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Unraveling the drivers of antimicrobial pharmacokinetic variability in individuals with obesity and hospitalized patients with multimorbidity

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CHAPTER 4

4

Patients with obesity should be recognized 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 patients 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 optimization of other phases of research, potentially increasing success rate of the drug, and provides clinicians with vital information as soon as it 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.

Introduction

Clinical problem

Patients with obesity (Body Mass Index (BMI) $>30\text{kg/m}^2$) 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 infections¹. Moreover, patients with obesity show increased length of stay in the intensive care unit although mortality is not necessarily increased¹. There is a great need to provide optimal care to patients with obesity with infectious diseases although clear guidance on how therapy should be individualized 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 maximize efficacy and simultaneously minimizing toxicity.

Obesity

Global obesity prevalence among adults was estimated at 650 million in 2016, 13% of the world population, and 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 areas³. Although obesity is defined as a BMI $>30\text{kg/m}^2$, the population of individuals with obesity is heterogeneous and could be viewed on a continuous scale as different classes of obesity are distinguished ranging from BMI 30-35kg/m² for class I to BMI $>40\text{kg/m}^2$ for class III². 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 obesity⁴.

Acute infection itself may simultaneously influence clearance as CYP 1A2, 2C19 and 3A activity is increased while 2B6 and 2C9 activity is decreased⁵. 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 microdialysis 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 reduces 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 taken into account for drugs with long half-life or drugs that depend on peak concentration⁹. For dose adjustments in individuals with obesity clearance is the primary parameter of interest as changes directly influence exposure.

Influence of obesity on clearance of antibacterial and antifungal agents

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 intravenous (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 70kg and 140kg individual was calculated based on the equation for clearance reported in the respective studies. In line with typical criteria for bioequivalence a 1.0 – 1.25 fold increase in clearance may be considered a non-significant influence, a 1.25 – 1.5 fold increase a moderate influence and >1.5 fold increase may be considered a strong influence of body weight on clearance. The 140kg reference weight corresponds with the 95th percentile body weight of Americans in 2016²⁷.

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 visualized in Figure 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 twofold increase in clearance corresponds with 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 Figure 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 visualize 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, ceftarolin, 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 aminoglycosides, cephalosporins, echinocandins and triazoles pronounced differences are observed which cannot be explained by hepatic versus renal clearance or differences in lipophilicity, protein binding or molecular weight.

Optimizing exposure; connecting obesity and dosing strategy

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 figure 1) and the employed dosing strategy, i.e. fixed dosing or mg/kg body weight. In individuals with obesity, it is as such of particular importance 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 Figure 1 would introduce a risk of underexposure for 7/19 (37%) antimicrobial agents and a risk of overexposure for 4/19 (21%) 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.

Fixed dosing regimen & 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 bodyweight^{6, 7, 11, 20, 22, 26}. Similar exposure in plasma is expected across all body weights.

Fixed dosing regimen & body weight associated with increased clearance

The drugs anidulafungin, caspofungin, ceftarolin, 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.

Weight based dosing regimen & 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 177kg. As a result, individuals with obesity are at risk of overexposure if doses are not capped at a body weight of 100kg¹⁴.

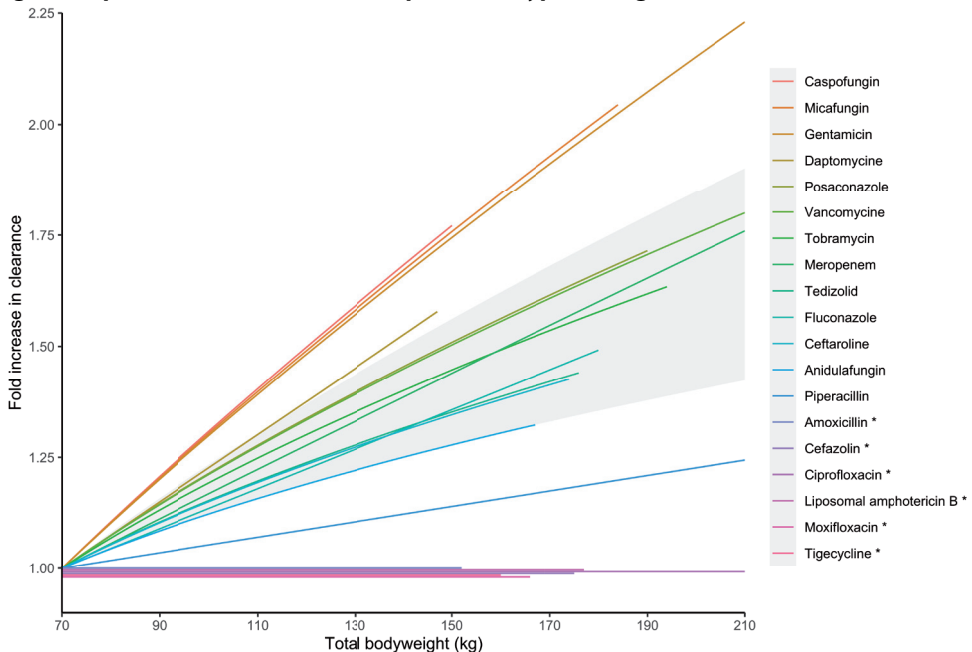
Weight based dosing regimen & body weight associated with increased clearance

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}. A mg/kg based dosing regimen provides a linear dose increase with body weight. Nevertheless, clearance may not necessarily increase linearly with bodyweight (Figure 1). As such a 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 bodyweight. The heterogeneity in figure 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 500mg are associated with creatinine phosphokinase elevation³¹. 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}.

Figure 1: Influence of increasing body weight on clearance of antibacterial and antifungal agents expressed as fold increase compared to a typical 70kg individual



Each line represents an antimicrobial agent visualizing 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, ceftarolin, 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 visualize 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 210kg.

(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 clearance³¹⁻⁴⁴.

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 clearance³¹. For cefazolin it remains unclear if increased doses for surgical prophylaxis lead to improved outcome in individuals with obesity for procedures >4 hours despite impaired tissue penetration³⁴.

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 characterization of the influence of body weight on clearance while minimizing 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 optimization for fluconazole, meropenem, piperacillin and vancomycin^{31, 34, 41-45}. For gentamicin dose optimization may be based on both renal function and admission to the ward or ICU³².

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.

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 recognized as special patient populations as they are at increased risk to develop 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 summarized 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 dosing 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.

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.

Scenarios for research in individuals with obesity

Regulating bodies recognize 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 emphasizing 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 authorization. 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 optimization and it has shown its value

in many patient populations for various diseases⁴⁹. 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, individualized 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 bodyweight 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 optimization in this special population as collecting data from sufficient multi-morbid individuals may not be feasible in a single center.

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 optimization.

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 of which clearance is not significantly increased with bodyweight. Dose adjustments, either a dose increase or a decrease, are required for 8/19 (42%) antimicrobial agents which puts the population of overweight 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 versus mg/kg) and 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 70kg vs 140kg individual. Furthermore, therapy optimization 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 individualize 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 recognized as a special patient population during drug development, especially for antibacterial and antifungal agents given the strong exposure – response relationship.

Disclosures

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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	Ref
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 >100kg 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 > 125kg if MIC >0.032mg/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 >140kg.	12
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 optimized based on MDRD and BSA.	17

Table 1: Overview of the influence of weight on clearance (continued)

	Influence of weight on clearance from plasma	Registered dosing strategy	Patients with obesity are at risk of	Clinical relevance	Clinical implications	Ref
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 an 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
Ceftarolin	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
Meropenem	Moderate increase	Fixed dose	-	Neutral	Individualized dosing solely based on weight is not necessary. Dose modification is not indicated for most frequently encountered sensitive pathogens (MIC <2mg/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

Table 1: Overview of the influence of weight on clearance (continued)

	Influence of weight on clearance from plasma	Registered dosing strategy	Patients with obesity are at risk of	Clinical relevance	Clinical implications	Ref
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
Tigecyclin	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 that do require dose individualization 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 individualization based on differences in clearance from plasma.

BSA: body surface area, MDRD: Modification of diet in renal diseases, MIC: Minimal inhibitory concentration, PK/PD: pharmacokinetic/pharmacodynamics, TBW: Total body weight

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*	Ref
Amoxicillin	No dose adjustment required based on bodyweight.	eGFR 30-10 ml/min: 50% reduced maintenance dose eGFR <10 ml/min: 75% reduced maintenance dose	No dose adjustment required	11
Anidulafungin	25% increased loading- and maintenance dose for TBW >140kg	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 >40kg/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
Ceftarolin	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: 120-160kg: increase dosing frequency to 3dd >160kg: 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 bodyweight.	eGFR 10-30 ml/min 100% prolonged dosing interval	No dose adjustment required	23
Fluconazole	50% increased loading dose for males >140kg	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

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

	Patients with obesity	Renal insufficiency*	Hepatic insufficiency*	Ref
Liposomal amphotericin B	Cap dosing weight at 100kg	No data	No data	14
Meropenem	No dose adjustment required based on bodyweight. Dose adjustment not needed for pathogen with MIC <2mg/L. Higher dosages may be needed for less sensitive pathogens.	eGFR 26-50ml/min 33% reduced daily dose eGFR 10-25ml/min 66% reduced daily dose eGFR <10ml/min 85% reduced daily dose	No dose adjustment required	21
Micafugin	Increase maintenance dose by 50-100% if TBW >125kg and MIC 0.016 - 0.032mg/L. Consider alternative therapy for overweight individuals if MIC >0.32mg/L.	No dose adjustment required	CP-A/B: No dose adjustment required CP-C: Insufficient data	15
Moxifloxacin	No dose adjustment required based on bodyweight.	No dose adjustment required	Insufficient data	22
Piperacillin	No dose adjustment required based on bodyweight.	eGFR 40-20ml/min up to 33% reduced daily dose eGFR <20ml/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 140-190kg and by 66% for individuals with TBW >190kg	No dose adjustment required	No dose adjustment required	12
Tedizolid	No dose adjustment required based on bodyweight.	No dose adjustment required	No dose adjustment required	19
Tigecyclin	No dose adjustment required based on bodyweight.	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

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

	Patients with obesity	Renal insufficiency*	Hepatic insufficiency*	Ref
Vancomycin	Daily dose of 35mg/kg (with a maximum of 5500mg/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

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