliakim A, Schwindt C, Zaldivar F, *et al.* Reduced tetanus antibody titers in overweight children. Autoimmunity 2006; 39:137–141.
15. Erstad BL. Dosing of medications in morbidly obese patients in the intensive care unit setting. Intensive Care Med 2004; 30:18–32.
16. Roe JL, Fuentes JM, Mullins ME. Underdosing of common antibiotics for obese patients in the ED. Am J Emerg Med 2012; 30:1212–1214.
17. Falagas ME, Karageorgopoulos DE. Adjustment of dosing of antimicrobial agents for bodyweight in adults. Lancet 2010; 375:248–251.
18. Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients. Pharmacotherapy 2007; 27:1081–1091.

19. Cheymol G. Drug pharmacokinetics in the obese. Fundam Clin Pharmacol 1988; 2:239–256.
20. Cheymol G. Clinical pharmacokinetics of drugs in obesity. An update. Clin Pharmacokinet 1993; 25:103–114.
21. Cheymol G. Effects of obesity on pharmacokinetics implications for drug therapy. Clinic Pharmacokinet 2000; 39:215–231.
22. Wurtz R, Itokazu G, Rodvold K. Antimicrobial dosing in obese patients. Clin Infect Dis 1997; 25:112–118.
23. Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. Clin Pharmacokinet 2010; 49:71–87.
24. ■ Jain R, Chung SM, Jain L, *et al.* Implications of obesity for drug therapy: limitations and challenges. Clin Pharmacol Ther 2011; 90:77–89.
See [26■].
25. Leykin Y, Miotto L, Pellis T. Pharmacokinetic considerations in the obese. ■ Best Pract Res Clin Anaesthesiol 2011; 25:27–36.
See [26■].
26. ■ Morrish GA, Pai MP, Green B. The effects of obesity on drug pharmacokinetics in humans. Expert Opin Drug Metab Toxicol 2011; 7:697–706.
This and [24■] and [25■] are recent reviews on pharmacokinetic considerations in obese patients.
27. ■ Brill MJ, Diepstraten J, van Rongen A, *et al.* Impact of obesity on drug metabolism and elimination in adults and children. Clin Pharmacokinet 2012; 51:277–304.
Comprehensive comparison of drug metabolism changes seen in obese patients.
28. Abernethy DR, Greenblatt DJ. Drug disposition in obese humans. An update. Clin Pharmacokinet 1986; 11:199–213.
29. Van Bambeke F, Tulkens PM. Macrolides: pharmacokinetics and pharmacodynamics. Int J Antimicrob Agents 2001; 18 (Suppl 1):S17–S23.
30. Green B, Duffull SB. What is the best size descriptor to use for pharmacokinetic studies in the obese? Br J Clin Pharmacol 2004; 58:119–133.
31. World Health Organisation. Obesity and overweight Fact sheet N°311. http://www.who.int/mediacentre/factsheets/fs311/en/index.html. [Accessed on 10 July 2012]
32. Devine BJ. Gentamicin therapy. Drug Intell Clin Pharm 1974; 8:650–655.
33. Han PY, Duffull SB, Kirkpatrick CM, Green B. Dosing in obesity: a simple solution to a big problem. Clin Pharmacol Ther 2007; 82:505–508.
34. Janmahasatian S, Duffull SB, Ash S, *et al.* Quantification of lean bodyweight. Clin Pharmacokinet 2005; 44:1051–1065.
35. Garrow JW. J. Quetelet's Index (W/H^2) as a measure of fatness. Int J Obes 1985; 9:147–153.
36. Bauer LA, Edwards WA, Dellinger EP, Simonowitz DA. Influence of weight on aminoglycoside pharmacokinetics in normal weight and morbidly obese patients. Eur J Clin Pharmacol 1983; 24:643–647.
37. Duffull SB, Dooley MJ, Green B, *et al.* A standard weight descriptor for dose adjustment in the obese patient. Clin Pharmacokinet 2004; 43:1167–1178.
38. Du Bois D, Du Bois E. Clinical calorimetry: tenth paper. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 1916; 17:863.
39. Mosteller R. Simplified calculation of body surface area. N Engl J Med 1987; 317:1098.
40. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004; 363:157–163.
41. Spellwin G. BMI for Men Increases Health Insurance for Bodybuilders and Athletes Available from http://bodybuilding.elitefitness.com/bmi-men-bodybuilder-athletes?s=7938c37dbc8b3fe898914db0aeee5605. [Accessed on 12 June 2012]
42. Pai MP, Paloucek FP. The origin of the 'ideal' body weight equations. Ann Pharmacother 2000; 34:1066–1069.
43. Maddox A, Horowitz M, Wishart J, Collins P. Gastric and oesophageal emptying in obesity. Scand J Gastroenterol 1989; 24:593–598.
44. Jackson SJ, Leahy FE, McGowan AA, *et al.* Delayed gastric emptying in the obese: an assessment using the noninvasive (13)C-octanoic acid breath test. Diab Obes Metab 2004; 6:264–270.
45. Medico CJ, Walsh P. Pharmacotherapy in the critically ill obese patient. Crit Care Clin 2010; 26:679–688.
46. Wojcicki J, Jaroszynska M, Drozdzik M, *et al.* Comparative pharmacokinetics and pharmacodynamics of propranolol and atenolol in normolipaemic and hyperlipidaemic obese subjects. Biopharm Drug Dispos 2003; 24:211–218.
47. Kotlyar M, Carson SW. Effects of obesity on the cytochrome P450 enzyme system. Int J Clin Pharmacol Ther 1999; 37:8–19.
48. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31–41.
49. Levey AS, Bosch JP, Lewis JB, *et al.* A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130:461–470.
50. Cirillo M, Anastasio P, De Santo NG. Relationship of gender, age, and body mass index to errors in predicted kidney function. Nephrol Dial Transplant 2005; 20:1791–1798.
51. Verhave JC, Fesler P, Ribstein J, *et al.* Estimation of renal function in subjects with normal serum creatinine levels: influence of age and body mass index. Am J Kidney Dis 2005; 46:233–241.
52. Aggarwal N, Porter AC, Tang IY, *et al.* Creatinine-based estimations of kidney function are unreliable in obese kidney donors. J Transplant 2012; 2012:872894.
53. Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150:604–612.
54. Demirovic JA, Pai AB, Pai MP. Estimation of creatinine clearance in morbidly obese patients. Am J Health Syst Pharm 2009; 66:642–648.
55. Salazar DE, Corcoran GB. Predicting creatinine clearance and renal drug clearance in obese patients from estimated fat-free body mass. Am J Med 1988; 84:1053–1060.
56. Nankivell BJ. Creatinine clearance and the assessment of renal function. Aust Prescriber 2001; 24:15–17.
57. ■ Mouton JW, Ambrose PG, Canton R, *et al.* Conserving antibiotics for the future: new ways to use old and new drugs from a pharmacokinetic and pharmacodynamic perspective. Drug Resist Updat 2011; 14:107–117.
Up-to-date discussion of PK–PD relationships and other dosing considerations.
58. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 2009; 37:840–851.
59. Barger A, Fuhst C, Wiedemann B. Pharmacological indices in antibiotic therapy. J Antimicrob Chemother 2003; 52:893–898.
60. Theuretzbacher U. Pharmacokinetic and pharmacodynamic issues for antimicrobial therapy in patients with cancer. Clin Infect Dis 2012; 54:1785–1792.
61. Begg EJ, Barclay ML, Duffull SB. A suggested approach to once-daily aminoglycoside dosing. Br J Clin Pharmacol 1995; 39:605–609.
62. Schwartz SN, Pazin GJ, Lyon JA, *et al.* A controlled investigation of the pharmacokinetics of gentamicin and tobramycin in obese subjects. J Infect Dis 1978; 138:499–505.
63. Korsager S. Administration of gentamicin to obese patients. Int J Clin Pharmacol Ther Toxicol 1980; 18:549–553.
64. Bauer LA, Black DJ, Lill JS. Vancomycin dosing in morbidly obese patients. Eur J Clin Pharmacol 1998; 54:621–625.
65. Ducharme MP, Slaughter RL, Edwards DJ. Vancomycin pharmacokinetics in a patient population: effect of age, gender, and body weight. Ther Drug Monit 1994; 16:513–518.
66. Vance-Bryan K, Guay DR, Gilliland SS, *et al.* Effect of obesity on vancomycin pharmacokinetic parameters as determined by using a Bayesian forecasting technique. Antimicrob Agents Chemother 1993; 37:436–440.
67. Leong JV, Boro MS, Winter M. Determining vancomycin clearance in an overweight and obese population. Am J Health Syst Pharm 2011; 68:599–603.
68. Rybak MJ, Lomaestro BM, Rotschafer JC, *et al.* Vancomycin therapeutic guidelines: a summary of consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis 2009; 49:325–327.
69. Lodise TP, Patel N, Lomaestro BM, *et al.* Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. Clin Infect Dis 2009; 49:507–514.
70. Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. Antimicrob Agents Chemother 2008; 52:1330–1336.
71. ■ Grace E. Altered vancomycin pharmacokinetics in obese and morbidly obese patients: what we have learned over the past 30 years. J Antimicrob Chemother 2012; 67:1305–1310.
Summary of vancomycin dosing in obese patients.
72. Brink AJ, Richards GA, Cummins RR, Lambson J. Recommendations to achieve rapid therapeutic teicoplanin plasma concentrations in adult hospitalised patients treated for sepsis. Int J Antimicrob Agents 2008; 32:455–458.
73. Wilson AP, Gruneberg RN, Neu H. Dosage recommendations for teicoplanin. J Antimicrob Chemother 1993; 32:792–796.
74. Wilson AP, Gruneberg RN, Neu H. A critical review of the dosage of teicoplanin in Europe and the USA. Int J Antimicrob Agents 1994; 4 (Suppl 1): 1–30.
75. Deman HVJ, Willems L, Spriet I. Dosing of piperacillin/tazobactam in a morbidly obese patient. J Antimicrob Chemother 2012; 2012:782–783.
76. Newman D, Scheetz MH, Adeyemi OA, *et al.* Serum piperacillin/tazobactam pharmacokinetics in a morbidly obese individual. Ann Pharmacother 2007; 41:1734–1739.
77. 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 (Larchmt) 2012; 13:38–42.
78. Wyeth Pharmaceuticals Inc. (March 2007) Pipracil™ US Product Information, Philadelphia, PA. [Accessed on 9 July 2012]
79. Wyeth Pharmaceuticals Inc. (May 2012) Zosyn™ US Product Information, Philadelphia, PA. [Accessed on 9 July 2012].
80. Edmiston CE, Krepel C, Kelly H, *et al.* Perioperative antibiotic prophylaxis in the gastric bypass patient: do we achieve therapeutic levels? Surgery 2004; 136:738–747.
81. Forse RA, Karam B, MacLean LD, Christou NV. Antibiotic prophylaxis for surgery in morbidly obese patients. Surgery 1989; 106:750–756.

82. Ho VP, Nicolau DP, Dakin GF, *et al.* Cefazolin dosing for surgical prophylaxis ■ in morbidly obese patients. Surg Infect 2012; 13:33–37.
Describes dosing and expected duration of efficacy of perioperative cephazolin dosing.

83. Cefazolin for Injection US Product Information, Sagent Pharmaceuticals. http://www.sagentpharma.com/Products/Cefazolin/Catalog/Cefazolin_PI1.pdf. [Accessed on 9 July 2012]

84. Rich BS, Keel R, Ho VP, *et al.* Cefepime dosing in the morbidly obese patient ■ population. Obes Surg 2012; 22:465–471.
Describes a recommended regimen to achieve T>MIC 60%.

85. Chen M, Nafziger AN, Drusano GL, *et al.* Comparative pharmacokinetics and pharmacodynamic target attainment of ertapenem in normal-weight, obese, and extremely obese adults. Antimicrob Agents Chemother 2006; 50:1222–1227.

86. Itani KM, Jensen EH, Finn TS, *et al.* Effect of body mass index and ertapenem versus cefotetan prophylaxis on surgical site infection in elective colorectal surgery. Surg Infect 2008; 9:131–137.

87. Merck and Co Inc (Feb 2012) Invanz™ US Product Information. http://www.merck.com/product/usa/pi_circulars/i/invanz/invanz_pi.pdf. [Accessed on 1 September 2012]

88. Pea F, Cojutti P, Sbrojavacca R, *et al.* TDM-guided therapy with daptomycin and meropenem in a morbidly obese, critically ill patient. Ann Pharmacother 2011; 45:e37.

89. AstraZeneca Pharmaceuticals (December 2010) Merrem™ US Product Information, Wilmington, DE. http://www1.astrazeneca-us.com/pi/merremiv.pdf. [Accessed 10 July 2012]

90. Taccone FS, Cotton F, Roisin S, *et al.* Optimal meropenem concentrations to treat multidrug-resistant Pseudomonas aeruginosa septic shock. Antimicrob Agents Chemother 2012; 56:2129–2131.

91. Bristol-Myers Squibb Pharmaceuticals (July 2008) Azactam™ Australian Approved Product Information Noble Park, Victoria, Australia. http://www.pbs.gov.au/meds/pi/bqpazact10709.pdf [Accessed 6 July 2012]

92. Boccazzi A, Langer M, Mandelli M, *et al.* The pharmacokinetics of aztreonam and penetration into the bronchial secretions of critically ill patients. J Antimicrob Chemother 1989; 23:401–407.

93. Dvorchik BH, Damphousse D. The pharmacokinetics of daptomycin in moderately obese, morbidly obese, and matched nonobese subjects. J Clin Pharmacol 2005; 45:48–56.

94. Rayner CR, Forrest A, Meagher AK, *et al.* Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin Pharmacokinet 2003; 42:1411–1423.

95. Caldwell JB, Nilsen AK. Intravenous ciprofloxacin dosing in a morbidly obese patient. Ann Pharmacother 1994; 28:806.

96. Allard S, Kinzig M, Boivin G, *et al.* Intravenous ciprofloxacin disposition in obesity. Clin Pharmacol Therapeut 1993; 54:368–373.

97. Luque S, Grau S, Valle M, *et al.* Levofloxacin weight-adjusted dosing and pharmacokinetic disposition in a morbidly obese patient. J Antimicrob Chemother 2011; 66:1653–1654.

98. Kees MG, Weber S, Kees F, Horbach T. Pharmacokinetics of moxifloxacin in plasma and tissue of morbidly obese patients. J Antimicrob Chemother 2011; 66:2330–2335.

99. Bayer Australia Ltd (October 2011) Avelox® Australian Product Information, Pymble, NSW, Australia. http://www.bayerresources.com.au/resources/uploads/PI/file9312.pdf. [Accessed on 11 July 2012]

100. Mayne Pharma International (December 2008) Eryc® Australian Product Information, Salisbury South, SA, Australia. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-02149-3. [Accessed on 10 July 2012]

101. Van Bambeke F. 'Erythromycin' in Grayson ML, Crowe S, McCarthy J *et al.* Kucers' The use of antibiotics: A clinical review of antibacterial, antifungal and antiviral drugs. 6th ed. Hodder Arnold, London; 2010. pp. 751–769.

102. Abbott Laboratories (July 2012) Biaxin™ US Product Information, North Chicago, IL. http://www.rxabbott.com/pdf/biapi.pdf. [Accessed on 10 July 2012]

103. Abbott Australasia http://www.aspenpharma.com.au/product_info/pi/PI_Klacid.pdf. (April 2011) Klacid™ Australian Product Information, Botany NSW. [Accessed on 10 July 2012]

104. Bedford Laboratories Inc. (September 2004) Doxycycline 100mg Injection, US Product Information, Bedford OH. http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Ben+Venue_Bedford+Labs/55390-110-10+DCY+100MG/5539011010. [Accessed on 10 July 2012]

105. Mayne Pharma International (January 2009) DoryxTM Australia Product Information, Salisbury South SA, Australia. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-02155-3. [Accessed on 10 July 2012]

106. Muralidharan G, Micalizzi M, Speth J, *et al.* Pharmacokinetics of tigecycline after single and multiple doses in healthy subjects. Antimicrob Agents Chemother 2005; 49:220–229.

107. Rubinstein E, Vaughan D. Tigecycline: a novel glycylcycline. Drugs 2005; 65:1317–1336.

108. Van Wart SA, Owen JS, Ludwig EA, *et al.* Population pharmacokinetics of tigecycline in patients with complicated intra-abdominal or skin and skin structure infections. Antimicrob Agents Chemother 2006; 50:3701–3707.

109. G.D. Searle LLC (Division of Pfizer) (April 2010) Flagyl™ US Product Information, New York, NY. [Accessed on 9 July 2012]

110. Mastrobattista JM, Klebanoff MA, Carey JC, *et al.* The effect of body mass index on therapeutic response to bacterial vaginosis in pregnancy. Am J Perinatol 2008; 25:233–237.

111. Halilovic J, Heintz BH, Brown J. Risk factors for clinical failure in patients hos- ■ pitalized with cellulitis and cutaneous abscess. J Infect 2012; 65:128–134.
Investigates a number of antibiotics where inadequate dosing was achieved, with particular attention to cotrimoxazole and clindamycin (first data on both of these antibiotics).

112. Teva Pharmaceuticals USA (October 2006) Sulphamethoxazole and Trimethoprim Injection USP, US Product Information. Sellersville, PA http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=b89b5502-ce87-45a6-a43c-9891da3cfca4. [Accessed on 10 July 2012]

113. Roche Products Pty Ltd (2011). Bactrim Australian Product Information. Dee Why NSW. http://www.roche-australia.com/fmfiles/re7229005/downloads/antibiotics/bactrim-pi.pdf. [Accessed on 11 September 2012]

114. Pfizer Australia (May 2009) Dalacin C™ Phosphate Injection, Australian Product Information West Ryde NSW. http://pfizer.com.au/sites/au/Products/Leaflets/PI_DalacinCPhosphateInjectio_271.pdf. [Accessed on 10 July 2012]

115. Kashuba AD, Nafziger AN, Drusano GL, Bertino JS Jr. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by Gram-negative bacteria. Antimicrob Agents Chemother 1999; 43:623–629.

116. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis 1987; 155:93–99.

117. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. Clin Pharmacokinet 2004; 43:925–942.

118. Patel N, Pai MP, Rodvold KA, *et al.* Vancomycin: we can't get there from here. Clin Infect Dis 2011; 52:969–974.

119. Kanazawa N, Matsumoto K, Ikawa K, *et al.* An initial dosing method for teicoplanin based on the area under the serum concentration time curve required for MRSA eradication. J Infect Chemother 2011; 17:297–300.

120. Anaya DA, Dellinger EP. The obese surgical patient: a susceptible host for infection. Surg Infect 2006; 7:473–480.

121. Toma O, Suntrup P, Stefanescu A, *et al.* Pharmacokinetics and tissue penetration of cefoxitin in obesity: implications for risk of surgical site infection. Anesth Analg 2011; 113:730–737.

122. Gendall KA, Raniga S, Kennedy R, Frizelle FA. The impact of obesity on outcome after major colorectal surgery. Dis Colon Rectum 2007; 50:2223–2237.

123. Merkow RP, Bilimoria KY, McCarter MD, Bentrem DJ. Effect of body mass index on short-term outcomes after colectomy for cancer. J Am Coll Surg 2009; 208:53–61.

124. Leader WG, Tsubaki T, Chandler MH. Creatinine-clearance estimates for predicting gentamicin pharmacokinetic values in obese patients. Am J Hosp Pharm 1994; 51:2125–2130.

125. Bauer LA, Blouin RA, Griffen WO Jr, *et al.* Amikacin pharmacokinetics in morbidly obese patients. Am J Hosp Pharm 1980; 37:519–522.

126. Blouin RA, Mann HJ, Griffen WO Jr, *et al.* Tobramycin pharmacokinetics in morbidly obese patients. Clin Pharmacol Ther 1979; 26:508–512.

127. Ortega A, Aldaz A, Giraldez J, Brugarolas A. Relationship between pharmacokinetic parameters of gentamicin and patient characteristics and/or clinical data in patients with solid organ tumours. Pharm World Sci 1999; 21:227–232.

128. Blouin RA, Brouwer KL, Record KE, *et al.* Amikacin pharmacokinetics in morbidly obese patients undergoing gastric-bypass surgery. Clin Pharm 1985; 4:70–72.

129. Blouin RA, Bauer LA, Miller DD, *et al.* Vancomycin pharmacokinetics in normal and morbidly obese subjects. Antimicrob Agents Chemother 1982; 21:575–580.

130. Penzak SR, Gubbins PO, Rodvold KA, Hickerson SL. Therapeutic drug monitoring of vancomycin in a morbidly obese patient. Ther Drug Monit 1998; 20:261–265.

131. Hall RG 2nd, Payne KD, Bain AM, *et al.* Multicenter evaluation of vancomycin dosing: emphasis on obesity. Am J Med 2008; 121:515–518.

132. Leonard AE, Boro MS. Vancomycin pharmacokinetics in middle-aged and elderly men. Am J Hosp Pharm 1994; 51:798–800.

133. Rushing TA, Ambrose PJ. Clinical application and evaluation of vancomycin dosing in adults. J Pharm Technol 2001; 17:33–38.

134. Reynolds DC, Waite LH, Alexander DP, Deryke CA. Performance of a vancomycin dosage regimen developed for obese patients. Am J Health Syst Pharm 2012; 69:944–950.

135. Truong J, Levkovich BJ, Padiglione AA. Simple approach to improving vancomycin dosing in intensive care: a standardised loading dose results in earlier therapeutic levels. Intern Med J 2012; 42:23–29.

136. Barbour A, Schmidt S, Rout WR, *et al.* Soft tissue penetration of cefuroxime determined by clinical microdialysis in morbidly obese patients undergoing abdominal surgery. Int J Antimicrob Agents 2009; 34:231–235.

137. Yost RL, Derendorf H. Disposition of cefotaxime and its desacetyl metabolite in morbidly obese male and female subjects. Ther Drug Monit 1986; 8:189–194.

138. Mann HJ, Buchwald H. Cefamandole distribution in serum, adipose tissue, and wound drainage in morbidly obese patients. Drug Intell Clin Pharm 1986; 20:869–873.

139. Pevzner L, Swank M, Krepel C, *et al.* Effects of maternal obesity on tissue concentrations of prophylactic cefazolin during cesarean delivery. Obstet Gynecol 2011; 117:877–882.

140. Vance-Bryan K, Larson TA, Rotschafer JC, Toscano JP. Investigation of the early killing of Staphylococcus aureus by daptomycin by using an in vitro pharmacodynamic model. Antimicrob Agents Chemother 1992; 36:2334–2337.

141. Bubalo JS, Munar MY, Cherala G, *et al.* Daptomycin pharmacokinetics in adult oncology patients with neutropenic fever. Antimicrob Agents Chemother 2009; 53:428–434.

142. Pai MP, Mercier RC, Allen SE. Using vancomycin concentrations for dosing daptomycin in a morbidly obese patient with renal insufficiency. Ann Pharmacother 2006; 40:553–558.

143. Stein GE, Schooley SL, Peloquin CA, *et al.* Pharmacokinetics and pharmacodynamics of linezolid in obese patients with cellulitis. Ann Pharmacother 2005; 39:427–432.

144. Mersfelder TL, Smith CL. Linezolid pharmacokinetics in an obese patient. Am J Health System Pharm 2005; 62:464.

145. Tsuji Y, Hiraki Y, Matsumoto K, *et al.* Evaluation of the pharmacokinetics of linezolid in an obese Japanese patient. Scand J Infect Dis 2012; 44:626–629.

146. Utrup TR, Mueller EW, Healy DP, *et al.* High-dose ciprofloxacin for serious Gram-negative infection in an obese, critically ill patient receiving continuous venovenous hemodiafiltration. Ann Pharmacother 2010; 44:1660–1664.

147. Hollenstein UM, Brunner M, Schmid R, Muller M. Soft tissue concentrations of ciprofloxacin in obese and lean subjects following weight-adjusted dosing. Int J Obes Relat Metab Disord 2001; 25:354–358.

148. Seeger JD, West WA, Fife D, *et al.* Achilles tendon rupture and its association with fluoroquinolone antibiotics and other potential risk factors in a managed care population. Pharmacoepidemiol Drug Safety 2006; 15:784–792.

149. Abdullahi M, Annibale B, Capoccia D, *et al.* The eradication of *Helicobacter pylori* is affected by body mass index (BMI). Obes Surg 2008; 18:1450–1454.

150. Cerqueira RM, Manso MC, Correia MR, *et al. Helicobacter pylori* eradication therapy in obese patients undergoing gastric bypass surgery: fourteen days superior to seven days? Obes Surg 2011; 21:1377–1381.

151. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. J Antimicrob Chemother 2006; 58:256–265.

152. Bulik CC, Wiskirchen DE, Shepard A, *et al.* Tissue penetration and pharmacokinetics of tigecycline in diabetic patients with chronic wound infections described by using in vivo microdialysis. Antimicrob Agents Chemother 2010; 54:5209–5213.

153. ClinicalTrials.gov. Pharmacokinetics of tigecycline in morbidly obese subjects http://clinicaltrials.gov/ct2/show/NCT01560143. [Accessed 1 September 2012]

154. Langebrake C, Bernhardt F, Baehr M, *et al.* Drug dosing and monitoring in obese patients undergoing allogenic stem cell transplantation. Int J Clin Pharm 2011; 33:918–924.

155. Yew WW, Leung CC. Update in tuberculosis 2007. Am J Respir Crit Care Med 2008; 177:479–485.

156. Leung CC, Lam TH, Chan WM, *et al.* Lower risk of tuberculosis in obesity. Arch Intern Med 2007; 167:1297–1304.

157. Geiseler PJ, Manis RD Jr, Maddux MS. Dosage of antituberculous drugs in obese patients. Am Rev Respir Dis 1985; 131:944–946.

158. Viriyayudhakorn S, Thitiarchakul S, Nachaisit S, *et al.* Pharmacokinetics of quinine in obesity. Trans Royal Soc Trop Med Hyg 2000; 94:425–428.

159. Chung-Delgado K, Revilla-Montag A, Guillen-Bravo S, *et al.* Factors associated with anti-tuberculosis medication adverse effects: a case-control study in Lima, Peru. PloS One 2011; 6:e27610. [Epub 2011 Nov 16]

160. Hasenbosch RE, Alffenaar JW, Koopmans SA, *et al.* Ethambutol-induced optical neuropathy: risk of overdosing in obese subjects. Int J Tuberc Lung Dis 2008; 12:967–971.

161. Roberts JA, Kruger P, Paterson DL, Lipman J. Antibiotic resistance: what's dosing got to do with it? Crit Care Med 2008; 36:2433–2440.