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## How should antibiotics be dosed in obesity?

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Before using this Q&A, read the disclaimer at <https://www.sps.nhs.uk/articles/about-ukmi-medicines-gas/> Date prepared: 6<sup>th</sup> November 2013

A review of the evidence was carried out in 2016 using the same literature search strategy by the Association of Scottish Antimicrobial Pharmacists and [Healthcare Improvement Scotland](#).

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### Background

The National Institute for Health and Care Excellence classify degrees of obesity according to a person's body mass index (BMI). Adults with a BMI greater than 30 kg/m<sup>2</sup> are defined as obese (1). Obesity results in physiological changes that can affect the volume of distribution and the clearance of many antibiotics (2). The extent of these changes is variable and depends upon patient characteristics (e.g. degree of obesity, underlying organ function) and the chemical properties of the antibiotic (3). Antibiotic concentrations achieved with conventional dosages may therefore differ significantly between obese and non-obese patients (3).

The dosing of antibiotic agents in obese patients is challenging due to the inability to utilise therapeutic drug monitoring for several agents and because of the importance of early appropriate therapy, particularly in the critically ill (4). Appropriate dosing as surgical prophylaxis is also important to prevent surgical site infections. Obese patients are generally underrepresented in clinical trials and therefore data on appropriate dosing and effectiveness is limited in this patient group (5). This Q&A aims to summarise the limited evidence available for dosing antibiotic agents in obese adult patients. The United Kingdom Clinical Pharmacy Association (UKCPA) produced guidance regarding drug dosing in extremes of body weight in critically ill patients, which provided some useful information about the dosing of certain antibiotics in obesity which is available to members via their website (6).

### Pharmacokinetic Parameters in Obesity

#### Absorption

Most published studies so far show that drug absorption does not differ between obese and non-obese patients, but this may be a reflection of the limited number of studies (7).

#### Volume of Distribution (Vd) (determines loading dose)

Volume of distribution is calculated by dividing the dose given by the plasma concentration. A high Vd shows that the drug is extensively distributed into tissue and a low Vd shows it is concentrated in the plasma (8). The extent of change in Vd in obese patients depends on the physiochemical properties of a drug and on other characteristics such as the level of protein binding and the degree of obesity (7). The current level of understanding of the comprehensive effects of obesity on Vd is limited and the data that are available are highly drug specific (7). Calculating the Vd can help determine the appropriate loading and maintenance doses for obese patients (3).

#### Clearance

**Metabolism:** Obesity has been linked to non-alcoholic fatty liver disease, and the accumulation of fat in the liver of obese individuals may alter hepatic blood flow which might in turn have an impact on hepatic drug clearance (9). There is limited data to suggest that obesity increases hepatic clearance of some drugs by enhancing glucuronidation and sulfation (5, 7). There is also limited evidence of an increase in cytochrome P450 (CYP) 2E1 activity with obesity (9). As few drugs are substrates of CYP 2E1, the clinical significance is probably minimal (9).

**Renal Elimination:** The effect of obesity on renal clearance is not clear. Studies of creatinine clearance (CrCl), used to estimate glomerular filtration rate (GFR) have found increased, decreased or similar GFR measurements in obese and non-obese people (9). Hanley *et al.* suggest that these results probably reflect the imprecision of CrCl as a measure of GFR (9).

**Measuring renal function in obesity:** Since many antibiotics are renally eliminated, an estimate of GFR is necessary to determine the dosage required. The MDRD formula and the CKD-EPI equations are normalised to a standard body surface area (BSA) of 1.73m<sup>2</sup>. Therefore there is a potential for under-dosing patients in patients with a BSA greater than 1.73m<sup>2</sup>. (10,11)

The British National Formulary (BNF) therefore advises that in patients with a BMI of greater than 30kg/m<sup>2</sup> absolute GFR or CrCl calculated from the Cockcroft and Gault formula should be used to adjust drug dosages (11). The Cockcroft-Gault equation uses total body weight as part of the calculation, which overestimates renal function in obese patients and may potentially result in a drug overdose (10,12). The controversy of which measure of weight should be used in the Cockcroft-Gault equation remains unresolved and there is no consensus on which weight should be used (11). Some authorities suggest using ideal body weight (IBW), but in general this has been shown to underestimate CrCl (3,11). Some studies suggest that adjusted body weight (AdjBW) with a correction factor of 0.4 is most accurate, whilst other studies and the UKCPA suggest the use of lean body weight. Brown et al propose that when Cockcroft-Gault is used for drug dosing purposes, a functional range of CrCl should be applied, with the use of IBW in the equation to determine the lower boundary and total body weight (TBW) to determine the upper boundary (6,11). The Salazar-Corcoran formula has been shown to result in more accurate predictions of CrCl in obese patients, in two retrospective studies (2,3). However, prospective validation in a large sample of obese patients has not occurred (2). Direct measurement of CrCl may be required in critically ill obese patients, as the accuracy of CrCl equations in this setting is unknown but is likely to be highly variable (2)

### Which measure of weight should be used?

One concern when dosing antibiotics in obese patients is how to dose agents that rely on weight-based dosing. For most antibiotic agents, the interaction between drug pharmacokinetics and body-size indices is complex, and there is a lack of consensus on a single size descriptor that should be used for dosage calculation (2). Several relevant indices exist and are given in Table 1. Total Body Weight (TBW) is sometimes referred to in the literature as Actual Body Weight (ABW), which can cause confusion with Adjusted Body Weight (AdjBW). Where data exists regarding the most accurate measure of weight to use for specific agents, it is given in this Q&A in Table 2 or in the text below.

**Table 1: Common measures of weight used when dosing antibiotics in obesity**

Weight (kg)	How/What to measure
<b>Total Body Weight (TBW)</b>	Weight in kg
<b>Body Mass Index (BMI)<sup>1</sup></b>	TBW(kg)/ (height (m) x height (m))
<b>Ideal Body Weight (IBW)<sup>12</sup></b>	Height in feet and inches. IBW = 2.3kg for each inch over 5 feet (+ (50kg if male or 45kg if female)
<b>Lean Body Weight (LBW) (Janmahasatian)<sup>8</sup></b>	Males = (9270 x TBW[kg])/ [6680 +(216 x BMI)] Females = (9270 x TBW[kg])/ [8780+(244 x BMI)]
<b>Adjusted Body Weight (AdjBW)<sup>14</sup></b>	IBW + Adjustment Factor ( this is variable but 0.4 is commonly used) x (TBW-IBW)

### Review of evidence 2016

Limited new evidence was found but details have been added to the relevant sections - see table 2 and following narrative. New information has been added to the following sections:

- Aminoglycosides
- Beta lactams
- Linezolid
- Vancomycin

## Answer

### Dosing recommendations for selected antibiotics in obesity

A limited number of antibiotics have been studied in patients with obesity. This Q&A is not intended as a comprehensive prescribing guide, does not cover all antibiotics but attempts to summarise the available evidence for antibiotic dosing in obesity.

Table 2 provides a summary of the evidence and the following narrative text provides further details of the literature and manufacturers recommendations for antibiotics in obesity.

**Table 2. Literature and Manufacturers Recommendations for Dosing of Selected Antibiotics in Obesity**

Antibiotic agent	Weight used for dosing	Manufacturers guidance	Recommendations from literature (refer to the text below this table and the references cited for further detailed guidance)
<b>Aminoglycosides</b> <sup>2,3,11,13,14,15,16,17,18,19, 20,21,22,23,124</sup>			
Amikacin	TBW or AdjBW	No specific advice provided	The majority of the evidence indicates initial doses should be based on AdjBW using an adjustment factor of 0.4 with an interval appropriate for estimated renal function. . Subsequent doses should be based on serum concentrations. But the BNF advises that IBW should be used to calculate doses with close monitoring of the serum concentrations. In critically ill patients, consider basing the initial dose on TBW in order to insure adequate serum concentrations. However, preliminary evidence suggests nephrotoxicity associated with aminoglycosides may be more common in obese patients. A recent review in critically ill obese patients concluded that current practice of adjusting dosing weight for aminoglycosides in obese patients should be maintained and highlighted the importance of frequent serum monitoring.
Gentamicin	TBW or AdjBW	Serum concentrations should be closely monitored and a reduction in dose should be considered.	
Tobramycin	TBW or AdjBW or LBW	Dosing in mg/kg should be based on LBW plus 40% of the excess	
<b>Beta-Lactams</b>			
Penicillins <sup>6,24,25, 26,27,28,29,30,31,32,33, 34,35,36,37</sup>	Standard dose	No specific advice provided.	Data are limited. UKCPA suggest dosing in critically ill obese patients should be at the upper end of the recommended treatment ranges.
Piperacillin tazobactam <sup>103, 125,126,127</sup>	Standard dose	No specific advice provided.	Data are limited. Extended infusions (over 4 hours) may be considered.
Cephalosporins <sup>6,38,39,40,41,42,43,44, 45,46,47,48,49,50,51,52, 53,54,55,56,57,58, 128,129</sup>	Standard dose	No specific advice provided.	Higher doses may be required for surgical prophylaxis in obese patients. One review and UKCPA guidance suggest dosing for cephalosporins in critically ill obese patients should be at the upper end of the recommended treatment ranges. Two RCT of using cefazolin (standard 2g dose versus 3g dose) as surgical prophylaxis in obese C-section patients concluded that a dose increase is not required but some expert opinion papers suggest that dose increase required in patients above 100kg.

<b>Carbapenems</b>			
Ertapenem <sup>2,59,60,61,103,130</sup>	Standard dose	No specific advice provided.	There are conflicting data regarding its efficacy for surgical prophylaxis- please refer to text. Higher dose than the standard 1g dose may be required for more resistant bacteria, particularly in morbidly obese patients with normal renal function. For certain organisms with MIC90s above 0.5µg/ml the standard 1g dose may not be effective.
Meropenem <sup>8,62,63,64,65,66,126,131,132</sup>	Standard dose	No specific advice provided.	Pharmacokinetic data is conflicting but several studies suggest standard dosing is adequate. Case reports have reported successful outcomes with high dose prolonged or continuous infusions in critically ill patients.
Doripenem <sup>67,68,130</sup>	Standard dose	No specific advice provided.	Limited data show larger doses and extended infusions may be beneficial in critically ill obese patients. In non-critically ill obese patients, standard dosing is acceptable.
<b>Quinolones</b>			
Ciprofloxacin <sup>69,70,71,72</sup>	Refer to text	No specific advice provided.	Conflicting data regarding pharmacokinetics in obesity. Dose adjustment may be required. Doses of 800mg IV 12 hourly have been used in severe morbid obesity.
Levofloxacin <sup>73,74,75</sup>	Standard dose	No specific advice provided.	Evidence is too limited to guide dosage recommendations in obese patients - further research is required.
Moxifloxacin <sup>76,77</sup>	Standard dose	No specific advice provided.	Limited data in obesity.
<b>Miscellaneous</b>			
Clindamycin <sup>78,79</sup>	Standard dose	No specific advice provided.	Preliminary evidence suggests higher doses required. Doses up to 4.8g daily have been used.
Colistimethate sodium <sup>80,81,82,83</sup>	IBW	Dosing of the infusion should be based on IBW. Standard dosing of the nebuliser solution can be used.	Excessive dosing as a result of using TBW instead of IBW has been associated with higher rates of nephrotoxicity in obese patients.
Daptomycin <sup>84,85</sup>	TBW	Dosing is based on TBW. Relative to non-obese subjects, systemic exposure was about 28% higher in patients with a BMI of 25-40 kg/m <sup>2</sup> and 42% higher in patients with a	Exposure to daptomycin in obese patients was increased in a small study, but was within the range of safety and tolerated well. The authors conclude daptomycin may be dosed on TBW and no dosage adjustment is required on the basis of obesity alone.

		BMI of > 40 kg/m <sup>2</sup> . However, no dose adjustment is considered to be necessary based on obesity alone. There is limited information on the safety and efficacy of daptomycin in the very obese and so caution is recommended.	
Linezolid <sup>86,87, 133, 134</sup>	Standard dose	No specific advice provided.	Limited data from two trials suggest no dose increase required in patients <150kg.
Teicoplanin <sup>11,88,89</sup>	Standard dose or TBW	Dose by weight in patients weighing >85kg and for some indications. No maximum dose stated.	No data found in obesity. Note the BNF advises it should be dosed by body weight (weight used for dosing not specified) in patients >70kg.
Vancomycin <sup>8,90, 91,92,93,94,95,96,135</sup>	TBW or AdjBW	The dose should be individually adapted according to weight, age and renal function. Modification of the usual daily doses may be required in obesity. Guidance on how to do this is not given	There are conflicting data regarding whether the loading dose should be based on TBW or AdjBW. Administration intervals should be based on estimated CrCl or standard nomograms. Monitoring of serum vancomycin concentrations is essential and doses should be adjusted accordingly. Shorter dosage intervals may be needed in obese patients with normal renal function. Studies have shown an increased risk of nephrotoxicity in patients >101kg or receiving doses of >4g in 24 hours. A study in surgical patients undergoing bariatric surgery showed increased rates of surgical site infection in patients receiving less than 2g vancomycin as a single agent for surgical prophylaxis.

### Surgical prophylaxis

Obesity is a risk factor for surgical site infection; the risk persists despite antibiotic prophylaxis in these patients (8,97). Several studies have evaluated the use of prophylactic cefazolin in morbidly obese patients and have shown that lower serum and tissue antibiotic concentrations occur, or that higher doses of the antibiotic are required to ensure adequate serum and tissue concentrations, in obese patients (3,98,99,100). However there is inconclusive evidence of a need for a higher dose to prevent surgical site infections. Reduced tissue penetration of antibiotics leading to subtherapeutic tissue concentrations, has been associated with an increased rate of surgical site infections (8).

There are conflicting data regarding the efficacy of ertapenem for surgical prophylaxis in obese patients. In one study in 219 surgical patients with complicated intra-abdominal infections ertapenem 1g daily had nearly identical cure rates in patients with BMI <30 kg/m<sup>2</sup> and ≥30 kg/m<sup>2</sup>. However, the confidence interval (CI) was wide (80% versus 81%, CI -22% to 19%) (101). Conversely in a post-hoc analysis of a multicentre randomised, double blind trial of 1002 patients undergoing elective colorectal surgery, patients with a BMI ≥30 kg/m<sup>2</sup> receiving prophylaxis with ertapenem 1g had higher rates of surgical site infections than patients with a BMI <30 kg/m<sup>2</sup> (26.7% versus 12.7%) (102). These studies suggest larger doses of certain prophylactic antibiotics may be needed in obese patients undergoing surgery (3). Further studies are needed to evaluate clinical outcomes and to establish which antibiotics require dose adjustment to achieve adequate tissue concentrations. Joint clinical practice guidelines for antimicrobial prophylaxis in surgery produced by specialist bodies in America state conclusive recommendations for weight-based dosing for antimicrobial prophylaxis in obese patients cannot be made due to a lack of supporting data (97).

### Aminoglycosides

The use of TBW to determine the daily dose of an aminoglycoside can result in higher than desirable serum concentrations, while doses based on IBW can lead to subtherapeutic serum concentrations (2,103). The British National Formulary (BNF) advises that IBW is used to calculate the doses of aminoglycosides in obese patients with close monitoring of the serum concentrations (11). However several authors and studies indicate initial aminoglycoside doses should be based on AdjBW, with an interval appropriate for the estimated renal function. Adjustment factors have been variable but 0.4 is commonly accepted, correlating with 40% of excess weight. Subsequent doses should be tailored based on serum concentrations (2, 3,13,14,15,16,17, 18). Some authors also suggest AdjBW is substituted in the standard Cockcroft-Gault equation to estimate CrCl in this population (3,16). But some obese patients may have sub-therapeutic serum aminoglycoside levels if AdjBW is used. Therefore, in critically ill patients it may be desirable to base the initial dose on TBW in order to ensure adequate serum concentrations (20).

Preliminary evidence suggests nephrotoxicity associated with aminoglycosides is more common in obese patients despite serum concentrations being maintained within the recommended range (19,103). Clinicians should be aware that obesity may increase the risk of nephrotoxicity even when careful dosage adjustment results in equivalent aminoglycoside exposure (21).

A literature review (124), which included 33 articles, cases and letters on pharmacokinetic changes and dose modifications in critically ill obese patients concluded that the current practice of adjusting dosing weight for aminoglycosides in obese patients should be maintained. Regular serum monitoring is particularly important in obese patients who are critically ill.

### Beta-Lactams

A case control study compared serum concentrations of broad spectrum beta-lactams (ceftazidime or cefepime, piperacillin-tazobactam, or meropenem) in critically ill obese patients to those in non-obese critically ill patients. No major differences between obese and non-obese patients were found, except in the sub-group of patients treated with meropenem, not receiving continuous renal replacement therapy, where serum concentrations were lower in the obese cohort. Sepsis appeared to alter the pharmacokinetics parameters more than obesity. The study attempted to validate a "correction dosage" formula for AdjBW, based on a correction factor of 0.3. This induced small changes in serum drug concentrations but had no impact on the adequacy of treatment. The authors recommend that until results from large prospective pharmacokinetic studies are available, therapeutic drug monitoring should be routinely performed in obese, critically ill patients (64). However this is not widely available in the UK for beta-lactams. Details of the national TDM service in Bristol are available at <http://www.bcare.nbt.nhs.uk/wp-content/uploads/Antibiotic-Assay-Guide-20151.pdf>

### Penicillins

There are limited data regarding the dosing of penicillins in obesity. A case report demonstrated altered pharmacokinetic parameters when piperacillin/tazobactam 3.375g was given every four hours to a morbidly obese patient (167kg) with recurrent cellulitis. The percentage of time above the

minimum inhibitory concentration (MIC) was calculated and levels remained above an MIC of 4mg/L at all times and above an MIC of 8mg/L 90.9% of the time. The percentage of time above higher MICs was lower, which could reduce its efficacy when treating patients with high MIC target organisms (104). Another case reported in a morbidly obese patient showed that appropriate pharmacokinetic and pharmacodynamic parameters were obtained in a morbidly obese patient (220kg), using piperacillin/tazobactam 4.5g six hourly. However, the authors state extended infusions may allow pharmacokinetic/pharmacodynamic targets to be reached more easily in morbidly obese patients infected with more resistant strains (105).

In surgical patients with complicated intra-abdominal infection, piperacillin/tazobactam 3.375g given every six hours showed lower cure rates in patients with a BMI of 30 or more, although this was non-significant (86% versus 65%; 21% difference; 95% CI -1 to 47%). The authors state the difference may be related to etiology of infection and gender (101). Further studies are needed to determine whether increased doses, more frequent dosing intervals or continuous infusions of piperacillin/tazobactam are required for the treatment of serious infections in obese patients (104). In a pharmacokinetic study of piperacillin/tazobactam levels in critically ill patients, trough concentrations were lower in obese patients compared to non-obese patients. No significant differences were found between total daily dose, duration of infusion or level of renal function between obese and non-obese patients. Clinical outcome was not assessed (126). Two studies used Monte Carlo simulation in obese and non-obese patients. Chung et al noted faster clearance and larger volume of distribution for piperacillin/tazobactam in obese patients. The authors note that a dosing regimen of 4.5g every 8 hours infused over 4 hours in obese patients achieves PTA (probability of target attainment) > 90% for organisms with MIC of  $\leq 16\text{mg/l}$  (127). In another smaller study, no difference was noted between the 4 hour and 30 minute infusion time in obese critically ill patients (125). Clinical outcome was not assessed in either of these two studies.

In addition therapeutic drug monitoring could be used to ensure efficacy. UKCPA guidance suggests doses of piperacillin/tazobactam 4.5g every six hours in obese critically ill patients, dependent on renal function (6).

One review and the UKCPA guidance suggest dosing for penicillins in critically ill obese patients should be at the upper end of the recommended treatment ranges, taking into account the patient's renal function, particularly in morbidly obese patients with more severe infections (6,38).

### Cephalosporins

As discussed above, higher doses of cephalosporins may be required for surgical prophylaxis in obese patients, but it is difficult to make absolute dosing recommendations. A small study assessed the pharmacokinetic parameters of cefotaxime sodium (1g) in 12 normal weight and 11 obese patients (190-210% IBW). The authors concluded that the difference between total body clearance in normal weight compared with obese patients was not statistically significant. They advise that dose adjustment for body weight in obese patients is not needed, but a dose adjustment on the basis of body surface area is reasonable (106).

One review and UKCPA guidance suggest dosing for cephalosporins in critically ill obese patients should be at the upper end of the recommended treatment ranges, taking into account the patient's renal and hepatic function (6,38).

One RCT in 57 patients (128) found no significant difference between adipose tissue concentrations in obese C-section patients receiving 2g or 3 g cefazolin. A pharmacokinetic study of cefazolin in similar patient group found higher serum levels in patients receiving a 3g dose than a 2g dose but the MIC was exceeded for all patients. (129) This study concluded that a higher dose may be considered for patients with resistant bacteria MIC >8mg/L otherwise a dose of 2 g is sufficient.

### Carbapenems

The pharmacokinetics and pharmacodynamics of ertapenem 1g were investigated in a small study of 30 healthy volunteers in three weight categories: normal weight (mean BMI 22.5kg/m<sup>2</sup>), class I-II obesity (mean BMI 33.4 kg/m<sup>2</sup>) and class III obesity (mean BMI 43.4 kg/m<sup>2</sup>) (59). Lower concentrations were achieved in all classes of obese patients with bacteriostatic effects only for

bacteria with an MIC  $\leq 0.25$  micrograms/mL, compared with an MIC  $\leq 0.5$  micrograms/mL in normal weight patients (8,61). This suggests that obesity impairs the ability to achieve the desired drug concentration (2). Achievement of adequate exposure for all weights was difficult for MICs in excess of 0.25 to 0.5 micrograms/mL. However, clearance and protein binding may be reduced in patients compared with healthy volunteers, therefore drug concentrations may be higher in the clinical setting. Nevertheless, doses above 1g daily of ertapenem may be required for more resistant bacteria, particularly in morbidly obese patients with normal renal function (2, 61). In contrast, a study investigating use of standard dose ertapenem as surgical prophylaxis for obesity surgery noted plasma levels with effective anti-bacterial activity against a wide range of gram negative pathogens. No activity was demonstrated against ESBL producers and other MDR gram negatives (*Pseudomonas*, *Burkholderia*), MRSA and coagulase negative staphylococci. In the case group, one superficial surgical site infection was diagnosed compared to 6 in the control group (130). For treatment of intra-abdominal infection, standard dose of ertapenem resulted in similar cure rate in both obese and non-obese patients (103). The UKCPA guidance in critically ill obese patients does not advise dosage adjustments outside the licensed dose but advises the MIC<sub>90s</sub> > 0.25 µg/ml for certain organisms are taken into account when prescribing ertapenem (6). The pharmacokinetics of meropenem have also been shown to be altered in obese patients (2,107). Please refer to the section beta-lactams for information about lower meropenem concentrations found in obese patients. Two case studies reported successful outcomes with high dose or continuous infusions of meropenem (3g every six hours as a 3-hour extended infusion and 2g daily as a continuous infusion) together with therapeutic drug monitoring in obese patients (8, 65,66). In contrast, two studies recommend standard dosing of meropenem and doripenem in obese subjects. Trough meropenem levels were measured in critically ill obese and non-obese patients. Patients received 2 to 3 grams per day given in 2 to 3 divided doses and similar trough levels were seen in both patient groups (probability of attaining 40% of dosing interval above the MIC was 84%). This study did not assess clinical outcome (126). A small pharmacokinetic study looked at optimal dosing of doripenem and meropenem in obese patients for a variety of infections. Standard doses of doripenem and meropenem are predicted to achieve acceptable pharmacokinetic parameters against susceptible *Enterobacteriaceae* and *P. aeruginosa* isolates. For more resistant isolates doses of 1g infused over 4 hours (doripenem) and 1g over 3 hours (meropenem) given every 8 hours may be considered (131). A small pharmacokinetic study of 5 obese patients also recommends using standard doses of meropenem, given over 3 hours to achieve the preferred 40% of dosing interval above the MIC for the organism (132). A small study in 31 critically ill patients showed that larger doses of doripenem (1-2 g 8-hourly depending on renal function) were required to achieve therapeutic levels. It also demonstrated that extended infusion (over 4 hours versus 1 hour) significantly improves exposure in obese patients (67).

## Quinolones

### Ciprofloxacin

The pharmacokinetics of 400mg intravenous (IV) ciprofloxacin was compared in 17 obese male patients and 11 controls. This found ciprofloxacin total clearance was significantly increased and the volume of distribution was significantly larger in obese patients. The authors concluded that ciprofloxacin dose should be based on adjusted body weight using an adjustment factor of 0.45 to take account of excess weight (108). Another study investigated the pharmacokinetics of 2.85mg/kg TBW in 12 obese and 12 non-obese patients. In contrast to the previous study a decreased volume of distribution and drug clearance was seen in the obese patients. Tissue penetration was significantly lower in the obese patients and the authors concluded that the dose in obese patients should be based on TBW to achieve adequate tissue levels, even though the higher plasma levels may increase the risk of side effects (109).

In two case reports a dose of 800mg IV 12 hourly was given to severely morbidly obese patients, with microbiological success (71, 72). One of these patients was receiving continuous venovenous haemodiafiltration (72).

### **Levofloxacin**

A small study in 15 patients investigated the pharmacokinetics of a single 750mg IV dose of levofloxacin in both hospitalised and ambulatory obese patients (mean BMI 50 kg/m<sup>2</sup>). The peak concentrations were similar in obese and normal-weight patients but there was marked variability in levofloxacin clearance in obese patients. The authors noted that obese patients with normal renal function may clear levofloxacin more efficiently than normal-weight individuals, particularly in the absence of acute illness. Further research is required to investigate this and to identify which patients may require higher levofloxacin doses (73).

A case in a morbidly obese patient (179kg) reported the use of weight-adjusted dosing of IV levofloxacin 750mg twelve hourly (4mg/kg every 12 hours). This resulted in double the adult exposure compared with a standard dose of 750mg per day in non-obese healthy volunteers. This questions the need for higher weight-adjusted doses of levofloxacin in obese patients. The authors suggest that due to the longer half-life observed it would be suitable to administer an initial loading dose, followed by doses given less frequently than 12 hourly in order to avoid further drug accumulation. However, confirmation is required in studies involving larger groups of patients (110).

### **Moxifloxacin**

In a small open-label, non-randomised study the pharmacokinetics of moxifloxacin 400mg daily, in 12 morbidly obese patients, was compared to historic controls. The plasma pharmacokinetics were comparable but concentrations in the subcutaneous fat were only one-quarter of those in the plasma. The authors conclude that no dose adjustment is required in the morbidly obese; however this conclusion may depend on the location of the infection (8,111).

### **Miscellaneous**

#### **Clindamycin**

The pharmacokinetics of clindamycin were studied in a retrospective study in 50 patients ranging in body weight from 23 to 133kg. Patients received 600mg clindamycin orally or intravenously (IV) three times a day for the treatment of bone and joint infections, except for one patient who received 600mg four times a day and two patients who received 600mg once daily. Clindamycin clearance increased with body weight and the authors concluded that 600mg three times daily seems to be effective in patients up to 75kg but the dose should be raised to 900mg three times daily thereafter. They state these assumptions should be prospectively confirmed (112). Weight over 100Kg and BMI ≥40 were identified as independent risk factors for clinical failure with clindamycin (dose not stated in abstract) in a retrospective cohort study in patients hospitalised with cellulitis. A subgroup analysis demonstrated that morbidly obese patients were at higher risk for clinical failure if they were discharged on a low dose of clindamycin or trimethoprim/sulfamethoxazole (113). UKCPA guidance for clindamycin in critically ill obese patients suggests doses up to 4.8g daily in divided doses (as per SPC) may be given (6).

#### **Daptomycin**

The pharmacokinetics of daptomycin (4mg/kg TBW) were studied in 24 adult volunteers who were moderately obese (BMI 25-39.9kg/m<sup>2</sup>) or morbidly obese (BMI ≥40kg/m<sup>2</sup>), and a matched (gender, age, renal function) nonobese control group. The TBW-normalised drug clearance and volume of distribution were significantly ( $p < 0.05$ ) lower in the morbidly obese group compared with the nonobese group. Exposure to daptomycin in obese subjects (C<sub>max</sub>, AUC) was increased 25% and 30% respectively, compared to nonobese matched controls, which the authors state is within the range that was previously determined to be safe and well tolerated. Despite these differences, the authors conclude that daptomycin may be dosed based on TBW and no adjustment to dosage is necessary based on obesity (85). UKCPA guidance for daptomycin in critically ill obese patients endorse dosing based on TBW together with monitoring for toxicity (6).

#### **Linezolid**

Unpublished data provided by the manufacturers of a pooled analysis of three, prospective randomised Phase IIIb/IV clinical trials in patients treated with linezolid for complicated skin and soft tissue infections, showed similar clinical outcomes across all weight quartiles (patients weighting up to 159 kg were included) (87). In addition, analysis of data from a prospective, double-blind randomised controlled clinical trial (available only as an abstract) of patients with nosocomial pneumonia due to methicillin-resistant staphylococcus aureus (MRSA), showed that the efficacy of linezolid 600mg IV every 12 hours was maintained regardless of body weight, and was consistently numerically higher than weight-based vancomycin dosing (15mg/kg 12 hourly). Patients were stratified into four weight quartiles (Quartile 1 <63kg, Quartile 2 >64 to ≤ 74kg, Quartile 3 >74 to ≤88kg, Quartile 4 >88kg) (114). A higher clinical success rate was also shown in obese patients on linezolid compared with vancomycin in an unpublished study provided by the manufacturers. This was a retrospective cohort study on national Veterans Affairs patients with MRSA pneumonia, presented only as a poster (89).

A retrospective chart review, published only as an abstract, of 35 obese patients (>120kg), found a success rate, defined as cure and improved, of 71.4%. The most common linezolid dosing regimen used was 600mg IV/PO every 8 hours: larger than the recommended doses of linezolid (600mg IV/PO every 12 hours). The authors concluded that empiric linezolid dose optimization is required when treating obese patients (115).

A study in 7 obese patients (>50% over their IBW), receiving oral linezolid 600mg every 12 hours for the treatment of cellulitis, showed lower serum concentrations, compared with those reported in historical normal-weight healthy volunteers. Prolonged serum inhibitory activity was still provided against common pathogens, but bactericidal activity was not demonstrated with most isolates. Limited sampling was performed in this small study, so caution is required in interpreting these results. A clinical cure was exhibited in all the patients in this study and the results suggest that standard doses (600mg every 12 hours) can be used in the treatment of selected pathogens in obese patients. However, the authors expressed concern that if an obese patient was infected with a less susceptible strain (MIC≥4.0micrograms/mL) coverage may not be provided (116).

A further study in 20 adult volunteers with BMIs of 30-54.9kg/m<sup>2</sup> assessed the pharmacokinetics of 5 doses of linezolid IV 600mg every 12 hours. This concluded that linezolid exposure in obese patients was similar overall to that of non-obese patients, implying that dosage adjustments based on BMI alone are not required, and standard doses may be used in patients weighing up to approximately 150kg. However, a correlation between volume of distribution and several body weight descriptors was observed, which the authors state suggest may alter concentrations in patients weighing more than 143kg (117). A small study in 20 healthy volunteers, assigned to low weight (50-55kg) and high weight (≥80kg) groups evaluated the pharmacokinetics of a single IV fixed dose (600mg) compared with weight-adjusted (10mg/kg) dose of linezolid. The findings suggest that a weight-adjusted, 10mg/kg regimen may be more appropriate than fixed doses for patients of different body weight; however this would need to be confirmed in larger studies in appropriate patient groups (118).

Two cases studies in obese patients (BMIs 86 and 37kg/m<sup>2</sup>) receiving linezolid 600mg every 12 hour (orally or IV) showed levels close to or below the minimum inhibitory concentration at which 90% of strains are inhibited, but showed successful treatment outcomes (119,120).

Intermittent versus continuous infusions of linezolid were compared in a small study in 22 critically ill obese patients (BMI ≥ 30) with ventilator associated pneumonia. Continuous infusion increased the time above MIC but this advantage was diminished with difficult to treat pathogens (MIC = 4 mg/L). (133)

A small pharmacokinetic study in 20 healthy volunteers weighing 78.2 – 143.1 kg showed a causal correlation observed between weight and Volume of distribution but no significant difference observed for AUC or Clearance in patients with increasing weight (134)

### Vancomycin

A multicentre study indicated that fixed doses of 1g twice a day achieved satisfactory initial dosing in just 27.7% of obese patients and only 0.6% of obese patients received adequate doses of at least 15mg/kg per dose recommended by several Infectious Diseases Society of America guidelines (121). There are conflicting data regarding the most appropriate weight to use when determining

vancomycin dosing in obese patients (91). Several small pharmacokinetic studies have concluded that TBW is the preferred method to calculate the initial dose of vancomycin in obese patients, with subsequent adjustment based on serum vancomycin concentrations (SVCs) (92, 93,94). However, a more recent study concluded AdjBW (with an adjustment factor of 0.4) in the Leonard and Boro vancomycin clearance calculation (0.9x CrCl, with AdjBW used in the Cockcroft-Gault equation) was superior to TBW when estimating vancomycin clearance in obese patients (91). However, this was a retrospective study that compared which measure of weight predicted SVCs closest to measured SVCs and it is not clear if these differences are clinically significant.

American consensus guidelines recommend that initial doses for all patients including the obese should be based on TBW and then adjusted based on SVCs (95). Most published data support the use of the Cockcroft-Gault equation with TBW to calculate CrCl and vancomycin clearance in non-obese patients. However, further studies are needed to determine which weight and equations should be used to calculate CrCl in obese patients (8, 96). Studies have shown an increased risk of nephrotoxicity in patients >101kg or receiving doses of >4g in 24 hours (8).

In a multi-centre cohort study of over 2000 patients with BMI >35 kg/m<sup>2</sup> undergoing bariatric surgery surgical site infection rates were higher in patients receiving vancomycin at doses below 2g as the single prophylactic agent. The authors concluded that if vancomycin is used for surgical prophylaxis, the dose (15mg/kg) should be calculated using actual bodyweight rather than lean bodyweight and a second agent with gram-negative cover should also be considered in this patient population (135).

## Summary

- Obesity results in physiological changes that can affect the volume of distribution and the clearance of many antibiotics. The extent of these changes is variable and depends upon patient characteristics (e.g. degree of obesity, underlying organ function) and the chemical properties of the antibiotic. Antibiotic concentrations achieved with conventional dosages may therefore differ significantly between obese and non-obese patients.
- Manufacturers do not routinely provide guidance on the dosing of drugs in obesity.
- Data and guidance regarding the pharmacokinetics, pharmacodynamics and dosing recommendations of most antibiotics in obesity is limited, making specific dose recommendations for obese patients difficult.
- There is relatively more guidance available for the dosing of aminoglycosides and vancomycin.
- This Q&A summarises the available evidence for the following antibiotics: aminoglycosides (amikacin, gentamicin and tobramycin), beta-lactams (penicillins, cephalosporins and carbapenems), quinolones (ciprofloxacin, levofloxacin and moxifloxacin), colistimethate sodium, clindamycin, daptomycin, linezolid, teicoplanin and vancomycin.
- Limited data suggest larger doses of certain antibiotics including cephalosporins may be required for surgical prophylaxis in obese patients.
- The available data needs to be interpreted with caution. For example, it is not known whether results from healthy obese volunteers can be applied to unwell obese inpatients and how the degree of obesity affects the interpretation of results.
- The type and location of infection may affect the dose regimen required in obese patients.
- Therapeutic drug monitoring should be used to guide the dosing of antibiotics in obesity where possible together with the monitoring of clinical response and toxicity. Further studies are needed to provide guidance on how to dose antibiotics in obesity to achieve optimal effectiveness and safety.

## Limitations

The information in this Q&A is based on limited evidence. This Q&A is not intended as a comprehensive prescribing guide and does not provide advice on all antibiotics in obesity, but rather a summary of the available evidence for antibiotics licensed in the UK, for which the largest amount of data regarding dosing in obesity was found at the time of writing. The current Summary of Product Characteristics for the antibiotic in question should be referred to for further information. Absence of an antibiotic from Table 2 or this Q&A does not imply that no dose adjustment is necessary in obesity. A detailed discussion of the effect of obesity on the pharmacokinetics of drugs is beyond the scope of this Q&A. This Q&A is intended for adult patients only. The dosing of antituberculosis and antileprotic drugs in obesity is not addressed in this Q&A.

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## Quality Assurance

### Original document

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### 2016 Update

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**Laura Whitney**, Consultant Pharmacist - Antimicrobials, St George's University Hospitals NHS Foundation Trust, London, and Research Lead for UKCPA Pharmacy Infection Network

### Search strategy (UKMI)

- Embase: exp ANTIBIOTIC AGENT OR exp ANTIBIOTIC THERAPY AND [\*WEIGHT OR \*BODY WEIGHT OR \*OBESITY] Limit to: Human and (Human Age Groups Adult 18 to 64 or Aged 65+years) and English Language on 24/04/13 and 28/04/16
- Medline: [\*BODY WEIGHT OR \*OBESITY] AND exp ANTI-BACTERIAL AGENTS on 24/04/13 and PubMed [\*BODY WEIGHT OR \*OBESITY] AND \* ANTI-BACTERIAL AGENTS [MeSH terms] on 13/04/16
- MICROMEDEX: “antibiotics and obesity”, “dosing in obesity”, “dosing in extremes of body weight”. Accessed via [www.thomsonhc.com](http://www.thomsonhc.com) on 30/04/13.
- MEDICINES COMPLETE including Martindale and British National Formulary Online: Accessed via [www.medicinescomplete.com](http://www.medicinescomplete.com) on 30/04/13
- NHS Evidence search: “antibiotics and obesity”, “obesity and dosage” Accessed via [www.evidence.nhs.uk](http://www.evidence.nhs.uk) on 05/06/2013 and antibiotics and obesity” filter = systematic reviews OR obesity and dosage” filter = systematic reviews; on 29/04/16
- Google search: “antibiotic dosing in obese patients”, “antibiotics and obesity”, “dosing at extremes of body weight”, “obesity and drug dosing”. [www.google.co.uk](http://www.google.co.uk) on 11/06/13 and 29/04/16
- Antimicrobial agents and chemotherapy. Accessed via [www.aac.asm.org/](http://www.aac.asm.org/) on 30/04/2013
- In-house database / resources: “obesity”, “body weight”, “antibiotics and obesity”
- Relevant Summary of Product Characteristics. Accessed via [www.medicines.org.uk/emc/](http://www.medicines.org.uk/emc/)
- Manufacturers:
  - Accord Healthcare Limited Email 29.05.13
  - Actavis Pharma Emails 03.05.13, 28.05.13, 04.06.13, 14.06.13.
  - Alliance Pharma plc and Alliance Pharmaceuticals Ltd. Email 29.05.13
  - Almirall Email 28.05.13
  - Amdipharm. Emails 22.05.13, 24.05.13, 09.06.13
  - Aspen Email 05.06.13
  - Astellas Pharma Ltd. Email 31.05.13
  - AstraZeneca Emails 21.05.13, 29.05.13
  - Athone Laboratories Email 13.05.13
  - Bayer Healthcare Email 06.06.13.

- Bristol Myers Squibb. Phone call 28.06.13.
- Chemidex Pharma Ltd. Email 30.04.13
- Flynn Pharma Emails 01.05.13, 20.05.13, 21.05.13, 28.05.13.
- Galderma Ltd. Email 22.05.13
- Genus Pharmaceuticals Ltd 30.04.13
- GlaxoSmithKline Phone call 01.05.13 and Emails 01.05.13, 02.05.2013, 10.05.13, 21.05.13
- Intraparm Laboratories Ltd 23.05.13
- Leo Pharmaceuticals Email 30.04.13 and Phone call 04.06.13
- Meda Pharmaceuticals Phone call 10.06.13
- MSD Emails 21.05.2013, 29.05.13, 11.06.13
- Norgine Email 29.05.13
- Novartis Email 03.06.13.
- Pfizer Medical Information. Emails 01.05.13, 21.05.13, 22.05.13, 28.05.13, 29.05.13.
- Profile Pharma Ltd. Email 28.05.13
- Roche Products Ltds Email 29.05.13
- Rosemont Pharmaceuticals Ltd Email 04.06.13.
- Sandoz Ltd. Emails 07.05.13, 07.06.13
- Sanofi. Emails 09.05.13, 23.05.13, 29.05.13, 30.05.13, 04.06.13.
- Teva UK 24.05.13,
- Wockhardt Email 23.05.13
- Clinical Expert: Specialist Anti-infective Pharmacist, University Hospitals Bristol NHS Foundation Trust (personal communication 29.10.13).

### Search strategy 2016 update

Medline, Embase and Cochrane databases with limits: English language and abstract, (included humans, humans and animals, not animals) sifted to SRs, RCTs and Observational

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#### pharmacokin and obesity terms

1. pharmacokinetics.mp. or \*Pharmacokinetics/
2. serum concentration.mp.
3. \*Biological Markers/ or blood concentration.mp.
4. \*Creatinine/ or creatinine clearance.mp.
5. plasma concentration.mp.
6. tissue concentration.mp.
7. tissue distribution.mp. or \*Tissue Distribution/
8. pharmacodynamics.mp.
9. \*absorption/ or \*area under curve/ or \*biological availability/ or \*biotransformation/ or \*toxicokinetics/
10. treatment failure.mp. or \*Treatment Failure/
11. bioavailability.mp. or \*Biological Availability/
12. weight adjusted dosing.mp.
13. \*Metabolic Clearance Rate/ or metabolic clearance.mp.
14. \*Dose-Response Relationship, Drug/ or dose response.mp.
15. dosage.mp. or \*Drug Dosage Calculations/
16. or/1-15
17. obesity.mp. or \*Obesity/ or \*Obesity, Morbid/ or \*Obesity, Abdominal/
18. obes\$.mp.
19. overweight.mp. or \*Overweight/ or \*Body Weight/
20. patient weight.mp.
21. body weight.mp.
22. \*Body Weight/

23. adiposity.mp. or \*Adiposity/ or \*Body Composition/ or \*Adipose Tissue/

24. or/17-23

25. 16 and 24

**Combined with**

**all drug terms**

1. antibiotics.mp. or \*Anti-Bacterial Agents/

2. \*anti-infective agents/ or anti-bacterial agents/ or \*antifungal agents/ or \*anti-infective agents, local/ or \*anti-infective agents, urinary/ or \*antiparasitic agents/ or \*antiviral agents/

3. antimicrobial.mp.

4. or/1-3

5. aminoglycosides.mp. or exp \*Aminoglycosides/

6. betalactams.mp. or exp \*beta-Lactams/

7. beta-lactams.mp.

8. carbapenems.mp. or exp \*Carbapenems/

9. cephalosporins.mp. or exp \*Cephalosporins/

10. echinocandins.mp. or exp \*Echinocandins/

11. \*"Fluoroquinolones"/

12. glycopeptides.mp. or exp \*Glycopeptides/

13. macrolides.mp. or exp \*Macrolides/

14. penicillins.mp. or exp \*Penicillins/

15. triazoles.mp. or exp \*Triazoles/

16. \*Anti-Infective Agents/ or \*Anti-Bacterial Agents/

17. or/5-16

18. aciclovir.mp.

19. amikacin.mp.

20. amoxicillin.mp.

21. anidulafungin.mp.

22. azithromycin.mp.

23. aztreonam.mp.

24. benzylpenicillin.mp.

25. caspofungin.mp.

26. cefalexin.mp.

27. cefazolin.mp.

28. cefotaxime.mp.

29. ceftaroline.mp.

30. ceftazidime.mp.

31. ceftobiprole.mp.

32. ceftriaxone.mp.

33. cefuroxime.mp.

34. chloramphenicol.mp.

35. ciprofloxacin.mp.

36. clarithromycin.mp.

37. clindamycin.mp.

38. co-amoxiclav.mp.

39. colistimethate sodium.mp.

40. co-trimoxazole.mp.

41. dalbavancin.mp.

42. daptomycin.mp.

43. doripenem.mp.

44. doxycycline.mp.

45. ertapenem.mp.

46. erthyromycin.mp.

47. ethambutol.mp.

48. famciclovir.mp.

- 
49. fidaxomicin.mp.
  50. flucloxacillin.mp. or Floxacillin/
  51. fluconazole.mp.
  52. Flucytosine/ or flucytosine.mp.
  53. foscarnet.mp.
  54. fosfomicin.mp.
  55. ganciclovir.mp.
  56. gentamicin.mp.
  57. imipenem.mp.
  58. cilastatin.mp.
  59. isavuconazole.mp.
  60. isoniazid.mp.
  61. itraconazole.mp.
  62. levofloxacin.mp.
  63. linezolid.mp.
  64. meropenem.mp.
  65. metronidazole.mp.
  66. micafungin.mp.
  67. moxifloxacin.mp.
  68. nitrofurantoin.mp.
  69. ofloxacin.mp.
  70. phenoxymethylpenicillin.mp.
  71. piperacillin.mp.
  72. pivmecillinam.mp. or \*Amdinocillin Pivoxil/
  73. posaconazole.mp.
  74. pyrazinamide.mp.
  75. rifampicin.mp.
  76. sodium fusidate.mp.
  77. fusidic acid.mp.
  78. tedizolid.mp.
  79. teicoplanin.mp.
  80. telavancin.mp.
  81. temocillin.mp.
  82. ticarcillin.mp.
  83. clavulanic acid.mp.
  84. tigecycline.mp.
  85. tinidazole.mp.
  86. tobramycin.mp.
  87. \*Trimethoprim-Sulfamethoxazole Combination/ or trimethoprim.mp.
  88. valaciclovir.mp.
  89. vancomycin.mp.
  90. voriconazole.mp.
  91. or/18-90
  92. 17 or 91
  93. or/5-92
  94. 4 or 93