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CURRENT OPINION

Patients with Obesity Should be Recognised as a Special Patient Population During Drug Development of Antibacterial and Antifungal Agents; A Call to Action

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Abstract
Individuals with obesity are at increased risk of developing infectious diseases. Timely administration of an effective dose of an antimicrobial agent is paramount to safeguard optimal therapy. For this purpose, special patient populations at risk for altered exposure such as renal or hepatic impairment are studied during drug development. Strikingly, there is no such evaluation in individuals with obesity despite a potential influence on exposure and a global obesity prevalence of 13 %. Optimal clinical decision making in patients with obesity is impossible without prior study of the drug of interest in this population. This statement is strengthened by an evaluation of 19 antimicrobial agents that showed tremendous variability in the influence of weight on clearance. In contrast to patient with renal or hepatic impairment who are mainly at risk of overexposure, individuals with obesity can be at risk of both under- and overexposure. Gaining knowledge on the influence of body weight on clearance during early phases of drug development may allow for optimisation of other phases of research, potentially increasing success rate of the drug, and can provide clinicians with vital information as soon as the drug reaches the market. Antimicrobial therapy should be tailored to obesity-related (patho)physiological changes and to reach this goal, obese individuals should be studied during drug development.

Key Points

Individuals with obesity should be recognised as a special patient population during drug development of antibacterial and antifungal agents. Suboptimal exposure may be anticipated for 37 % of antimicrobial agents as dosing strategy does not match the influence of weight on clearance.

1 Introduction

1.1 Clinical Problem

Patients with obesity (body mass index [BMI] ≥ 30 kg/m^2) are at increased risk of nosocomial infections such as surgical-site infections, pneumonia and *Clostridium difficile* colitis and are also more likely to develop severe complications from infections [1]. Moreover, patients with obesity show increased length of stay in the intensive care unit, although mortality is not necessarily increased [1]. There is a great need to provide optimal care to patients with obesity with infectious diseases although clear guidance on how therapy should be individualised is often lacking. We are of the opinion that antimicrobial therapy should be tailored according to obesity-associated physiological changes that impact drug pharmacokinetics thereby assuring sufficient exposure and thus maximise efficacy and simultaneously minimising toxicity.

1.2 Obesity

Global obesity prevalence among adults was estimated at 650 million in 2016, 13 % of the world population, and has tripled since 1975 [2, 3]. Historically, prevalence was concentrated in high-income countries but is on the rise in low- and middle-income countries, especially in urban areas [3]. Although obesity is defined as a BMI > 30 kg/m^2, the population of individuals with obesity is heterogeneous and could be viewed on a continuous scale as different

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classes of obesity are distinguished ranging from class I for BMI 30–35 kg/m^2 to class III for BMI > 40 kg/m^2 [2]. An overabundance of adipose tissue is the key characteristic of obesity, although physiological changes may simultaneously happen in various organ systems like the kidneys, liver and the cardiovascular system [3, 4].

Glomerular filtration rate increases at an early stage of obesity while it decreases in the long term. Additionally, tubular secretion is enhanced in individuals with obesity. Cardiac output increases, which leads to increased liver blood flow that is an important determinant for clearance of medium to high extraction ratio drugs. The intestinal and hepatic cytochrome P450 (CYP) 3A4- and 2C19-mediated metabolic capacity is reduced while CYP 2E1 and Phase II metabolism are enhanced while CYP 1A2 and 2C9 activity remains uninfluenced by obesity [4, 5]. Moreover, the expression of drug transporters like organic anion transporter, organic anion transporting polypeptides and multidrug resistance protein 2 and 3 may be either suppressed or increased by obesity [4].

Acute infection itself may simultaneously influence clearance as CYP 1A2, 2C19 and 3A activity is increased while 2B6 and 2C9 activity is decreased [5]. Fat disposition in individuals with obesity mainly takes place in the subcutis, abdominal visceral depot, heart, liver, pancreas and kidney. For the treatment of infections in these organs, increased systemic exposure in plasma may be needed to overcome impaired tissue penetration as was demonstrated for several antimicrobial agents using clinical micro-dialysis studies [3, 6–8]. Nevertheless, it remains unclear if higher plasma concentrations lead to improved clinical or microbiological cure.

Investigations on the plasma pharmacokinetics are of important relevance given the difficulties measuring exposure at the site of infection. Plasma exposure or area under the curve (AUC) in steady state is determined by the ratio of clearance and the maintenance dose. For patients with obesity both the influence of body weight on clearance and the dosing regimen, i.e., mg/kg body weight or fixed dose, determine whether an adjusted maintenance dosage is required. An increased volume of distribution would prolong the time to steady state conditions and reduce peak concentrations. A common assumption is that lipophilicity can be used to predict changes in volume of distribution for patients with obesity, however particularly for lipophilic drugs changes are unpredictable and there is high inter-drug variability. Obesity-associated changes in volume of distribution need to be considered for drugs with long half-life or drugs that depend on peak concentration [9]. For dose adjustments in individuals with obesity, clearance is the primary parameter of interest as changes directly influence exposure.

2 Influence of Obesity on Clearance of Antibacterial and Antifungal Agents

2.1 Non-infectious Individuals with Obesity

To motivate our position presented in this viewpoint, literature on the influence of body weight on clearance of commonly used antibiotic and antifungal agents in otherwise healthy, i.e., non-infectious, individuals with (morbid) obesity was reviewed [6, 7, 10–26]. Studies reporting on intravenously (iv) administered drugs were included and those only providing clearance for an obese and non-obese cohort without specifying an equation describing clearance over a large weight span were excluded. The fold increase in clearance between a 70 kg and 140 kg individual was calculated based on the equation for clearance reported in the respective studies. In line with typical criteria for bioequivalence a 1.0- to 1.25-fold increase in clearance may be considered a non-significant influence, a 1.25- to 1.5-fold increase a moderate influence and a ≥ 1.5-fold increase may be considered a strong influence of body weight on clearance. The 140 kg reference weight corresponds with the 95th percentile body weight of Americans in 2016 [27].

We identified 19 reports describing the influence of body weight on clearance of antimicrobial agents, i.e., 13 antibacterial agents and 6 antifungal agents. Either a non-significant, moderate or a strong influence of weight on clearance was identified for 7/19 (37 %), 8/19 (42 %) and 4/19 (21 %) antimicrobial agents, respectively [6, 7, 10–26].

The results are visualised in Fig. 1, in which clearance for a typical 70-kg individual was set to 1.0. Each line represents the fold increase in clearance with increasing body weight for the respective antimicrobial agent. A large heterogeneity in influence of increasing body weight on clearance is shown. A 2-fold increase in clearance corresponds to a 50 % decrease in exposure (measured as AUC) for patients with a body weight of 140 versus 70 kg receiving an equal dose. The grey area in Fig. 1 represents a moderate influence of body weight on clearance, the area below and above represents non-significant and strong influence, respectively. If non–weight-based patient characteristics (age, height or serum creatinine) are predictive for clearance, the median value from the study population was fixed in order to visualise the influence of bodyweight on clearance. As a result, clearance may differ for patients with the same weight if difference in age, height or serum creatinine are present as is the case for cefazolin, ceftaroline, daptomycin, meropenem, piperacillin and tobramycin. From the figure it can be deduced that predicting the influence of body weight on clearance is challenging as even within the therapeutic classes of macrolides, cephalosporins, echinocandins and

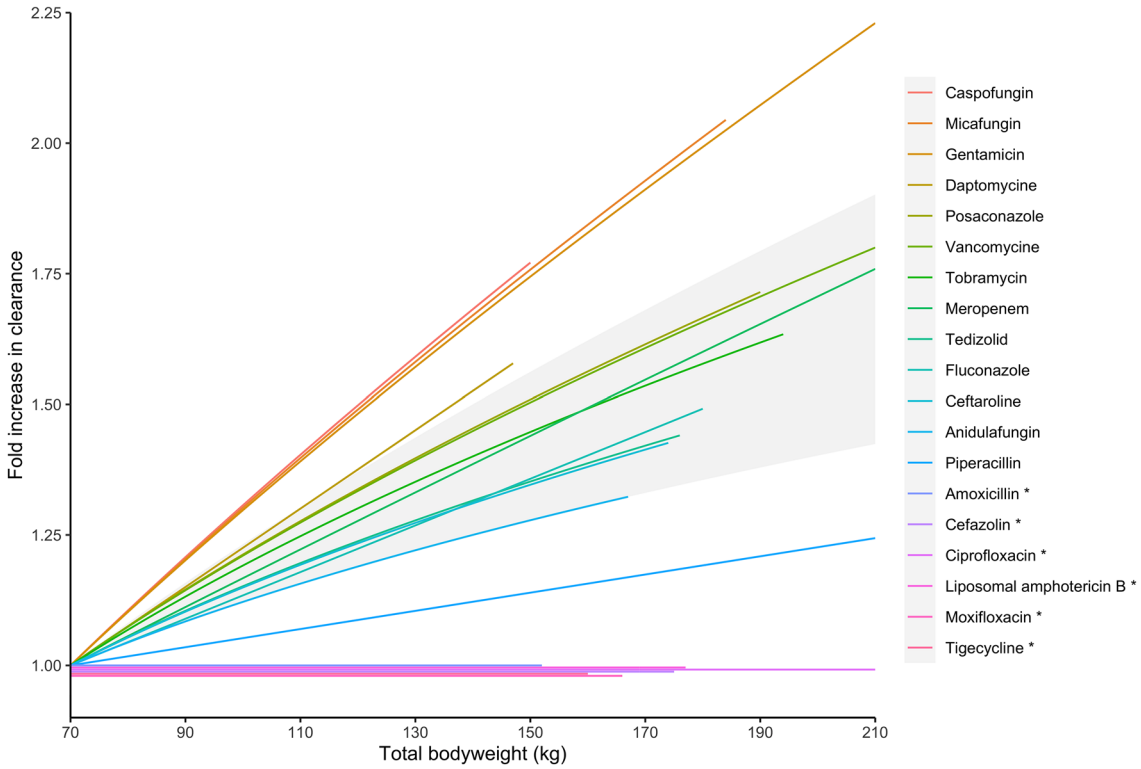

Fig. 1 Influence of increasing body weight on clearance of antibacterial and antifungal agents expressed as fold increase compared to a typical 70 kg individual. Each line represents an antimicrobial agent visualising the fold increase in clearance from plasma with increasing body weight. *Amoxicillin, cefazolin, ciprofloxacin, liposomal amphotericin B, moxifloxacin and tigecycline show no influence of body weight on clearance and therefore overlap at fold increase in clearance = 1.0. The grey shaded area represents a moderate influence of body weight on clearance. A fold increase in clearance below the grey area represents no significant influence on clearance, a fold increase in clearance above the grey area represents a strong influence of body weight on clearance. For cefazolin, ceftaroline, daptomycin, meropenem, piperacillin and tobramycin drivers of clearance were identified that are not strictly weight based (age, height, serum creatinine); for these drugs values of the respective drivers were fixed at the median value in order to visualise the influence of body weight on clearance. The length of the line corresponds with the maximum total body weight in the study population, with a maximum of 210 kg

triazoles pronounced differences are observed, which cannot be explained by hepatic versus renal clearance or differences in lipophilicity, protein binding or molecular weight.

3 Optimising Exposure: Connecting Obesity and Dosing Strategy

3.1 Body Weight and Dosing Strategy

Exposure to antimicrobial agents in steady state across different body weights is determined by both the influence of body weight on clearance (as depicted in Fig. 1) and the employed dosing strategy, i.e., fixed dosing or mg/kg body weight. In individuals with obesity, it is particularly important that dose adjustments match the direction and magnitude of effect of weight on clearance. In Table 1 we show that applying the labelled dosing strategy (fixed dosing or mg/kg dosing) to individuals with obesity for the antimicrobial drugs from Fig. 1 would introduce a risk of underexposure for 7/19 (37 %) of antimicrobial agents and a risk of overexposure for 4/19 (21 %) of antimicrobial agents. Four different scenarios are distinguished in data presented in Table 1; fixed dosing regimen & *body weight not associated with increased clearance*, fixed dosing regimen & *body weight associated with increased clearance*, weight-based dose & *body weight not associated with increased clearance* and mg/kg dose & *body weight associated with increased clearance*. These scenarios are discussed below for the selected 19 antimicrobial agents.

3.1.1 Fixed Dosing Regimen and Body Weight Not Associated with Increased Clearance

The drugs amoxicillin, cefazolin, ciprofloxacin, moxifloxacin, piperacillin and tigecycline, are given in a fixed dose and their clearance is not influenced by body weight [6, 7, 11, 20, 22, 26]. Similar exposure in plasma is expected across all body weights.

3.1.2 Fixed Dosing Regimen and Body Weight Associated with Increased Clearance

The drugs anidulafungin, caspofungin, ceftaroline, fluconazole, meropenem, micafungin, posaconazole and tedizolid are also given at fixed dosages, yet their clearance is reported to be influenced by body weight and therefore individuals with obesity may be at risk of underexposure [10, 12, 15, 18, 19, 21, 24, 25]. These drugs may require higher maintenance dosages when the same exposure is aimed for, yet the need and magnitude of dose increase depends on the exact influence of body weight on clearance and the width of the therapeutic window.

3.1.3 Weight-Based Dosing Regimen and Body Weight Not Associated with Increased Clearance

Amphotericin B is dosed as mg/kg whereas no influence of body weight on clearance was identified in individuals up to 177 kg. As a result, individuals with obesity are at risk of overexposure if doses are not capped at a body weight of 100 kg [14].

3.1.4 Weight-Based Dosing Regimen and Body Weight Associated with Increased Clearance

For the drugs daptomycin, gentamicin, tobramycin and vancomycin a weight-based dosing regimen is employed and weight is of influence on clearance [13, 16, 17, 23]. An mg/kg-based dosing regimen provides a linear dose increase with body weight. Nevertheless, clearance may not necessarily increase linearly with body weight (Fig. 1). As such an mg/kg dose leads to overexposure for individuals with extreme body weights. In order to mitigate the risk of overexposure, alternative body size descriptors like adjusted body weight (ABW) or lean body weight (LBW) may be used to calculate dosing weights as these metrics also increase in a non-linear manner with body weight, similar to the non-linear increase of clearance with body weight. The heterogeneity in Fig. 1 illustrates that no single alternative body size descriptor is suited for use as a universal body size descriptor for predicting clearance in individuals with obesity. Moreover, care is to be taken when using LBW for this purpose, as the inclusion of gender in the calculation of LBW may introduce undesired differences in exposure between men and women [28–30, 32].

For these antimicrobial agents, the width of the therapeutic window determines if dose adjustment is needed. Daptomycin has a relatively wide therapeutic window although doses beyond 500 mg are associated with creatinine phosphokinase elevation [31]. Gentamicin on the other hand has a narrow therapeutic window and is usually dosed on ABW in clinical practice. Interestingly this approach introduces a risk of underexposure in individuals with severe obesity and consequently may be dosed on a nomogram that ensures similar exposure across different body weights [17, 32].

3.2 (Critically) Ill Patients with Obesity

Real-world data from (critically) ill patients with obesity treated with amoxicillin, cefazolin, daptomycin, fluconazole, gentamicin, meropenem, micafungin, moxifloxacin, piperacillin and vancomycin show that, besides body weight, patient characteristics like renal function, renal replacement therapy, admission to ward or ICU, age and class of obesity may be associated with altered clearance [31–44].

The influence of body weight on clearance in (critically) ill patients with obesity was similar to the influence identified for their non-infectious counterparts for most antimicrobial agents. Nevertheless, for meropenem several studies in critically ill patients did not report an influence of weight on clearance; hence, dose modification solely based on body weight does not seem warranted [36, 37]. Fixed dosing of daptomycin in (critically) ill patients with obesity is associated with a lower incidence of creatinine phosphokinase elevation, despite a significant influence of weight on clearance [31]. For cefazolin it remains unclear if increased doses for surgical prophylaxis lead to improved outcome in individuals with obesity for procedures > 4 h despite impaired tissue penetration [34].

A major strength of studies in non-critically ill patients with obesity is the wide weight range compared with studies in (critically) ill patients. This allows for precise characterisation of the influence of body weight on clearance while minimising the influence of other potentially relevant influences on clearance like varying renal function. Nevertheless, findings from non-(critically) ill individuals with obesity need external validation in (critically) ill individuals as is illustrated by the need for fixed dosing of daptomycin in individuals with obesity and renal function-based dose optimisation for fluconazole, meropenem, piperacillin and vancomycin [31, 34, 41–45]. For gentamicin, dose optimisation may be based on both renal function and admission to the ward or ICU [32].

In conclusion, obesity-related changes in exposure to antimicrobial agents can be predicted using studies investigating the influence of body weight on clearance and volume of distribution together with the dosing strategy. Whether the resulting exposure is acceptable depends on the width of the therapeutic window, but also on the sensitivity of the causative pathogen towards the employed antimicrobial agent and penetration of the drug into the site of infection.

Table 1 Overview of the influence of weight on clearance

	Influence of weight on clearance from plasma	Registered dosing strategy	Patients with obesity are at risk of	Clinical relevance	Clinical implications	References
Anidulafungin	Moderate increase	Fixed dose	Underexposure	++	Patients with obesity are at risk of underexposure as a result of fixed dosing and increased clearance compared to non-obese individuals	18
Caspofungin	Strong increase	Fixed dose	Underexposure	++	Patients with obesity are at risk of underexposure as a result of fixed dosing and increased clearance compared to non-obese individuals	25
Fluconazole	Moderate increase	Fixed dose	Underexposure	++	Fixed dosing leads to decreased exposure in plasma in patients with obesity compared to non-obese individuals	10
Gentamicin	Strong increase	Weight based	Overexposure	++	Total body weight–based dosing leads to overexposure in individuals with obesity compared to non-obese individuals. ABW-based dosing is often applied in individuals with obesity although this approach shows a trend towards underexposure in individuals with severe morbidity individuals for which a dosing nomogram was proposed	16, 32
Liposomal amphotericin B	No significant increase	Weight based	Overexposure	++	Body weight–based dosing leads to overexposure in individuals with obesity compared to non-obese individuals. Doses should be capped for individuals with TBW >100 kg when aiming for similar exposure compared to non-obese patients	14
Micafungin	Strong increase	Fixed dose	Underexposure	++	Fixed dosing leads to decreased exposure in individuals with obesity compared to non-obese individuals. Increased maintenance dose for individuals with TBW>125 kg if MIC ≥0.032 mg/L	15
Posaconazole	Moderate increase	Fixed dose	Underexposure	++	Fixed dosing leads to decreased exposure in plasma in patients with obesity compared to non-obese individuals. Doses should be increased for the treatment of fungal disease for individuals with TBW >140 kg	12

Table 1 (continued)

	Influence of weight on clearance from plasma	Registered dosing strategy	Patients with obesity are at risk of	Clinical relevance	Clinical implications	References
Tobramycin	Moderate increase	Weight based	Overexposure	++	Total body weight–based dosing leads to overexposure in individuals with obesity compared to non-obese individuals. In obese patients, especially in individuals with good renal function, doses should be optimised based on MDRD and BSA	17
Vancomycin	Moderate increase	Weight based	Overexposure	++	Total body weight–based dosing leads to similar exposure in individuals with obesity compared to non-obese individuals even though a dose cap is proposed for extremely obese individuals and renal function will determine the optimal dose	13
Cefazolin	No significant increase	Fixed dose	Underexposure	+	Fixed dosing leads to similar exposure in plasma in individuals with obesity compared to non-obese individuals. Higher dosages may be needed in obese patients when used for surgical prophylaxis because of reported reduced impaired penetration into subcutaneous tissue	7
Ciprofloxacin	No significant increase	Fixed dose	Underexposure	+	Fixed dosing leads to similar exposure in plasma in individuals with obesity compared to non-obese individuals. Higher dosages may be needed for skin and soft tissue infections in obese patients because of reported decreased tissue penetration	6
Amoxicillin	No significant increase	Fixed dose	–	Neutral	Fixed dosing leads to similar exposure in plasma in obese patients compared to non-obese individuals	11
Ceftaroline	Moderate increase	Fixed dose	–	Neutral	Total body weight showed no influence on clearance although Cockcroft-Gault in which weight is used was a predictor. No need for dose adaptation solely based on body weight	24
Daptomycin	Strong increase	Weight based	–	Neutral	Body weight–based dosing leads to mildly increased exposure (25 %–30 %) in individuals with obesity compared to non-obese patients which would not lead to safety issues according to the authors	23

Table 1 (continued)

	Influence of weight on clearance from plasma	Registered dosing strategy	Patients with obesity are at risk of	Clinical relevance	Clinical implications	References
Meropenem	Moderate increase	Fixed dose	–	Neutral	Individualised dosing solely based on weight is not necessary. Dose modification is not indicated for most frequently encountered sensitive pathogens (MIC ≤2 mg/L) using a PK/PD target of Time(%) >MIC = 40	21
Moxifloxacin	No significant increase	Fixed dose	–	Neutral	Fixed dosing leads to similar exposure in plasma in individuals with obesity compared to non-obese individuals	22
Piperacillin	No significant increase	Fixed dose	–	Neutral	Fixed dosing leads to similar exposure in plasma in individuals with obesity compared to non-obese individuals	26
Tedizolid	Moderate increase	Fixed dose	–	Neutral	Fixed dosing leads to similar exposure in plasma in individuals with obesity compared to non-obese individuals	19
Tigecycline	No significant increase	Fixed dose	–	Neutral	Fixed dosing leads to similar exposure in plasma in individuals with obesity compared to non-obese individuals	20

The clinical relevance is determined by the combination of both the influence of body weight on clearance and the registered dosing strategy

The clinical relevance is scored neutral if no dose adjustment is needed. "+" is used to indicate differences between individuals with obesity and non-obese patients who do require dose individualisation that is not based on differences in clearance from plasma between obese and non-obese patients. "++" is used to indicate differences between individuals with obesity and non-obese patients that require dose individualisation based on differences in clearance from plasma

ABW actual body weight, *BSA* body surface area, *MDRD* modification of diet in renal diseases, *MIC* minimal inhibitory concentration, *PK/PD* pharmacokinetic/pharmacodynamics, *TBW* total body weight

4 The Unpredictable Effect Size of Obesity on Clearance Necessitates Early Research, Similar to Renal and Hepatic Insufficiency

Nowadays, patients with renal and hepatic insufficiency are recognised as special patient populations as they are at increased risk of developing drug-related toxicity as a result of impaired clearance. Similarly, exposure may be altered in individuals with obesity and the lack of appropriate dose adjustment can put individuals with obesity at the same risk of toxicity. In contrast to individuals with renal or hepatic impairment, individuals with obesity may also be at risk of therapy failure as illustrated above.

To compare the effect size on clearance of increasing body weight versus renal and hepatic insufficiency, we summarised the dose adjustments required for individuals with obesity in order to achieve exposure in plasma that is similar to their normal-weight counterparts and dose adjustments proposed by the package inserts for renal and hepatic insufficiency for the aforementioned 19 antimicrobial agents (Table 2) [46]. Nevertheless, for some special patient populations additional data on dose adjustment may be available in the field.

For individuals with obesity, dose adjustments are required for 8/19 (42 %) antimicrobial agents. Of these eight agents, a dose increase of 25 %–100 % is proposed for four antimicrobial agents with a fixed-dose regimen while a dose reduction of up to 36 % is proposed for four antimicrobial agents with a weight-based dosing regimen. For individuals with renal impairment, dose reductions are proposed for 11/19 (58 %) of the identified antimicrobial agents. Typical dose adjustments range from 33–95 % of the daily dose. For only 2/19 (11 %) identified antimicrobial agents, a 50 % reduced daily maintenance dose is required depending on the severity of hepatic impairment. This low percentage may be explained by the large metabolic capacity of the liver implying that hepatic insufficiency (Child-Pugh class B/C) does not always require dose adjustment for drugs that are subject to hepatic metabolism.

Table 2 Overview of the proposed dosing recommendations for patients with obesity compared to dose adjustments for renal and hepatic insufficiency

	Patients with obesity	Renal insufficiency*	Hepatic insufficiency*	References
Amoxicillin	No dose adjustment required based on bodyweight	eGFR 30–10 mL/min: 50 % reduced maintenance dose eGFR <10 m/min: 75 % reduced maintenance dose	No dose adjustment required	11
Anidulafungin	25 % increased loading- and maintenance dose for TBW > 140 kg	No dose adjustment required	No dose adjustment required	18
Caspofungin	Individuals with obesity will have low caspofungin concentrations despite being on the recommended doses No dosing advice provided	No dose adjustment required	CP-A: no dose adjustment required CP-B: 50 % reduced maintenance dose CP-C: No data	25
Cefazolin	No dose adjustment required based on exposure in plasma Surgical prophylaxis: Consider a 50 % dose increased for BMI > 40 kg/m^2	eGFR 40–70 mL/min: 50 % reduced daily dose eGFR 20–40 mL/min: 80 %–85 % reduced daily dose eGFR 5–20 mL/min: 90 %–95 % reduced daily dose	No dose adjustment required	7
Ceftaroline	No dose adjustment required based on bodyweight.	eGFR 30–50 mL/min: 33 % reduced daily dose eGFR 10–30 mL/min: 50 % reduced daily dose eGFR < 10 mL/min: 66 % reduced daily dose	No dose adjustment required	24
Ciprofloxacin	No dose adjustment required based on exposure in plasma Skin and soft tissue infection: 120–160 kg; increase dosing frequency to 3 dd > 160 kg; increase dosing frequency by to 4dd	30–60 mL/min: 50 % reduced daily dose < 30 mL/min: 75 % reduced daily dose	No dose adjustment required	6
Daptomycin	No dose adjustment required based on body weight	eGFR 10–30 mL/min 100 % prolonged dosing interval	No dose adjustment required	23
Fluconazole	50 % increased loading dose for males > 140 kg	eGFR < 50 mL/min 50 % reduced maintenance dose	No dose adjustment required	10
Gentamicin	Up to 25 % dose reduction compared to TBW based dose depending on total body weight	Up to 90 % reduced daily dose depending on severity of renal insufficiency, apply TDM	No dose adjustment required	16, 32
Liposomal amphotericin B	Cap dosing weight at 100 kg	No data	No data	14
Meropenem	No dose adjustment required based on body weight Dose adjustment not needed for pathogen with MIC ≤ 2 mg/L. Higher dosages may be needed for less sensitive pathogens	eGFR 26–50 mL/min 33 % reduced daily dose eGFR 10–25 mL/min 66 % reduced daily dose eGFR < 10 mL/min 85 % reduced daily dose	No dose adjustment required	21
Micafugin	Increase maintenance dose by 50–100 % if TBW > 125 kg and MIC 0.016–0.032 mg/L. Consider alternative therapy for overweight individuals if MIC > 0.32 mg/L	No dose adjustment required	CP-A/B: no dose adjustment required CP-C: Insufficient data	15
Moxifloxacin	No dose adjustment required based on body weight	No dose adjustment required	Insufficient data	22
Piperacillin	No dose adjustment required based on body weight	eGFR 40–20 mL/min up to 33 % reduced daily dose eGFR < 20 mL/min 33 %–50 % reduced daily dose	No dose adjustment required	26
Posaconazole	In case of treatment, increase loading and maintenance dose by 33 % for individuals with TBW 140–190 kg and by 66 % for individuals with TBW > 190 kg	No dose adjustment required	No dose adjustment required	12

Table 2 (continued)

	Patients with obesity	Renal insufficiency*	Hepatic insufficiency*	References
Tedizolid	No dose adjustment required based on body weight	No dose adjustment required	No dose adjustment required	19
Tigecycline	No dose adjustment required based on body weight	No dose adjustment required	CP-A/B: no dose adjustment required CP-C: 50 % reduced maintenance dose	20
Tobramycin	Optimise dose based on MDRD and body surface area nomogram	Up to 80 % dose reduction depending on severity of renal insufficiency, apply TDM	No data	17
Vancomycin	Daily dose of 35 mg/kg (with a maximum of 5500 mg/day) for individuals without renal impairment	Apply TDM after the first dose	No dose adjustment required	13

The dosing recommendations for patients with obesity are compared to dose adjustments for renal and hepatic insufficiency, as stated in the summary of product characteristics (*) [46]. For some special patient populations additional data on dose adjustment may be available in the field

BMI body mass index, *CP* Child Pugh (class A,B,C), *eGFR* estimated glomerular filtration rate, *MDRD* modification of diet in renal diseases, *MIC* minimal inhibitory concentration, *TBW* total body weight, *TDM* therapeutic drug monitoring

Including individuals with obesity as a special patient population in drug labelling information seems justified as for the 19 evaluated drugs both the number of antimicrobial agents that require dose modification and the corresponding magnitude of the required dose modification are similar to those encountered in individuals with renal impairment and exceed those encountered in individuals with hepatic impairment.

5 Scenarios for Research in Individuals with Obesity

Regulating bodies recognise the importance of studying drug exposure in individuals with obesity and the current lack of guidance for industry. The Food and Drug Administration (FDA) already propagates enhancement of the diversity of clinical trial populations and the European Medicines Agency (EMA) published a reflection paper emphasising the importance of studying drug exposure in individuals with obesity [47, 48].

Individuals with obesity are currently often excluded from the early stages of drug research, which impedes detecting the influence body weight may or may not have on clearance. As a result, studies identifying the influence of weight on clearance are often conducted during Phase IV, after gaining market authorisation. In this process, unlocking access to vital information is postponed by several years, although this influence could be elucidated through small sample size pharmacokinetic studies. Model Informed Precision Dosing is an important tool for therapy optimisation and it has shown its value in many patient populations for various diseases [49]. In order for these models to provide valid predictions of exposure in individuals with obesity, it is of utmost importance to collect data in individuals over a wide weight range.

As a first step, admitting individuals with different classes of obesity to early stages of drug development will yield important information at a pivotal moment as findings can be carried over to later stages of pharmaceutical research. In case body weight shows a strong influence on clearance at an early stage, individualised doses may be administered during subsequent phases of research in order to achieve similar exposure in plasma across different body weights. In contrast, when no influence of body weight on the plasma pharmacokinetics is identified, fixed-dosing schedules can be applied in subsequent studies without limits for body weight at inclusion of the study.

The clinical population of individuals with obesity may still be heterogeneous with respect to additional factors that may influence clearance such as changes in renal or hepatic function, age or critical illness. As a second step,

establishing a platform for sharing and bundling individual data from multi-morbid patients with obesity may potentiate therapy optimisation in this special population as collecting data from sufficient multi-morbid individuals may not be feasible in a single centre.

We propose to no longer exclude individuals with obesity at any phase of pharmaceutical research and specifically study individuals with (extreme) obesity during drug development. When the influence of weight on clearance is known the moment an antimicrobial agent reaches the market, clinicians are equipped with essential information for therapy optimisation.

6 Conclusion and Future Perspectives

From our overview, we conclude that obesity has a varying influence on exposure to antimicrobial agents with 7/19 (37 %) drugs indicating that clearance is not significantly increased with body weight. Dose adjustments, either an increase or a decrease, are required for 8/19 (42 %) antimicrobial agents, placing the population of over weight and patients with (morbid) obesity at increased risk of suboptimal exposure. While patients with renal or hepatic impairment are mostly at risk of overexposure, patients with increased body weight are at double jeopardy as both an increased risk of underexposure and overexposure should be anticipated depending on both the dosing strategy (fixed dose vs mg/kg). Also, the magnitude of the influence of body weight on clearance as the fold increase in clearance was found to vary between 1.0 and 1.7 for a 70 kg versus 140 kg individual. Furthermore, therapy optimisation is increasingly guided by model-informed decision making while individuals with obesity are not typically studied; hence, it remains uncertain whether models are fit for purpose in predicting exposure in individuals with obesity. In order to enable clinicians to individualise antimicrobial therapy in patients with obesity, determining the influence of body weight on exposure to antimicrobial agents should be done at an early stage, ideally from Phase I onwards, as it has proven to yield vital information for various antimicrobial agents.

We propose a call to action: patients with (extreme) obesity should be recognised as a special patient population during drug development, especially for antibacterial and antifungal agents given the strong exposure-response relationship.

Declarations

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author contribution KR, CK, PvdL, RB helped with conceptualisation of this personal view. KR helped with the original draft and visualisation. KR, CK and RB conducted data curation and formal analysis. CK, PvdL, RB helped with review and editing of the draft.

Ethical approval Not applicable.

Informed consent Not applicable.

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