Updates on
Antimicrobial Stewardship
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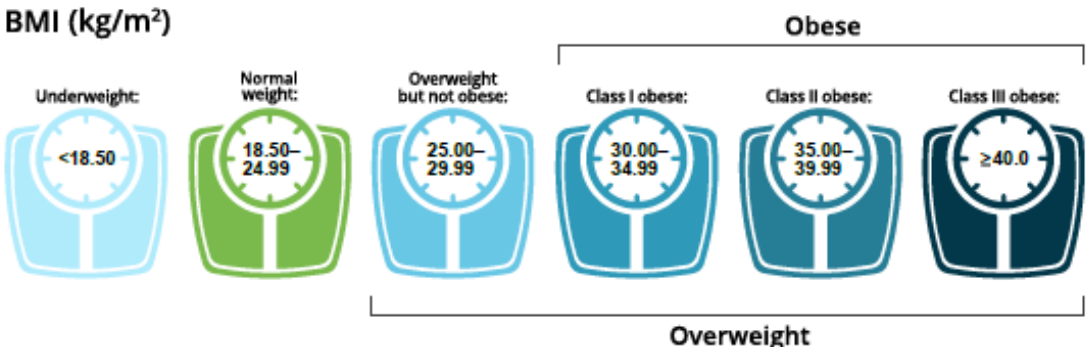
# Dosing of Antimicrobials for Obese Patients

The prevalence of obesity is growing within the Australian population and with it come a number of physiological changes which add complexity to drug dosing. Obese patients have documented differences in pharmacokinetic (PK) and pharmacodynamic (PD) properties compared to normal-weight patients. These impact the clinical success and toxicity of antimicrobials. Physiological changes in obesity mean these individuals have a higher risk of infection-related mortality, increased post-operative surgical site infections, longer intensive care unit stay and higher risk for severe pneumonia and influenza.[1,2]

Obesity is defined as weight ≥ 20% over ideal body weight or a body mass index (BMI) >30.[3, 4]




## Physiological and pharmacokinetic parameters altered in obese patients

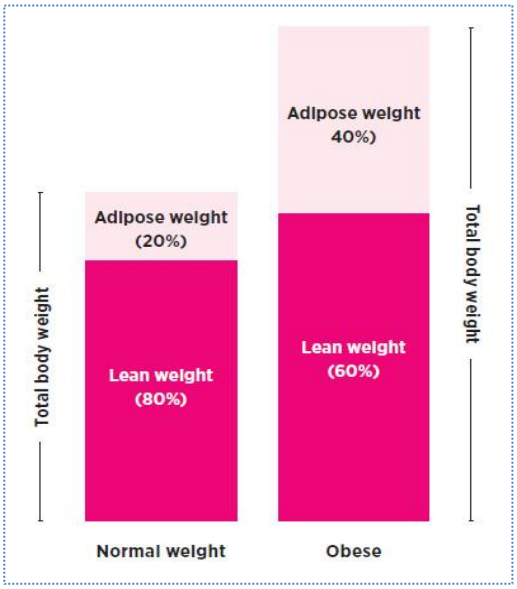
There is limited evidence for dosing of antimicrobials in obesity as obese individuals are often under-represented or excluded in clinical trials.[2] Dosing is often driven by the impact that obesity-related physiological changes may have on the PK/PD properties of the drug (see Issue 2) with the aim to avoid sub-therapeutic concentration's and subsequent treatment failures as well as avoid adverse drug reactions.[1,3]

### Body composition and drug clearance

Body composition changes with increased total body weight. In "normal" weight individuals their total body weight consists of lean tissue and adipose tissue in a ratio of approximately 4:1. In obesity additional adipose tissue is accompanied by an increase in lean tissue but not in the same proportion. In obese individuals this ratio changes to approximately 3:2.[5]

In the example below, the higher estimated lean body weight in Patient B takes into account the expected increase in muscle required to support the extra body weight.

| EXAMPLE | Mr A | Mr B |
|---|---|---|
| Height | 180cm | 180 cm |
| Actual body weight | 85 kg | 150 kg |
| Ideal body weight | 75 kg | 75 kg |
| Lean body weight | 64 kg | 84 kg |




**Body composition in a normal-weight (BMI 25kg/m$^2$) and obese patient (BMI 30 kg/m$^2$)**
*(Source: Australian Prescriber [5])*

Drug clearance correlates to lean rather than adipose weight as adipose tissue has little metabolic activity.[6] As clearance determines an antimicrobial's maintenance dose, a higher dose may be required in patients with a larger lean body weight.

### Distribution

Lipophilic (fat-soluble) drugs distribute more readily into adipose tissue and therefore have a higher volume of distribution (Vd) and lower plasma concentrations compared to less lipophilic drugs.[5] Hence actual body weight should be used when estimating doses of lipophilic antimicrobials to avoid low plasma concentrations.

Hydrophilic (water-soluble) drugs are best dosed using an estimate of 'fat-free' weight such as ideal body weight or adjusted body weight.

## Body weight measurements and where they are useful

Many methods for measuring weight and body size have been proposed for determining antimicrobial dosing in obese patients.[1,2, 6] The most appropriate one to use depends on the PK/PD properties of the antimicrobial. The limitations of these descriptors however should always be considered (see comments in table below) bearing in mind they are estimates and should be used as a guide for dosing strategies.

| Body Weight Descriptor | Equation | Comment |
|---|---|---|
| Actual Body Weight (ABW) | Weight (kg) | More appropriate for lipophilic drugs that distribute into adipose tissue. |
| Body Mass Index (BMI) | Weight (kg) / height $(m)^2$ | Most commonly used body size descriptor to define obesity. Used primarily to estimate dosing of chemotherapy agents. Does not account for varying body compositions. |
| Ideal Body Weight (IBW) | Female: 45.5kg + [0.9 x (height – 152cm)]<br>Male: 50 kg + [0.9 x (height – 152cm)] | Assumes a direct correlation between height and weight. Assumes drug does not distribute into the excess adipose tissue.<br>Used to limit potential for toxicity of narrow therapeutic index drugs. |
| Adjusted Body Weight (AdjBW) | IBW + (Dose Weight Correction Factor x [ABW – IBW]) | Applies a dose weight correction factor (e.g. 0.4 for aminoglycosides) to account for adipose tissue, which does not affect drug clearance.<br>Useful for hydrophilic drugs. |
| Lean Body Weight (LBW) | Female = [9270 x ABW] / [8780 + (244 x BMI)]<br>Male = [9270 x ABW] / [6680 + (216 x BMI)] | Aims to quantify the weight of the muscles and bone while eliminating the weight contributed by the fat component. LBW contributes to approx. 99% of clearance.<br>Complex formula, rarely used. |
| Body Surface Area (BSA) | https://www.eviq.org.au/calculators/BSA | Used mainly for chemotherapy agents. |

For renally excreted antimicrobials, dosage adjustment for renal impairment remains important.[1, 7] Obese patients may have reduced renal clearance of drugs due to a higher incidence of renal impairment associated with co-morbidities such as diabetes and hypertension. Many formulae are available for renal function assessment with the most common one being the Cockcroft-Gault equation (using IBW). However in a study of 2065 obese adults, use of adjusted body weight (with correction factor 0.4) instead of IBW was found to be the most accurate and least biased method for estimating renal function.[8] In critically ill patients an 8- or 24-hour urine collection is recommended to be the most suitable and easily available method.[9]

# Examples of antimicrobials requiring dose adjustment in the obese population

(Note: this list is not exhaustive. Always consider the patient's renal function - consult AMH/TG.)

| Antimicrobial / Class | Distribution | Dosing in Obesity ( if BMI > 30) | Comments | References |
|---|---|---|---|---|
| Aciclovir | Hydrophilic | Use AdjBW | Use of ABW in obese patients may increase the risk of nephrotoxicity. Hydration important, monitor renal function. | 3 |
| Aminoglycosides (gentamicin and tobramycin) | Hydrophilic | Use AdjBW | Increased risk of nephrotoxicity in obese patients. Use TDM to guide ongoing dosing. | 1, 2, 3, 7, 10 |
| Amphotericin Liposomal | Lipophilic | Use ABW | Insufficient data. Monitor for signs of drug toxicity including renal function and electrolytes. | 1, 2, 7 |
| Anidulafungin | Hydrophilic | Consider dose increase in patients weighing > 140kg with invasive fungal infection | Limited data. PK modelling data suggest a 25% increase in loading and maintenance dose. | 1, 3 |
| Ciprofloxacin | Lipophilic | Fixed dose - consider 8-hourly dosing in critically ill patients<br><br>See comments | Insufficient and conflicting data. Poorer tissue perfusion in obese patients. Obese patients are likely to benefit from increased doses. Doses up to 800mg IV twice daily have been used in BMI > 40 (based on 4mg/kg ABW twice daily). Monitor QTc interval closely. | 1, 11 |
| Clindamycin | Lipophilic | Fixed dose – consider 900mg PO/IV 8-hourly for serious infections | Case reports suggest larger doses required to achieve adequate serum concentrations. Doses up to 4800mg (1200mg 6-hourly) have been used in life-threatening infections. | 1, 10, 11, |
| Daptomycin | Hydrophilic core | Use ABW | Fixed dosing suggested in some papers, more data is emerging – watch this space! Monitor CK levels. Hold HMG-CoA reductase inhibitors during treatment. | 3 |
| Fluconazole | Hydrophilic but does not correlate with dosing | Consider weight based dosing using ABW[1] or LBW[7] | Insufficient data. Case reports suggest larger dose required in critically ill obese patients. Wide therapeutic index, toxicity generally low. | 1, 3, 7 |
| Trimethoprim/ Sulfamethoxazole | Lipophilic | Fixed dose (Use ABW for PJP) See comments | Insufficient and conflicting data. Dose depends on indication, severity and pathogen. Refer to TG/AMH. IV: Based on case reports, AdjBW suggested in some papers (2, 8) when using higher doses but insufficient evidence to support this recommendation. ORAL: Consider using the upper end of the dosing range for morbidly obese patients when treating skin/soft tissue infections. | 1, 2, 10, 11 |
| Vancomycin | Hydrophilic but wide Vd in critically ill | Loading dose – use ABW (usually capped at 3 grams). Maintenance dose – consider renal function and TDM | Consider shorter dosing intervals. Use TDM to guide ongoing dosing. Consider site of infection as concentration varies in different bodily fluids. | 1, 3, 11 |
| Voriconazole | Lipophilic | Use AdjBW if BMI > 35 (up to 1000mg/day) | Use TDM to guide ongoing dosing (caution - non-linear kinetics, drug interactions) | 1, 2 |

Abbreviations: ABW = actual body weight; AdjBW = adjusted body weight; CK = creatine kinase; PK = pharmacokinetic; PJP = *Pneumocystis jiroveci* pneumonia; LBW = lean body weight; TG = Therapeutic Guidelines: Antibiotic; AMH = Australian Medicines Handbook; TDM = therapeutic drug monitoring, $V_d$ = Volume of Distribution

There is limited evidence to recommend dose adjustments in obesity for beta-lactam antibiotics, including penicillins and cephalosporins. These are hydrophilic drugs and are not usually dosed according to weight. Most of the literature suggests dosing at the upper end of the dosing ranges especially if treating more serious infections [2, 10, 11,].

## Antimicrobials for surgical prophylaxis

Obesity has been identified as a risk factor for post-operative wound infections likely in part to inadequate antimicrobial dosing.[1] The efficacy of antimicrobials in surgical prophylaxis is dependent on the drug reaching sufficient concentrations at the surgical site and surrounding adipose tissue. SAAGAR surgical antibiotic prophylaxis guidelines recommend:

**Cefazolin:** 2 grams IV for patients weighing < 120kg or 3 grams for patients weighing > 120kg

**Vancomycin**: 1 gram IV for patients weighing < 80kg or 1.5 grams for patients weighing > 80kg

## What does this mean clinically?

There are many potentially confounding factors when assessing the literature on dosing of antimicrobials in obesity. It is not known whether results from healthy obese volunteers can be extrapolated to the sick obese population or the critically ill patient with renal impairment, cancer or diabetes.

> ***Always consider the location and severity of the infection, type of pathogen and MIC, patient characteristics (degree of obesity, age, mobility and co-morbidities) and PK/PD indices of the drug when considering dosing of antimicrobials in obese patients. Where possible, use TDM to guide monitoring, especially in critically ill patients. Above all, monitor clinical and microbiological response.***

**References:**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**Produced by the Central Adelaide Local Health Network (CALHN) Antimicrobial Stewardship Committee**

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