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Shaping the pharmacokinetic landscape for renally cleared antibiotics in obesity: Studies in adults, adolescents and children

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Studies in adults, adolescents and children

Cornelis Smit

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Studies in adults, adolescents and children

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Shaping the pharmacokinetic landscape for renally cleared antibiotics in obesity - studies in adults, adolescents and children

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Studies in adults, adolescents and children

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Part I



Introduction and background





1



Introduction

SCOPE

A 45-year-old patient is admitted to the ICU with a life-threatening bloodstream infection. Treatment with intravenous antibiotics is immediately started. However, this specific patient is unlike any other: the patient is not only severely ill, but also weighs 165 kg, needs to be mechanically ventilated and is being treated with multiple vasoconstrictive agents to maintain blood pressure. Moreover, the lab results show that the patient's kidneys are failing. The medical team knows that the antibiotic treatment might save the patient's life, but could also result in serious side effects in case of overdose which might actually worsen the patient`s situation. Given the high body weight and kidney failure, how do we know that the prescribed dose will lead to an effective, but not toxic treatment in this particular individual?

This question is central to the scientific field of pharmacometrics, with pharmacokinetics (PK) and pharmacodynamics (PD) as primary domains. Pharmacokinetics (derived from the Greek *pharmakon* or `drug` and *kinetikos* or `movement`) is the study of the time course of drug absorption, distribution, metabolism and elimination, also referred to as ADME. How the drug exposure subsequently translates to an effect (for example a drop in blood pressure or pain relieve) is studied in the field of pharmacodynamics (*dynamikos* in Greek means `power`).

In the case of the discussed ICU patient, there are multiple factors that can influence a drug`s pharmacokinetics that need to be accounted for when dosing the right dose for the antibiotic. First, it is important to consider the fact that the patient is morbidly obese. Often drugs are dosed with a 'one-size-fits-all' fixed dose. It is however common for this antibiotic to 'individualize' the dose by dosing on body weight (in mg/kg). But can we use 165 kg as a dosing weight in our patient or should this be adjusted, and if so, how must we adjust the dose? How does the disposition of the drug change in an obese individual? As it is primary renally eliminated, we need to know how these processes change in obese patients. In addition, the patient`s deteriorating kidney function needs to be accounted for in selecting the dose. Lastly, we should consider the fact that our patient is also critically ill, and hemodynamically unstable for which ICU treatment is necessary, which can have additional effects on a drug`s pharmacokinetics.

The work presented in this thesis aims to provide answers to these issues. How should renally cleared drugs be dosed in obesity, especially in obese individuals who are renally impaired and/or critically ill? We have conducted studies to investigate the pharmacokinetics of renally cleared drugs in adult, adolescent and paediatric patients who are obese, renally impaired and/or critically ill. In these studies, we focus on the widely used antibiotics gentamicin, tobramycin and vancomycin, which are primary examples of the group of renally cleared (antibiotic) drugs that are used for severe infections.

GENTAMICIN, TOBRAMYCIN AND VANCOMYCIN

The 'antibiotic era', roughly from 1910 to 1970, commenced by the discovery of the antisyphilic antibiotic arsphenamine in 1909, by Paul Erlich and Sahachiro Hata [1]. During this period, discoveries of new classes of antibiotic drugs followed one another, with Alexander Fleming's serendipitous discovery of penicillin in 1929 as probably the most well-known example [2]. Three major events mark prominent highlights of the antibiotic era: the introductions of the aminoglycosides gentamicin, tobramycin and the glycopeptide antibiotic vancomycin.

In 1943, streptomycin was discovered as the first agent of the aminoglycoside class, a potent group of natural and semisynthetic antibiotics active against a wide range of both gram-positive and gram-negative bacteria [3]. This was later followed by introduction of less toxic aminoglycosides such as gentamicin (1963), tobramycin (1967) and the semisynthetic amikacin (1972) [4]. They inhibit bacterial growth by binding to ribosomes, essential organelles for protein synthesis and are especially synergistic in combination with other antimicrobial drugs. Because of a poor absorption from the gastrointestinal tract, aminoglycosides are usually administered parenterally [4]. With their low molecular weight (both around 470 g/mol) and hydrophilic properties, they easily penetrate intro interstitial fluid of different organ tissues. This makes them suitable for both empirical and directed treatment of a wide variety of (severe) infections, such as sepsis, endocarditis, intra-abdominal or urinary tract infections [4–6]. Gentamicin and tobramycin are renally cleared, with 81 – 88% of the administered drug being recovered in the urine in the first 24 hours [5]. In the first decades after their discovery, when the daily aminoglycoside dose was divided over multiple administrations, their use was complicated by nephro- and ototoxicity. To provide a better efficacy-toxicity balance, extension of the drug interval was investigated. Such an extension was possible given the fact that aminoglycosides possess a prolonged post-antibiotic effect, i.e. the period after complete removal of the drug during which there is no bacterial growth. Indeed, in 1993, a once daily regimen of gentamicin was shown to be less nephrotoxic and equally effective compared to a more frequent dosing schedule [7].

Another important discovery in the 'antibiotic era' was the isolation of the glycopeptide antibiotic vancomycin in 1958 [8]. Vancomycin inhibits bacterial cell growth by binding to the D-Ala-D-Ala dipeptide terminus of peptidoglycan precursors, thereby inhibiting cross-linking of peptidoglycan in the bacterial cell wall. This lack of cross-linking reduces the integrity of the cell wall, resulting in bacterial death [9]. Its antibacterial spectrum includes most gram-positive organisms, including penicillin-resistant *Staphylococci*, which is an emerging problem since the 1950s [10]. Nowadays, it is mainstay treatment for various severe infections with gram-positive organisms, including bacteraemia, endocarditis or osteomyelitis. However, given its high molecular weight (~ 1400 g/mol) tissue penetration is moderate and shows large

variability [8,11]. Vancomycin has a short half-life of 3 – 9 hours in healthy adults, with over 80% excreted unchanged in urine within 24 hours after a dose [12]. Elimination is mostly depended upon glomerular filtration and possibly some tubular excretion [12]. Short after introduction, vancomycin's clinical use was tempered due to (nephro)toxicity concerns. These could mainly be attributed to impurities present in these early formulations, which gave vancomycin its brownish colour and renowned nickname 'Mississippi mud' [10]. To date, the introduction of purified formulations, routine use of therapeutic drug monitoring to individualize dosages and increased use of continuous infusion dose regimens have minimalized vancomycin nephrotoxicity [13,14].

OPTIMAL DOSING OF ANTIBIOTICS

When designing dose regimens for antibiotics like aminoglycosides and vancomycin, it is crucial to consider exposure targets that maximize efficacy while minimizing toxicity. For efficacy, this target concentration relies heavily on the susceptibility of the offending pathogen. This susceptibility is expressed as the minimal inhibitory concentration (MIC), which is specific for each combination of a drug and pathogen. Three different general exposure-response relations or 'PK/PD indices' have been defined to link exposure metrics, MIC and efficacy: (1) the ratio of the maximum (unbound) drug concentration to the MIC (fC_{max}/MIC), (2) the ratio of the area-under-the-curve of the unbound drug to the MIC (fAUC/MIC) or (3) the percentage of time over a 24 hour period that the (unbound) drug concentration is above the MIC (%fT>MIC) [15,16]. PK/PD indices are determined by investigating multiple dosing strategies with varying dosing intervals in *in vitro* or *in vivo* animal research, thereby resolving which parameter (fAUC/MIC, fC_{max}/MIC or (%fT>MIC) correlates best with a parameter that reflects outcome (survival, pathogen load, etc). Based on these studies an antibiotic is allocated to one of these categories and used as a driver for dose adaptation strategies. Ideally, this knowledge is combined with a toxicity threshold, although toxicity is usually less well studied since most antibiotics are relatively well tolerated. In such toxicologic studies, drug concentrations (for example AUC or trough concentrations) are directly correlated to the risk of toxicity, as this is obviously independent of pathogen susceptibility. This approach to design dose regimens for antibiotics has nowadays become widely accepted, although there are some limitations [15]. For example, exposure metrics can be highly correlated, as is the case with AUC and C_{max}, with individuals with a high AUC often also having a high C_{max}, which complicates discrimination between these PK/PD indices. Also, the choice of PK/PD indices is sensitive to the study design, for example whether or not a continuous infusion regimen has been included [15]. Lastly, PK/PD indices show some dependency towards pharmacokinetic processes such as drug clearance [15].

For gentamicin, tobramycin and vancomycin, strong relationships between blood concentrations and efficacy/toxicity have been described. Regarding the aminoglycosides, mostly preclinical studies have shown that both C_{max}/MIC and the 24-hour AUC (AUC_{24h})/MIC are predictive for effectiveness, where in many situations these PK/PD indices are correlated [17–19]. Since the total 24-hour exposure can be difficult to measure in clinical practice, reaching a sufficient peak level has long been considered the primary target for aminoglycoside dosing. Currently, most evidence points to AUC_{24h}/MIC as parameter driving aminoglycoside efficacy [15,19–21]. The most convincing evidence comes from individuals with a reduced clearance, for example due to renal impairment, where the correlation between C_{max} and AUC_{24h} disappears [15]. Recently, AUC_{24h}/MIC as driver for aminoglycoside efficacy has also been adopted by leading susceptibly testing organisations such as USCAST and EUCAST [22,23]. For aminoglycosides, serum drug levels also strongly correlate to toxicity, where trough levels above 1 mg/L increase the risk on nephro- and ototoxicity [7]. For vancomycin, both efficacy and toxicity correlate with the AUC_{24h}. Several studies have shown that to maximize vancomycin's efficacy (at least for treating *S. Aureus* infections) the AUC_{24h}/MIC should be at least 400 (which corresponds to an AUC_{24h} of 400 mg*h/L for an MIC of 1 mg/L) [24–28]. Vancomycin related (nephro)toxicity appears to be more frequent in patients with AUC_{24h} exposures >700 mg*h/L [14]. Based on this data, the recently revised, leading vancomycin dosing guideline drafted under aegis of several American organisations of infectious diseases specialists and pharmacists recommends to target an AUC_{24h} of 400 – 700 mg*h/L [29].

OBESITY AND DRUG DISPOSITION

Over the last five decades, the global prevalence of overweight and obesity, defined by the World Health Organisation (WHO) as an 'abnormal or excessive fat accumulation that may impair health', has increased enormously [30,31]. In adults, obesity is typically quantified using the Body Mass Index (BMI, in kg/m^2), which is the ratio of the body weight (in kg) and the square of the height (in m). Cut-offs for BMI values in overweight and obesity are ≥25 kg/m^2 and ≥30 kg/m^2, respectively, while morbid obesity, also known as Class III obesity, is generally defined as a BMI ≥40 kg/m^2 [30]. In their guideline, Dutch bariatric surgeons defined a BMI ≥40 kg/m^2 or ≥35 kg/m^2 in the presence of obesity-related comorbidities such as diabetes mellitus or hypertension as one of the indications for bariatric surgery [32]. For children and adolescents, BMI is age and sex dependent. Therefore, typical growth charts are used to identify under- or overweight. Children in the 85th – 95th BMI-percentile, adjusted for gender and age, are considered overweight, whereas children above the 95th percentile are regarded as obese [33]. Another, related definition defines paediatric overweight and obesity as being more than 1 or 2 standard deviations, respectively, above the age and gender adjusted median of the growth reference line [34].

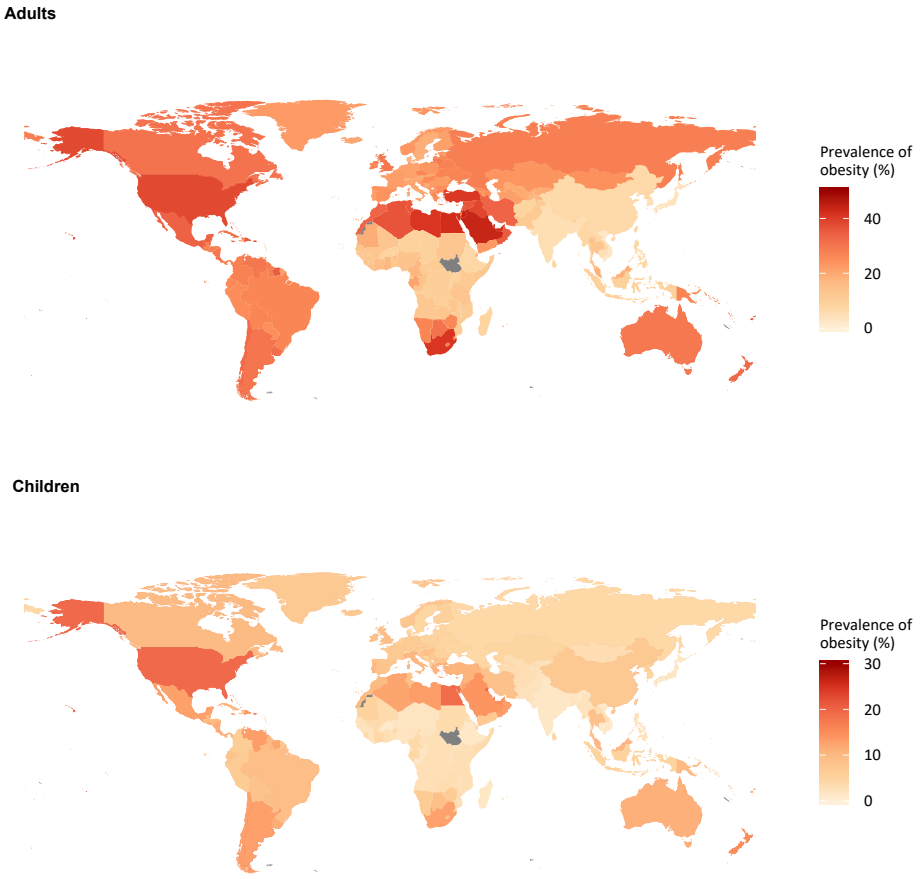


Figure 1. Worldwide prevalence of obesity for adults (upper panel, defined as BMI ≥30 kg/m²) and children (lower panel, defined as a BMI-for-age ≥2 standard deviations from median BMI-for-age). Data used from the NCD Risk Factor Collaboration (NCD-RisC) [31,34].

Since 1975, the global prevalence of adult obesity (BMI ≥30 kg/m²) tripled from 3.2% and 6.4% to 10.8% and 14.9% in men and women, respectively [31]. In regions such as Northern America, the Middle East and Northern Africa, over 30% of the adult population is nowadays considered obese (Figure 1). In some countries, the mean BMI increased with more than 1.5 kg/m² per decade since the 1970s. If these trends continue, global prevalence of obesity will reach 18 – 21% by 2025 [31]. Similar alarming trends are seen in children and adolescents (Figure 1) [34]. The past five decades global prevalence of childhood obesity increased from virtually non-existent (0.7% for girls and 0.9% for boys) to 5.6% and 7.8% for girls and boys, respectively [34]. In the United States of America, about one in every five infants shows excessive weight [34]. Obesity increases the risk on several diseases, such as hypertension, cardiovascular diseases, diabetes mellitus and certain types of cancer and is associated with an increased mortality

[30]. In 2015, around four million global deaths were attributed to a high BMI, mostly due to cardiovascular diseases [35]. Obesity also has a strong link with infectious diseases, as it appears to have a profound effect on the immune system, thereby increasing the susceptibility for infections [36]. Recently, this has been strikingly illustrated for COVID-19, where studies show that patients with a BMI > 35 kg/m^2 were two times more likely to be admitted to a critical care unit than normal weight patients [37].

The rapid escalation of obesity prevalence necessitates knowledge on how to dose drugs in obese patients. Obesity is associated with many (patho)physiological changes that may influence the pharmacokinetics of drugs [38]. The most striking impact is the increase in fat mass which can impact drug distribution into the body. Although the magnitude of this effect on drug distribution is often assumed to be related to a drug's lipophilic properties, there has been an increasing number of reports showing that lipophilicity alone is not a good predictor for changes in drug distribution [39]. Other, maybe less discernible but perhaps even more important physiological shifts occur with obesity. Due to an increase in cardiac output, blood flow to the kidney and liver, key organs in drug elimination, can be enhanced which can lead to in increased drug clearance. Here, we should however take into account that hepatic drug clearance is the result of liver flow, protein binding and intrinsic hepatic clearance, all of which can be differently impacted by obesity [40]. Regarding the intrinsic hepatic clearance, there is increasing evidence that overweight influences the activity of important drug metabolizing and transporting enzymes, where activity can be either decreased, increased or unaffected [40,41]. Due to pathological processes, such as non-alcoholic fatty liver disease (NAFLD) or a chronic increase in intraglomerular pressure, obesity ultimately might lead to a decline in liver- or renal function [42,43]. Taken together, it remains highly complex to predict the influence of obesity on a drug's clearance.

Estimating the renal function to guide drug dosing can be an additional challenge in obesity. In clinical practice, it is common to estimate a patient's renal function (depicted by the glomerular filtration rate or GFR) by using equations that incorporate serum creatinine (a breakdown product of creatinine phosphate in the muscle) and patient characteristics such as body weight, race or gender. Commonly used equations are the Modification or Diet in Renal Disease equation (MDRD), Chronic Kidney Disease Epidemiology equation (CKD-EPI), the Cockcroft-Gault equation (CG) or, in paediatrics, the Schwartz equation [44–46]. These equations have been developed in a predominantly non-obese population originally to be used to diagnose and stage kidney disease. MDRD, CKD-EPI and Schwartz estimate GFR are standardized to a body surface area of 1.73 m^2, which is also referred to as 'indexation'. CG uses total body weight (TBW) as a variable, where the estimate increases with body weight. As a result, these equations can possibly overpredict the absolute GFR (in mL/min) when used to estimate renal function in obese individuals. To correct for this overprediction, other body

size descriptors have been proposed to use as alternative for total body weight in the CG formula, where most studies advocate the use of lean body weight (LBW) [47–49]. Moreover, it remains a topic of debate how these equations perform in predicting clearance of renally excreted drugs in obesity [50].

DOSING GENTAMICIN, TOBRAMYCIN AND VANCOMYCIN IN OBESE PATIENTS

When treating severe infections with aminoglycosides or vancomycin, obtaining an optimal exposure is paramount to ensure a high efficacy with minimal risk of toxicity. Therefore, clinicians must consider the potential differences in pharmacokinetics related to obesity when using these antibiotics in obese patients.

In normal weight patients, gentamicin and tobramycin are usually dosed on the basis of body weight, typically 5 – 7 mg/kg [23]. Dosing of gentamicin and tobramycin in obesity has been subject to investigations since their first introduction [51–58]. Since these drugs are hydrophilic and, in the past, peak concentrations were assumed to be the primary driver of aminoglycoside efficacy, most of these studies have focused on characterizing changes in distribution volume. Unfortunately, only few report on clearance of aminoglycosides in obese individuals, even though to date drug clearance is the primary parameter of interest since this determines exposure and drives efficacy. In these studies, mostly conducted in individuals with a normal renal function, conflicting conclusions are reported, where some report that clearance correlates with body weight [52,54], while others found a relationship between aminoglycoside clearance and renal function estimates [55,56]. Moreover, a large part of these trials were conducted before the turn of the century, in a time where obesity was commonly defined as a total body weight above 20% of the 'ideal body weight'. As a consequence, 'obese' patients in these studies typically had a mean body weight around 85 – 100 kg, which today would at most be classified as moderately obese. Results from these studies therefore cannot simply be extrapolated to the obese individuals we nowadays see in clinical practice. Given the lack of high-quality evidence on this matter, we still remain ignorant as to if and how the gentamicin or tobramycin dose should be adapted in (morbidly) obese individuals with and without renal impairment.

The same applies to dosing vancomycin in overweight and obese adults. A widely accepted vancomycin therapeutic guideline published in 2009 by American infectious disease specialists and pharmacists, recommended a rather broad dose regimen of 15 – 20 mg/kg 2 – 3 times daily for both non-obese and obese patients [14]. This recommendation is based on several studies that were mostly performed with sparse data consisting of routinely collected peak

and trough levels [59–64]. Unfortunately, conclusions on how clearance changes with obesity differ between these studies. Similar to what is reported for aminoglycosides, some authors found body weight to be the most predictive covariate, while others describe clearance using renal function estimates or a combination of covariates. This might be explained by differences in study population with respect to renal function and body weight, or in study design. Considering the latter, accurate assessment of pharmacokinetic parameters and covariates has been shown to be highly sensitive to the sparseness of the data, for example when there is a low variability and range in time after dose or a low number of samples per individual [65]. This can be relevant when there is only TDM data consisting of peak and trough concentrations available for analysis as is the case for many of these studies. Altogether, there is currently no consensus on how vancomycin should be dosed in obese adults.

Even less evidence is available on vancomycin dosing in obese adolescents and children. In general, the basic principles discussed for obese adults presumably also apply to obese children and adolescents, although well-designed studies that explore this are limited [40,66]. Specifically for vancomycin, a small number of retrospective studies show that with similar mg/kg dosing, higher trough concentrations (as a marker for 24-hour exposure) are achieved in obese children compared to their non-obese counterparts, so a dose adjustment seems necessary [67–69]. Characterization of the pharmacokinetics in obese children can be particularly complex since processes of maturation, growth and increasing fat-mass intermingle. A weight-excess model that was recently proposed for midazolam pharmacokinetics in obese and non-obese adolescents, has not been investigated yet for vancomycin [70]. Several maturation functions for vancomycin clearance have been published, however both adolescents and obese individuals were underrepresented in these studies [71,72]. Given the fact that prevalence of obesity in this group increases alarmingly, the full pharmacokinetic profile of vancomycin in paediatric obesity need to be urgently characterized to design specific dosing guidelines for this group [66,73].

POPULATION PHARMACOKINETIC MODELLING AND SIMULATION

To be able to answer the questions raised in the previous sections it is important to conduct studies with a sound design and pharmacokinetic analysis. A major, well established methodologic strategy is to use population pharmacokinetic modelling and simulation techniques. These are widely considered leading tools for understanding and quantifying drug behaviour across different patient populations to design rational drug dose regimens [74]. Using this approach, a population pharmacokinetic model is developed that defines the relationship between a dose and a drug's blood or tissue concentration(s) over time. These models consist

of structural pharmacokinetic parameters (such as volume of distribution or clearance, described as algebraic equations) with different sources of random variability (usually inter-individual variability and residual variability). Patient characteristics or time independent covariate effects (for example body weight or a genotype) can be identified as predictors for pharmacokinetic parameters and subsequently included in the pharmacokinetic model. The population approach is also known as non-linear mixed effects modelling (NLME). NLME is a particularly suitable technique for the topic of this thesis, since it is powerful in separating and quantifying the influence of combinations of covariates on pharmacokinetic parameters, such as obesity and renal function or obesity and maturation processes in paediatrics. After a model is developed, simulations are performed incorporating the random and fixed effects (so called stochastic simulations) using different dose regimens in a large number of virtual subjects to find the optimal dose regimen. To date, population pharmacokinetic modelling and simulation has become broadly accepted by drug registration authorities as essential components in drug development programs, especially to inform dose regimens for special populations [75–77].

AIMS AND SCOPE OF THIS THESIS

In this thesis we aim to characterize the influence of obesity on the pharmacokinetics of gentamicin, tobramycin and vancomycin in (morbidly) obese adults, in conjunction with other possibly relevant patient characteristics such renal impairment or (critical) illness as occurring in the real-world. Additionally, we aim to investigate the influence of obesity, renal function and maturation on pharmacokinetics in a clinical population of lean and overweight children and adolescents with and without renal impairment and were treated with vancomycin. With this knowledge, we intent to gain more knowledge on changes of such renally cleared drugs in obesity and provide dose recommendations for (morbidly) obese children, adolescents and adults for the studied drugs. Using these dose recommendations, we aim to improve antibiotic treatment for (morbidly) obese patients by maximizing the antibiotic's efficacy and minimizing toxicity.

In **Chapter 2**, a comprehensive overview is provided on what is currently known regarding the physiological changes associated with obesity and their influence on pharmacokinetics and/or pharmacodynamics of drugs. In the next section, we specifically quantify the influence of obesity on the pharmacokinetics of gentamicin, tobramycin and vancomycin in non-obese and morbidly obese, but otherwise healthy individuals. To this end, several prospective, rich-sampling, clinical studies were conducted, for which the results are presented in **Chapter 3** for gentamicin, in **Chapter 4** for tobramycin and in **Chapter 5** for vancomycin. In the third section, we extend our studies to two real-world, clinical special populations. In **Chapter 6**, the pharmacokinetic model and dose recommendations for gentamicin are extended by

combining the prospectively collected data in non-obese and morbidly obese otherwise healthy individuals with real-world clinical TDM data from (morbidly) obese patients treated with gentamicin. In **Chapter 7** we study the pharmacokinetics in a large multicentre clinical cohort of children and adolescents treated with vancomycin. Finally, in **Chapter 8**, a general discussion is provided where we summarize the results, reflect on the clinical impact of our results and lessons learned from these studies, discuss on future perspectives and provide overall conclusions.

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2



Obesity and drug pharmacology: A review of the influence of obesity on pharmacokinetic and pharmacodynamic parameters

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ABSTRACT

Introduction Rising prevalence of obesity confronts clinicians with dosing problems in the (extreme) overweight population. Obesity has great impact on key organs that play a role in the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs, however the ultimate impact of these changes on how to adapt the dose may not always be known.

Areas covered In this review, physiological changes associated with obesity are discussed. An overview is provided on the alterations in absorption, distribution, drug metabolism and clearance in (morbid) obesity focusing on general principles that can be extracted from pharmacokinetic studies. Also, relevant pharmacodynamics considerations in obesity are discussed.

Expert opinion Over the last two decades, increased knowledge is generated on PK and PD in obesity. Future research should focus on filling in the knowledge gaps that still remain, especially in connecting obesity-related physiological changes with changes in PK and/or PD and vice versa. Ultimately, we can use this knowledge to develop physiologically based PK and PD models on the basis of quantitative systems pharmacology principles. Moreover, efforts should focus on thorough prospective evaluation of developed model-based doses with subsequent implementation of these dosing recommendations in clinical practice.

INTRODUCTION

Since the 1980s, the global prevalence of obesity, which is defined as a body mass index (BMI) > 30 kg/m2, has increased alarmingly [1]. In 2015, more than 100 million children and 600 million adults were estimated to be obese worldwide [2]. In 2014, nationwide representative surveys in the United States showed that 35-40% of the adult population met the criteria for obesity [3]. Recently, several leading medical associations classified obesity as a disease [4].

Obesity and in particular morbid obesity is known to influence several physiological processes such as gut permeability, gastric emptying, cardiac output, liver- and renal function [5]. As a consequence, pharmacokinetic (PK) properties of drugs may be altered in (morbidly) obese patients [6–8]. In addition, the pharmacodynamics (PD) of drugs may be different in obesity. For instance, benzodiazepines or opioid analgesics may have a more pronounced effect in obesity because of the increased incidence of obstructive sleep apnoea (OSA) in obese individuals. As a result, for different reasons adjusted doses may be necessary in obese patients. Although the number of publications on this topic is increasing over the last decades, evidence on PK, PK/PD and drug dosing strategies for specific drugs in obesity remains scarce, particularly for morbidly obese patients.

An important strategy for characterizing drug PK/PD profiles in special populations such as the obese is a model-based approach in which nonlinear mixed effect modelling has been instrumental [9]. With this approach PK and/or PD is modelled on a population level, while concurrently quantifying the inter-individual variability. Subsequently, it is assessed how patient-specific characteristics (covariates) can (partially) explain observed differences between patients. The fact that this approach can adequately deal with limited data makes it particularly suited for application in PK/PD of special populations such as neonates and children, but also for other special populations such as the obese.

Ideally, pharmacological and physiological knowledge obtained from different drugs and studies is integrated to identify drug-specific and system-specific properties that can be employed to guide drug dosing in the future [9]. To aid in this concept, this review aims to give an overview of the different physiological changes in obesity and to provide an update of the current knowledge on the influence of these changes in (morbid) obesity on different PK and/or PD parameters.

OBESITY-RELATED PHYSIOLOGICAL CHANGES

Obesity is defined as a body mass index (BMI) ≥ 30 kg/m^2, with morbid or severe obesity generally being defined as a BMI ≥ 40 kg/m^2 or a BMI ≥ 35 kg/m^2 with comorbidities [10]. It has become widely accepted that obesity is characterized by a chronic low-grade inflammation state of adipose tissue [11]. Together with significant anatomical and physiological alterations, this could influence the PK and/or PD of drugs.

In obesity, gut wall permeability as well as gastric emptying has been reported to be accelerated with obesity [12–14]. To provide nutrients and oxygen to the excess tissue, blood volume, capillary flow and cardiac output also increase in obese patients [15–17]. With this enhancement in cardiac output, liver blood flow is expected to increase with flow into the liver as the fraction of cardiac output remains stable [15]. However, due to non-alcoholic fatty liver disease (NAFLD) resulting in steatosis or steatohepatitis (NASH) together with sinusoidal narrowing, liver blood flow might decline over time, particularly in morbidly obese individuals [18,19]. Total protein concentrations and serum albumin seem to be unaltered by obesity, while alpha 1-acid glycoprotein (AAG) seems to be elevated in morbidly obese patients, although contradicting studies exist regarding the latter [20,21]. Effects of obesity on pulmonary function have been well established. Lung volumes, especially the residual capacity and expiratory reserve volume, are negatively correlated with BMI [22,23]. Furthermore, obesity is associated with asthma and can lead to OSA or obesity hypoventilation syndrome (OHS) [24]. The effect of obesity on renal function appears ambiguous, since some studies report an increase in glomerular filtration rate (GFR), while others show that severe overweight is strongly correlated with chronic kidney disease (CKD) [25–27]. It is now generally believed that during the lifespan of an obese patient, renal clearance is initially enhanced by a compensatory hyperfiltration and hyperperfusion, though eventually declines as a result of a constantly elevated intra-glomerular pressure [25,27]. An overview of physiological changes associated with obesity is shown in Figure 1.

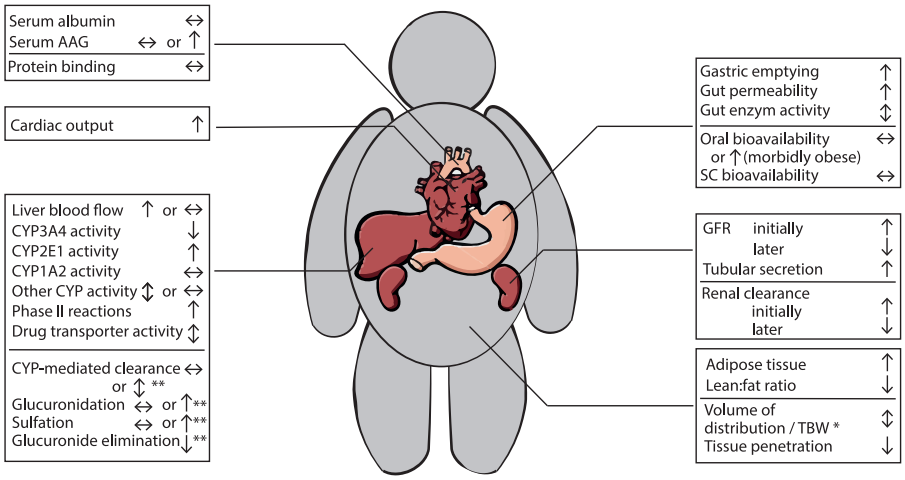


Figure 1. Summary of physiological changes in obesity and corresponding effects on PK parameters. ↑ increases with obesity, ↓ decreases with obesity, ↕ can either increase or decrease with obesity, ↔ unaltered with obesity. *AAG* alpha 1-acid glycoprotein, *GFR* Glomerular Filtration Rate, *TBW* total body weight.

BODY SIZE DESCRIPTORS

Beside total body weight (TBW) in (morbidly) obese patients, other body size descriptors have been proposed to guide drug dosing (Table 1). Lean body weight (LBW) or fat free mass (FFM) globally represents bone tissue, muscles, organs and blood volume and was reported to relate well with renal function in obesity [28,29]. Strictly, in contrast to FFM, LBW does include a small fraction of adipose tissue (cellular membrane lipids) and therefore does not always exactly correspond to FFM. However, in relation to TBW, this portion is generally small (3-5%) and therefore these two descriptors can in general be used in the same way [29]. LBW or FFM is commonly calculated using the Janmahasatian method, taking into account TBW, height and gender [29]. Since the introduction of this formula, LBW is increasingly being proposed as a body size descriptor in obesity pharmacology, especially for renally cleared drugs [30]. However, as LBW also takes gender into account with higher LBW in males compared to females even when TBW is the same, it should be realized that the use of this descriptor leads to substantially higher dosages in males compared to females, even in case of similar body weights [29]. Therefore, when conducting a PK study, both genders should be included in sufficient amount as gender is a driver in the calculation of LBW. Besides TBW and LBW, other body size descriptors such as ideal body weight (IBW) or adjusted body weight have occasionally been proposed to guide drug dosing for specific drugs [31–33], even though to date

there seems limited interest in these scalars. BMI, widely used in defining and quantifying obesity, as a descriptor of body shape and not body composition, also seems less suitable for use as body size descriptor for drug dosing in the obese [34]. Finally, estimated body surface area (BSA) is traditionally used when dosing cancer chemotherapy [35]. From this overview, it seems that each body size descriptor has its own (dis)advantages for application in drug dosing in obesity, while no body size descriptor has been shown to be universally applicable for prediction of PK parameters in obesity [36]. Besides the body side descriptor, also the scaling factor is of relevance when relating parameters to weight. While one may anticipate a linear (scaling factor of 1) or allometric (scaling factor of 0.75) function between TBW and clearance, assuming that obese individuals differ only in being larger than normal weight individuals, this seems a considerable simplification [34]. In this respect it is also important to realize that for instance LBW and BSA relate in a nonlinear manner to TBW [6]. As a consequence, the use of another descriptor will influence the value of the exponent or scaling factor. Moreover, even though an increase in a certain parameter or dose may be anticipated for obese individuals, plasma clearance or volume of distribution is not always reported to increase or might even decrease, implying a zero or negative value for the scaling factor [6,7].

Table 1. Body size descriptors with corresponding formula's.

Body size descriptor	Formula	Reference
Total body weight (TBW)	-	-
Body Mass Index (BMI)	$BMI\ (kg/m^2) = \frac{TBW\ (kg)}{HT^2\ (m^2)}$	[37]
Body Surface Area (BSA)	$BSA\ (m^2) = 0.007184 \times TBW\ (kg)^{0.425} \times HT\ (m)^{0.725}$	[38]
Ideal Body Weight (IBW)	IBW (male, kg) = 49.9 + 0.89 × (HT (cm)-152.4) IBW (male, kg) = 49.9 + 0.89 × (HT (cm)-152.4)	[39]
Adjusted Body Weight (ABW)	ABW (kg) = IBW + F × (TBW - IBW) F = drug specific correction factor (generally 0.3-0.6)	[40]
Lean Body Weight (LBW)	$LBW\ (male, kg) = \frac{9.27 \times 10^3 \times TBW\ (kg)}{6.68 \times 10^3 + 216 \times BMI\ (kg/m^2)}$ $LBW\ (female, kg) = \frac{9.27 \times 10^3 \times TBW\ (kg)}{8.78 \times 10^3 + 244 \times BMI\ (kg/m^2)}$	[29]

INFLUENCE OF OBESITY ON PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS

Obesity and drug absorption

After oral ingestion of a drug, the absorption from the intestine is determined by the rate of absorption (k_a) and the total amount of drug absorbed (bioavailability, or F). F is dependent upon fraction absorbed (F_a) and gut and hepatic (first pass) metabolism (F_g and F_h). Since it is known that, in obesity, gut permeability increases and gastric emptying is accelerated, while CYP-mediated gut and or liver metabolism might also be affected, it is plausible that obesity influences overall oral absorption [7,12–14,41]. Although beyond the scope of this review, we know that in addition to obesity itself, also diet and bariatric surgery might greatly affect PK in terms of rate and/or extend of drug absorption. Therefore, obese individuals are prone to changes in F or k_a.

The classic approach to quantify F is by obtaining data after both oral and intravenous (IV) administration of a drug within the same subjects on separate occasions. However, since this method requires an experimental setting and a washout period, only few such studies have been done in the obese population [42–47]. In these studies, regarding cyclosporine, dexfenfluramine, midazolam, moxifloxacin, propranolol and trazodone, no significant differences were observed in bioavailability or (if reported) rate of absorption between obese and lean subjects, although for propranolol, a trend towards a higher bioavailability was observed [45].

Another method to determine oral bioavailability is via a semi-simultaneous design, in which F can be studied in a single occasion [48,49]. A disadvantage of this approach is that absorption has to be virtually complete before the IV formulation is administered, which may be difficult to predict in obese patients. Nevertheless, a semi-simultaneous study design can provide useful information on drug absorption in morbidly obese patients as was demonstrated for midazolam [50]. In this trial, morbidly obese subjects undergoing bariatric surgery received midazolam orally, followed by an IV dose after 150 minutes. In this study, a higher F in the obese group (60% vs. 28%) was found. The increase in F was hypothesized to be related to a decreased gut CYP3A4 activity and/or an increased gut blood flow or permeability [44,50]. Notably, in contrast to the earlier mentioned 'classic approach' studies, where some included obese subjects with average body weights of <120 kg, the latter midazolam study included patients with mean body weight of 144 kg (range 112 - 186 kg). Therefore, it might be possible that alterations in F are only significant in severely obese individuals.

In addition to these results, studies on orally administered levothyroxine and acetaminophen found a delay in time to peak concentration (T_{max}) in morbid obesity compared to lean subjects [51,52]. In contrast, for morphine, similar absorption rates were found in morbidly obese patients in comparison to what is found in healthy volunteers [53,54]. It should however be noted that T_{max} is also determined by elimination clearance and therefore does not necessarily represent drug absorption rate. Unfortunately, in these studies no data were obtained after IV administration, hence no definite conclusions can be drawn upon bioavailability of these drugs. Despite this limitation, the authors of the acetaminophen study do relate the fact that they found a lower area-under-the-curve (AUC) in the obese population to a lower bioavailability. It can however not be excluded that the lower AUC is caused by an augmented drug clearance rather instead of hampered bioavailability, which was reported later in another study [55].

Since morbidly obese patients are characterized by an excess of (subcutaneous) adipose tissue, one could hypothesize that drug absorption from parenteral forms such as intramuscular or subcutaneous injection might be altered as well in obese patients. Only few studies have assessed drug absorption in these situations. Enoxaparin was investigated in a study in moderately obese (mean TBW 100 kg, range 78 – 144 kg) and non-obese volunteers [56]. Participants received enoxaparin subcutaneously once daily for four consecutive days and once intravenously with a washout period of at least seven days in between. No difference in F was observed between obese and non-obese individuals. In another study, twelve moderately obese Chinese women (BMI 28.2-32.8 kg/m^2) and twelve non-obese women (BMI 19.8 – 22.0 kg/m^2) were given an intramuscular and subcutaneous injection with a fixed dose of 10.000 IU of human chorionic gonadotropin with a four week interval [57]. In this population, the AUC was substantially lower in the obese group with both routes of administration. While this may be caused by a decreased absorption in obesity, another explanation could be an increased clearance in the obese individuals. In addition, in two other studies a delayed absorption in obese patients was seen for subcutaneous administered insulin lispro, but not for nadroparin [58,59]. For nadroparin, also an increase in apparent clearance with body weight was reported which may not only be the result of an increase in clearance but could theoretically also be due to a decrease in (subcutaneous) bioavailability. However, as in this study no information was available upon IV administration of nadroparin, we cannot distinguish between the two explanations.

With respect to drug absorption, it seems that the evidence on the effect of (severe) obesity is limited. Despite an apparent increase in gut permeability and possible decrease in gut CYP3A4 metabolism in obesity, only for midazolam an increased bioavailability was reported [50]. Since in the midazolam study severely obese patients were studied, it could be speculated that bioavailability is only significantly increased in case of extreme obesity. The drug absorption rate or bioavailability from subcutaneous injections seems to be unaltered in obesity, however there is not yet enough evidence to draw firm conclusions.

Obesity and drug distribution

Volume of distribution (V_d) is an important theoretical PK parameter defining the peak concentration (C_{max}) after each dose of a drug, and, together with drug clearance, determines the elimination half time of a drug. The first is of particular significance for choosing the optimal loading dose, the latter for time to reach steady state in a multiple dosage regimen.

In morbidly obese patients, changes in V_d might depend on several drug properties, such as the lipophilicity of the drug, ionization properties, blood:plasma ratio and protein binding [60,61]. As such, lipophilicity alone does not necessarily predict the change in V_d [5,60]. In theory, lipophilic compounds are expected to easily diffuse into adipose tissue, and therefore V_d is expected to increase with TBW for these drugs. This principle is illustrated in study with diazepam [62]. In this study in six moderately obese and five normal weight subjects, this highly lipophilic drug shows a dramatic increase in V_d with increasing body weight. On the contrary, hydrophilic drugs are expected to be restricted to aqueous compartments such as blood and extracellular water. Since the volume of these compartments does not linearly increase with TBW, V_d/TBW is expected to decrease for these drugs. This is delineated by ranitidine, a hydrophilic drug, in which one study showed that V_d/TBW decreased in obese subjects [63]. However, as stated earlier, lipophilicity does not necessarily predict changes in V_d [5]. For example, propofol and digoxin, both (highly) lipophilic drugs, do not show an increase in V_d in obese patients [64,65]. In addition, it has been shown that the V_d of vancomycin, which is a water-soluble drug, shows a strong linear increase with TBW [66,67]. As such, lipophilicity should be considered only one of the drug properties to consider when predicting changes in volume of distribution related in obesity.

Concerning serum protein concentrations in obesity, albumin and total protein concentrations seem to be unaltered between lean and obese subjects, although AAG, which is particularly important in binding basic drugs, could be elevated in morbid obese patients [20]. Differences in protein binding in relation to PK parameters such as V_d or CL in obese and non-obese patients have been assessed in studies concerning alprazolam, cefazolin, daptomycin, lorazepam, midazolam, oxazepam, propranolol and triazolam [21,44,68–71]. In these studies, unbound concentrations appeared unchanged in morbidly obese patients. In addition to unbound fractions, the study with daptomycin also reported serum albumin concentrations, which were unaltered in morbid obesity [70]. In the propranolol study, albumin concentrations were reduced, with AAG serum concentrations unaltered [21]. While the latter is in contrast with what was reported earlier [20], this explains the unchanged protein binding for propranolol, which is mainly AAG-bound. In a study regarding clindamycin in obese children, V_d decreased with increasing AAG and albumin serum concentrations [72]. Unfortunately, unbound clindamycin concentrations were not measured, so it remains unclear whether free concentrations were influenced [72].

Another important aspect of drug distribution in morbidly obese individuals concerns tissue penetration. This can be especially relevant for antibiotics used for localized infections or perioperative prophylaxis, where sufficient tissue concentrations need to be achieved in order to be effective. To measure concentrations at the target site, it is for instance possible to measure drug concentrations in the epithelial lining fluid for pulmonary penetration or in interstitial fluid (ISF) using microdialysis techniques [73,74]. Drug concentrations in the ISF are measured by inserting a probe, which is continuously perfused with a physiological solution, in the tissue of interest. A major advantage of this method is that it enables us to measure the unbound (pharmacologically active) drug on multiple time-points. This is in contrast with the classic approach that uses tissue biopsy specimens, which are homogenized before measurement of drug concentrations. As a consequence, overall drug concentrations are determined, thereby mixing up intra- and extracellular concentrations, and both bound and unbound concentrations, instead of the pharmacologically active, unbound, drug concentration only. Since most anti-infective drugs are distributed exclusively to the intra- or extracellular space, PK studies employing this technique should be interpreted with caution [75,76].

So far, studies regarding tissue penetration in morbid obesity using microdialysis have been done for cefazolin, cefuroxime and ciprofloxacin [69,77,78]. Ciprofloxacin was administered as a single IV bolus dose to twelve obese subjects (mean weight 122 ± 22.6 kg) and twelve normal weight controls, after which ciprofloxacin concentrations were measured in plasma and ISF of skeletal muscle and subcutaneous tissue [77]. Plasma concentrations of ciprofloxacin were significantly higher in the obese, while ISF concentrations were similar. The authors conclude that, to yield adequate concentrations in peripheral tissue, ciprofloxacin should be dosed on actual body weight, although it is unclear whether the resulting high (peak) plasma concentrations might lead to increased side effects. Besides, fluoroquinolones are primarily used in pulmonary infections or urinary tract infections. Since tissue penetration in these organ systems may be different from subcutaneous tissue, future research should focus on whether the same hampered tissue penetration also applies for these organ systems [79]. For cefazolin, which is commonly used as a prophylactic agent during surgery, a study using microdialysis techniques showed that in morbidly obese patients (mean weight 140 kg, range 107–175 kg) cefazolin concentrations in the ISF of the subcutaneous tissue were significantly lower after a single 2 g IV dose compared to non-obese patients [69]. Subsequent Monte Carlo simulations demonstrated a reduced probability of target attainment for obese patients with a BMI>40 kg/m^2, with specifications for different minimal inhibitory concentrations and duration of surgery. As a consequence, the Dutch guidelines for perioperative antibiotic prophylaxes prescribe for morbidly obese patients a single dose of 3 g cefazolin instead of 2 g [80]. Lastly, a microdialysis study in six obese patients (109-140 kg) showed that cefuroxime distributed extensively into ISF in muscle and subcutaneous tissue and seems to yield adequate

concentrations for common pathogens such as *Staphylococcus aureus*, but not for *Escherichia coli* [78]. Unfortunately, no control group was included in this study, so no definite conclusions can be made upon changes in tissue penetration in obese versus non-obese individuals.

In conclusion, it is evident that changes in volume distribution are difficult to predict upfront based on drug properties such as lipophilicity alone, and that ionization properties, blood:plasma ratio and protein binding need to be taken into account as well. Protein serum concentrations seem unaltered in obese, with the exception of AAG which is reported to be elevated in some studies. Nonetheless, it has not been shown that this leads to relevant pharmacokinetic changes yet. Lastly, differences in tissue penetration between obese and non-obese individuals can be significant. Until now, this has been studied for several antibiotics. In studies regarding cefazolin and ciprofloxacin, tissue penetration was significantly reduced. As a result, higher dosages and/or increased frequency of dosing might be necessary even when this leads to higher plasma concentrations.

Obesity and drug clearance

As clearance impacts the maintenance dose of drugs, it is generally considered as the PK parameter with the greatest impact for clinical applications.

The liver forms the main organ responsible for drug metabolism, where enzymes are responsible for modification and conjugation of drugs (phase I and II reactions, respectively). It is noted that these reactions can also take place in other tissues such as plasma, kidneys or the gut wall. Hepatic drug metabolism is dependent on intrinsic liver clearance (Cl_{int}), which is determined by enzyme activity and transporters in the liver. Together with hepatic blood flow (Q_h) and protein binding (f_u), Cl_{int} determines the hepatic plasma clearance (Figure 2). Variation in these parameters may more or less influence the hepatic plasma clearance of a drug depending on its hepatic extraction ratio. The extraction ratio depicts the efficiency of an organ to clear a drug from the circulating blood. High extraction ratio drugs typically have a clearance independent of enzyme capacity or plasma protein binding and depend primarily on hepatic blood flow. In contrast, the clearance of low or intermediate extraction ratio drugs is mainly dependent of the intrinsic metabolizing capacity of the liver (Figure 2).

In obesity, the prevalence of liver abnormalities is extremely high and in patients undergoing bariatric surgery, can exceed over 90% [81]. Abnormal fat deposition and inflammation in the liver results in a range of conditions from steatosis to NASH and can influence hepatic enzyme and drug transporter expression and/or activity as well as liver blood flow. With respect to the influence of obesity on hepatic blood flow, different scenarios can be hypothesized. While it is known that cardiac output increases with obesity, one study showed that liver blood flow increases with liver blood flow being a percentage of cardiac output [15]. This was confirmed

with studies on propofol and fentanyl, where an increased clearance with increasing TBW was seen [64,82–84]. Since both drugs are high extraction drugs, changes in clearance are expected to represent changes in liver blood flow. However, due to fatty liver disease, liver microcirculation was shown to decrease in animal models [19].

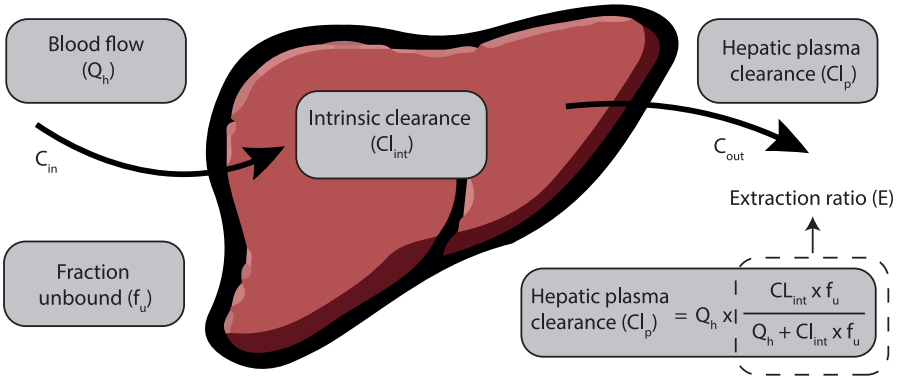


Figure 2. Overview of processes involved in hepatic metabolism. Intrinsic clearance (Cl_{int}) is influenced by enzyme activity and transporters in the liver. Together with the fraction unbound (f_u) and hepatic blood flow (Q_h), Cl_{int} determines the hepatic plasma clearance (Cl_p). The extent to which Cl_p is influenced by variation in these parameters depends on the extraction ratio E, with high extraction ratio drugs mainly being influenced by Q_h, and medium to low extraction ratio drugs mainly being influenced by Cl_{int}.

When considering Cl_{int}, hepatic drug metabolism is generally divided into phase I and phase II reactions. Phase I reactions are mediated by enzymes, the most important being the cytochrome P450 system. About 50% of all metabolized drugs are metabolized by CYP3A4, which is primarily present in hepatocytes and the gut wall. Midazolam is primarily metabolized by CYP3A and generally considered a probe for CYP3A enzyme activity. Several animal and in vitro human studies showed a reduced CYP3A4 activity related to obesity or NAFLD [85–88]. It has been hypothesized that low-grade inflammation decreases expression of pregnane X receptor (PXR) and constitutively activated receptor (CAR) resulting in less expression of certain CYP enzymes, including CYP3A4 [89]. However, in morbidly obese patients, midazolam plasma clearance appeared to be unchanged when compared to healthy volunteers [44,50]. Since midazolam is considered a medium-to-high extraction ratio drug, it might be possible that reduced CYP3A4 activity is compensated by an increased liver size or liver blood flow. A follow-up study in the same study population one year later showed that, after weight loss, midazolam clearance exceeded clearance in the non-obese population. To explain this, it was hypothesized that CYP3A4 activity is restored, thereby surpassing the expected reduction in liver size after bariatric surgery [90].

Besides CYP3A, other CYP enzymes are involved in phase I drug metabolism, albeit to a much smaller extent. Orally administered chlorzoxazone, which is a probe drug for CYP2E1, has a higher metabolic clearance (CL/F) in obese patients compared to non-obese subjects [91]. Unfortunately, the number of participants in this study was small and chlorzoxazone was not administered IV, so CL could not be assessed apart from F. An increase in CYP2E1 activity might be likely as this was also seen in another study where acetaminophen was administered intravenously in obese patients [55]. In contrast to CYP3A4 and CYP2E1, no significant impact of obesity on CYP1A2 activity was seen in a study regarding caffeine, which is metabolized via this enzyme. In this study, where caffeine was administered in an oral dose of 200 mg to obese and non-obese subjects, CL/F was comparable in both groups [92].

Given the potential pathophysiological effects of obesity on the human body, duration of obesity might also be an important factor in hepatic metabolism. This is illustrated by the results on a study on midazolam in obese adolescents and obese adults where in obese adolescents, mean midazolam clearance was higher compared to obese adults [93]. These results are surprising as body weights were similar in these two populations. Particularly because in (non-obese) adolescents typically lower clearance values may be assumed for which 0.75 allometric scaling on the basis of body weight is relatively undebated [94,95]. Therefore, the larger clearance in obese adolescents was explained by the lack of suppression of CYP3A in view of the relative short duration of obesity compared to obese adults. Similar results were found for clearance of fentanyl (a high extraction ratio drug for which liver blood flow is relevant) which appeared larger in obese adolescents compared to literature values in obese adults which may aim at less liver changes with respect to liver flow in obese adolescents compared to obese adults [96]. Finally, a strong positive correlation was found between the severity of hepatic steatosis and increase in CYP2E1-mediated metabolic clearance of chlorzoxazone, which adds to this hypothesis [91].

Phase II conjugation reactions generally seem to be elevated in morbid obesity, as can be illustrated by studies performed with low-to-medium extraction ratio drugs such as acetaminophen, oxazepam and lorazepam [55,71]. When glucuronidation and sulfation of acetaminophen in morbidly obese patients were studied together with data from healthy volunteers in a meta PK analysis, a significant increase in both of these pathways was found [55]. Also in the studies regarding oxazepam and lorazepam, of which excretion is primarily dependent on glucuronidation, drug clearance markedly increased in the obese population [71].

However, recent studies on morphine which is also mainly glucuronidated showed somewhat surprising results. In these studies, higher morphine glucuronide concentrations were seen in obese compared to non-obese as well in NASH patients [97–99]. Two of these studies showed similar morphine concentrations together with increased glucuronide concentrations, which

indicated no significant increase in glucuronidation, but instead a decrease in clearance of glucuronides [98,99]. As discussed earlier, the lack of increase in glucuronidation clearance may be explained by the fact that morphine is a medium-to-high extraction ratio drug, assuming liver blood flow was unchanged in these populations. A decreased elimination clearance of morphine glucuronides in both obese and NASH patients might be explained by the involvement of drug transporters such as multidrug resistance proteins (MRP) 2 and 3. It was shown in rat models that NASH, commonly associated with obesity, influences transporter expression [100]. These specific transporters are responsible for the transport of bile acids, anionic drugs and hepatically derived metabolites (such as glucuronides) from hepatocytes to the blood plasma (MRP3) or hepatocytes to the bile (MRP2) [101]. The results from the morphine studies led to the conclusion that elimination of glucuronides is possibly decreased due to a suppression of MRP2 and upregulation of MRP3 in obese patients [98,99].

Over the last years, increasing evidence is generated on altered drug transporter function in obesity. Despite the fact that literature is still scarce, most knowledge has been generated on transporter activity in NASH, a condition that is common in the obese population [81]. In addition to earlier described changes in MRP2 and MRP3, studies suggest that NASH might also influence the functionality of other drug transporters such as organic anion transporting polypeptides (OATP) and organic anion transporters (OAT), which play an important role in uptake of several drugs such as statins or angiotensin-converting enzyme (ACE)-inhibitors such as enalapril [102,103].

In conclusion, based on the provided examples, it is clear that predicting drug clearance in obesity for hepatically metabolized drugs is challenging. In general, enzyme activity of CYP2E1 and phase II metabolism seems to increase, while CYP3A4 activity seems to decrease and CYP1A2 is likely to be unaffected. However, for translating these results into overall plasma clearance, several factors should be taken into account, such as drug properties like extraction ratio, liver size, duration of obesity and an additional influence from transporters (see also Figure 2).

Regarding renal drug clearance, the relationship between obesity and kidney function is complex, since obesity is associated with an enhanced renal function, but also an important risk factor for the development of CKDs [25,104].

In clinical practice, GFR is often estimated using creatinine clearance (CL_{cr}) as a surrogate estimate. In these situations, estimated GFR (eGFR) is calculated by imputing serum creatinine in a formula together with other patient characteristics such as race, age, gender or body weight. Nowadays, mostly the modification of diet in renal disease (MDRD) and the CKD and epidemiology (CKD-EPI) formulas are employed, of which the latter has the advantage that

it is also accurate in renal functions above 60 mL/min/1.73m^2 [105]. However, these methods express eGFR normalized to BSA (mL/min/1.73 m^2), and tend to overestimate the GFR in patients with a large body weight when corrected for BSA and expressed as absolute eGFR in mL/min [106,107]. This is also the case with the Cockcroft-Gault (CG) formula, which uses TBW to estimate CL_{cr}. For example, calculation of CL_{cr} using CG formula with TBW in morbidly obese subjects overestimated clearance with +107.4 mL/min compared to CL_{cr} measured with 24-h urine collection [106]. Recently, several studies suggest to use LBW in the CG formula to adequately estimate GFR in obese patients [106–108]. This seems plausible, since it was shown that LBW normalizes changes in GFR in obese patients [28].

As a consequence of an enhancement in GFR, it might be expected that drug excretion increases in obesity when renal drug excretion is dependent upon GFR. For instance, gentamicin, tobramycin and vancomycin, almost exclusively excreted unchanged via urine, showed an increased clearance in morbidly obese patients [40,66,67]. In contrast, this influence of obesity on drug clearance was not seen for cefazolin or fluconazole, both renally excreted drugs that showed similar total drug clearances in morbidly obese subjects [69,109]. However, fluconazole was studied in a group of obese and non-obese critically ill patients with no differences in CL_{cr} within these groups [109]. In the study regarding cefazolin, even though renal function was anticipated to be unaffected, no CL_{cr} or eGFR values were reported while in addition the sampling time may have been too short to pick of changes in clearance [69]. An increase in renal excretion in obese is also consistently seen in several studies on oseltamivir and its active metabolite oseltamivir carboxylate, both undergoing active renal tubular secretion besides GFR-mediated clearance [110–112], indicating that tubular secretion might also be augmented in obese. This was supported by studies regarding procainamide, metformin and ciprofloxacin, drugs that undergo active tubular secretion, where an increase in clearance was seen in obese patients or with increasing body weight [113–115]. These drugs are partly excreted via the organic cation transporters (OCT) drug transporter system, which might be enhanced in NASH or obesity. Although a trend in increased OCT2 renal expression was seen in a mouse study, this hypothesis remains uncertain [116]. In another study, clearance of lithium was shown to be enhanced in obesity, even though no difference in CL_{cr} was found [117]. The authors conclude that an increase in lithium clearance could be explained by an impaired tubular reuptake of lithium in overweight patients.

In summary, despite an initial increase in GFR in overweight patients, renal drug clearance does not necessarily increase. This might be explained by the fact that on the longer term, GFR might actually decrease in obesity. Another possibility is that studied patients might have a reduced renal function due to comorbidities such as sepsis. The distinction between glomerular and tubular processes in renal excretion is difficult. However, it appears that, in general, tubular secretion is enhanced in obesity.

A summary of relevant physiological changes in obesity and corresponding effects on PK parameters is shown in Figure 1.

Obesity and pharmacodynamic changes

While much pharmacological research in obesity focusses on drug PK, this might not necessarily suffice for translation to an optimized drug dosing regimen. More evidence shows that PD changes, i.e. a difference in drug efficacy or toxicity even when corrected for PK differences, play an important role as well. For example, adipocytes secrete adipokines such as leptin, which reduces macrophage and T-cell differentiation and activity [118]. It has been demonstrated that due to this cross talk between adipose tissue and the immune system, several infectious diseases in obese patients are associated with a worse outcome compared to the normal weight population. It can be hypothesized that not only PK changes of antimicrobial drugs (leading to lower plasma concentrations) but also changes in drug effectiveness (due to changes in the immune system) could underlie a worsened outcome from infections [118]. An interesting example of the relevance of changes in the PD is depicted by the intravenous anesthetic propofol. The PK/PD profile of propofol was investigated in twenty morbidly obese patients, based on propofol blood concentrations and bispectral index monitoring [64]. Clearance increased allometrically with an exponent of 0.72, but similar maximal effect (E_{max}) or propofol concentrations at half-maximum effect (E_{50}) were observed for obese individuals when compared to literature values of lean subjects. In contrast, a more recent Chinese PD study showed similar results on PK, with an increased clearance in morbid obesity, but a reduction in E_{50} for obese individuals [82]. The authors hypothesize that this might be caused by an increased sensitivity of the brain to propofol. Also, differences in co-medication might underlie these differences, even though both obese and non-obese patients underwent similar gastrointestinal surgery. For reasons of changes in PD, the authors advise LBW-based dosing of propofol, where lower plasma concentrations yield similar sedative effects [82]. Another example of a PD study was done with the neuromuscular blocking agent atracurium, for which in a PK study a similar V_d and Cl in obese and non-obese patients was found [119]. Whether atracurium should be dosed on TBW or IBW was investigated in a subsequent PD study [33]. In this study, twenty morbidly obese patients (range 112 - 260 kg) were randomized to receive either atracurium dosed on TBW or IBW. The PD endpoint, i.e. time to recovery of the neuromuscular blockade, was significantly prolonged in the TBW group. It was concluded that atracurium should be dosed on IBW, since this gave full recovery after 60 minutes, allowing conditions for adequate intubation and no antagonists would be needed [33]. A last example of a possible difference in PD in obese can be found in the use of hypnosedative agents. As stated earlier in this review, obesity is associated with OSA. In theory, hypnosedative agents such as benzodiazepines or opioid analgesics could worsen OSA-related symptoms by reducing effective breathing. Despite the fact that deleterious effects of these drugs on parameters such as apnoea-hypopnoea index or oxygen saturation are still under debate, caution is advised when sedative drugs are used in obese patients with OSA [120,121].

To conclude, only few studies have been done including PD parameters in morbid obesity. To be able to adequately translate PK models into dosing regimens for certain pharmacological domains, for example anaesthetics, antibiotics or sedatives, more research is warranted on PD of these drugs in obesity.

EXPERT OPINION

Since the prevalence of obesity is appallingly increasing, physicians and pharmacists are increasingly confronted with drug dosing problems in (severely) overweight patients. Fortunately, more evidence on PK and to a lesser extent on PD in morbid obesity is generated, particularly in the last two decades. However, as we showed in this review, we are still unsure what the exact effect of obesity is for many drugs. This relates to the fact that there is a lack of specific and quantitative information on obesity related changes in physiological parameters like hepatic blood flow, gastric permeability and enzyme and transporter activity. It is clear that translation of a single drug property into a subsequent effect on a PK parameter, as has been tried with lipophilicity and volume of distribution, is not adequate and tends to oversimplify the matter.

Despite more insight in the changing metabolic and elimination pathways associated with obesity, there are still gaps in our current knowledge. The lack of studies that simultaneously investigate oral and IV administered drugs in both obese and non-obese individuals makes it difficult to determine the effect of obesity on oral bioavailability. Also, only a few studies report unbound concentrations of drugs, so information on the influence of obesity on protein binding is limited. More insight is needed in the pathophysiological changes that accompany with severe or prolonged obesity with respect to the liver, liver blood flow, (hepatic) transporters, gut metabolism and perfusion. Taken together, one of the major challenges nowadays in the field of obesity-PK/PD is to gather quantitative information on these parameters for the development of physiologically based PK models in which various drug and patient properties can be integrated. With such models, PK/PD and ultimately drug dosing of other drugs can be predicted for individual patients. This 'quantitative systems pharmacology' approach is currently an important, rising field in PK/PD research [122]. With this approach, quantitative PK and physiological information is incorporated that can be applied to predict the PK and/or PD for new or existing drugs to yield appropriate dosing recommendations. Until then, assumptions and simplifications have to be employed in these models where current evidence is inconclusive, which is the case in several domains in obesity, as we have shown in this review. Therefore, future research should focus on filling in these knowledge gaps to aid in the development of quantitative systems pharmacology models.

A second challenge is the implementation of dose recommendations for obese patients in clinical practice. Most PK studies conclude with dosing recommendations based on the developed PK/PD model, but implementation of these recommendations is often overlooked. Depending on the strength of the underlying evidence and the type of drug, this can be either done in a clinical study, or by implementing the dose recommendations in daily practice with close monitoring of relevant outcomes and drug levels by therapeutic drug monitoring (prospective evaluation). One example from our own research group was the prospective validation of an amikacin dose regimen based on an earlier developed neonatal PK/PD model [123]. The use of this regimen yielded adequate peak and through concentrations across the entire neonatal population in a prospective study where only limited sampling was applied [124]. Another example is the successful implementation of a cefazolin dose regimen in the Dutch guidelines for perioperative antibiotic prophylaxes as mentioned elsewhere in this review [69,80]. Regarding implementation, dilemmas may rise especially for drugs known to be toxic when high plasma concentrations are reached but where current evidence suggests they should be dosed on TBW. An example is vancomycin, where studies recommend dosing based on TBW to reach adequate drug exposure in the obese as both V_d and Cl increase. However, high peak concentrations of vancomycin may increase the risk of nephrotoxicity. Therefore, physicians are generally reluctant to prescribe doses > 4000 mg/day in morbidly obese patients, and as a consequence morbidly obese patients might initially be undertreated for infectious diseases.

In conclusion, over the last two decades, more and more knowledge is gained on obesity pharmacology. Future research should focus on filling in the knowledge gaps, especially in connecting obesity-related physiological changes with changes in PK/PD for specific drugs. Ultimately, we can use this knowledge in development of physiologically based PK/PD models using quantitative systems pharmacology approaches. In addition, researchers must also focus on prospective evaluation of developed models, and implementation of subsequent dosing recommendations in clinical practice.

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Part II



Studies on obesity in otherwise healthy individuals





3



A prospective clinical study characterizing the influence of morbid obesity on the pharmacokinetics of gentamicin: towards individualized dosing in obese patients

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ABSTRACT

Background and objective Gentamicin is an aminoglycoside antibiotic predominantly used in bloodstream infections. Although the prevalence of obesity is increasing dramatically, there is no consensus on how to adjust the dose in obese individuals. In this prospective clinical study, we study the pharmacokinetics of gentamicin in morbidly obese and non-obese individuals to develop a dosing algorithm that results in adequate drug exposure across body weights.

Methods Morbidly obese subjects undergoing bariatric surgery and non-obese healthy volunteers received one IV dose of gentamicin (obese: 5 mg/kg based on lean body weight, non-obese: 5 mg/kg based on total body weight [TBW]) with subsequent 24-hour sampling. All individuals had a normal renal function. Statistical analysis, modelling and Monte Carlo simulations were performed using R and NONMEM 7.3.

Results A two-compartment model best described the data. TBW was the best predictor for both clearance ($CL = 0.089 \times (TBW/70)^{0.73}$) and central volume of distribution ($V_c = 11.9 \times (TBW/70)^{1.25}$) (both $p < 0.001$). Simulations showed how gentamicin exposure changes across the weight range with currently used dosing algorithms and illustrated that using a nomogram based on a 'dose weight' ($70 \times (TBW/70)^{0.73}$) will lead to similar exposure across the entire population.

Conclusions In this study in morbidly obese and non-obese individuals ranging 53-221 kg we identified body weight as an important determinant for both gentamicin CL and V_c. Using a body weight based dosing algorithm, optimized exposure across the entire population can be achieved, thereby potentially improving efficacy and safety of gentamicin in the (morbidly) obese population.

Registered in the Dutch Trial Registry (NTR6058)

INTRODUCTION

Gentamicin is an aminoglycoside antibiotic that is frequently used in severe life-threatening infections. Aminoglycosides are widely used antibiotics, predominantly used empirically to expand Gram-negative coverage, although emerging aminoglycoside resistance is a widely recognized threat [1]. Clearly, gentamicin's favorable outcome can only be achieved if adequate exposure is ensured. For aminoglycosides, a distinct relation between aminoglycoside blood concentrations and both efficacy and toxicity has been reported [2]. Many, mostly in vitro and animal in vivo studies, have shown that both the gentamicin peak concentrations relative to the minimal inhibitory concentration (C_{max}/MIC) and the 24-hour free drug area under the curve ($fAUC_{0\text{-}24h}$)/MIC is predictive for effectiveness [3–5]. While these pharmacodynamic indices are to some extent correlated, the general consensus is nowadays that $fAUC_{0\text{-}24h}$/MIC is the primary pharmacodynamic index for aminoglycosides driving efficacy [2,6,7]. Aminoglycoside (nephro- and oto)toxicity correlates with minimum (trough) concentrations (C_{min}) >1 mg/L [8].

(Morbid) obesity, commonly defined as a Body Mass Index (BMI) of >40 kg/m^2, is known to influence different pharmacokinetic parameters such as clearance and volume of distribution, even though exact quantification is still warranted for many drugs [9,10]. This is especially true for gentamicin, which in normal weight patients is typically dosed on a mg/kg basis [11]. For obese individuals, several dosing strategies have been proposed, mostly based on alternative body size descriptors such as adjusted body weight (ABW). ABW uses a scaling factor for correcting for limited drug diffusion in adipose body tissue [12]. Several studies found that with increasing body weight ABW was predictive for changes in aminoglycoside volume of distribution [12–16] and therefore for C_{max}. More recently, lean body weight (LBW; represents fat-free mass consisting of bone tissue, muscles, organs and blood volume calculated according to the Janmahasatian formula), was suggested to be used in dosing gentamicin, also because of its correlation with volume of distribution [17,18]. However, as gentamicin *exposure* drives efficacy, changes in gentamicin clearance are to be taken into account when optimizing drug dosing in the obese. Previous studies report an increase in total body clearance with increasing body weight [12–14,16], with two studies suggesting that ABW might be a predictive covariate for gentamicin clearance [13,14]. However, compared to current practice, the degree of obesity in these studies was limited with average body weights that do not exceed 100 kg in most studies. Moreover, many studies rely on sparse sampling from therapeutic drug monitoring, in an era where aminoglycosides were typically dosed three times daily, and as such many studies obtained only a limited amount of samples up to eight hours post infusion. As a consequence, the exact influence of obesity on the pharmacokinetics of gentamicin, especially clearance, remains yet to be quantified across the current body weights that we are facing in the clinic.

In this prospective clinical study, we study the pharmacokinetics of gentamicin in (morbidly) obese individuals versus non-obese individuals in order to develop a dosing algorithm that can be used across the whole clinical population, and that will lead to similar exposure ($AUC_{0\text{-}24h}$) and optimal C_{min} (<1 mg/L) in obese individuals compared to their non-obese counterparts.

PATIENTS AND METHODS

Participants

Morbidly obese patients (BMI above 40 kg/m^2 or above 35 kg/m^2 with comorbidities), scheduled to undergo laparoscopic bariatric surgery (either a gastric bypass or sleeve gastrectomy) and non-obese healthy volunteers (BMI 18-25 kg/m^2) were considered for inclusion in this study. Exclusion criteria were a known allergy to aminoglycosides, renal insufficiency (defined as an estimated glomerular filtration rate (eGFR) below 60 mL/min based on the Cockcroft-Gault (CG) formula with LBW and the Modification of Diet in Renal Disease (MDRD) formula for obese and non-obese individuals, respectively) [18–20], pregnancy or breastfeeding or treatment with potentially nephrotoxic medication in the week before surgery. Before inclusion, participants provided written informed consent. The study was registered in the Dutch Trial Registry (NTR6058), approved by the local human research and ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki.

Study procedures and data collection

Morbidly obese patients received a single gentamicin dose of 5 mg/kg LBW (calculated using the Janmahasatian formula [18]), administered intravenously in 30 minutes, 1-2 hours prior to induction of anesthesia. We chose a LBW-based dose regimen for obese individuals because the use of total bodyweight was expected to lead to very high doses and because LBW may be a good body size descriptor for gentamicin dosing [17]. Gentamicin was administered as part of the study protocol, not as part of routine care. Non-obese healthy volunteers received a dose of 5 mg/kg total body weight (TBW) infused over 30 minutes. Venous blood samples were collected 5, 30, 60, 90, 120, 180, 240, 360, 720 and 1440 minutes after end of infusion. Blood samples (3 mL) were collected in lithium-heparin tubes, centrifuged at 1900 g for 5 minutes, and stored at -80 ^{o}C until analysis.

For each patient, data was recorded on body weight, body length, sex, age, self-reported history/duration of obesity (estimation of number of years the patient fulfils definition of morbid obesity). Serum creatinine was measured and 24-hour urine was collected on the study day, with which the glomerular filtration rate (GFR) was calculated. In addition, serum creatinine based GFR estimates were calculated for each patient using either the Cockcroft Gault (using LBW for obese and TBW for non-obese individuals as described before [19]) or the Modification of Diet in Renal Disease (MDRD) formula (de-indexed for body surface area [BSA]).

For the population pharmacokinetic (PK) analysis, for each individual BSA was calculated using the Du Bois-Du Bois formula [21]. ABW was calculated with equation (1) as published before [12]:

$$ABW = IBW + 0.4 \times (TBW - IBW) \quad (1)$$

where IBW represents ideal body weight in kg, calculated with the Devine formula [22] and TBW represents the total body weight in kg. When TBW was smaller than IBW, IBW was imputed as ABW.

Drug assay

Total gentamicin plasma concentrations were quantified using a commercially available, validated immuno-assay kit (Roche Diagnostics GmbH, Mannheim). The lower limit of quantification (LLOQ) of this assay was 0.4 mg/L and the lower limit of detection (LOD) was 0.3 mg/L.

Non-compartmental statistical analysis

Individual gentamicin $AUC_{0\text{-}24h}$ was calculated using the trapezoidal rule. C_{max} and C_{min} were defined as the gentamicin plasma concentration measured at 1 and 24 hours after start of infusion, respectively. Categorical data was analysed by Chi-square test. Continuous data are shown as mean ± standard deviation (SD) and analysed by t-test when normally distributed or as median ± interquartile range (IQR) and analysed by Mann-Whitney-Wilcoxon test when not normally distributed. Statistics were performed using R (version 3.4.4) [23]. Differences with a p-value <0.05 were considered statically significant.

Population pharmacokinetic analysis and validation

Gentamicin concentrations in both obese and non-obese were analysed using non-linear mixed effect modelling (NONMEM 7.3, Pirana 2.9.7 and PsN 4.6.0) [24,25]. Concentrations below LLOQ (n = 24/280, 8.6%) were incorporated in the analysis using the M3 method [26].

Model development was done in three stages: (1) defining the structural model, (2) development of the statistical model and (3) a covariate analysis. In these steps, discrimination between models was made by comparing the objective function value (OFV, defined by -2 log likelihood). A p-value of <0.05, representing a decrease of 3.84 in the OFV value between nested models, was considered statistically significant. Furthermore, goodness-of-fit plots, differences in parameter estimates' coefficients of variation or individual plots were evaluated to discriminate between models. Inter-individual variability on parameter estimates was assumed to be log-normal distributed in the population. For residual variability, e.g. resulting from assay errors, model misspecifications or intra-individual variability, a combined additive and proportional error model was investigated.

For the covariate analysis, potentially relevant relations between covariates and pharmacokinetic parameters were visually explored by plotting inter-individual variability estimates independently against the individual covariate values. Covariates that were explored in this manner were TBW, LBW, ABW, BMI, age, sex, GFR and eGFR (BSA corrected MDRD or CG using LBW). After visual inspection, potential covariates were separately entered into the model. Continuous covariates were introduced using equation (2) for exponential relations and (3) for linear relations:

$$P_i = P_p \times \left(\frac{COV}{COV_{standard}}\right)^X \quad (2)$$

$$P_i = P_p \times \left(1 + Z \times \left(COV - COV_{standard}\right)\right) \quad (3)$$

where P_i and P_p represent individual and population parameter estimates, COV represents the covariate, $COV_{standard}$ represents a population standardized (e.g. 70 kg for TBW) or median value for the covariate, X represents the exponent for a power function and Z is the slope parameter for the linear covariate relationship. Categorical covariates were entered into the model by calculating a separate pharmacokinetic parameter for each category of the covariate. If applicable, it was evaluated whether the inter-individual variability in the concerning parameter decreased upon inclusion of the covariate and whether the plot of the inter-individual variability versus covariate improved. Additionally, goodness of fit was assessed as described earlier. Using forward inclusion ($p < 0.05$, OFV decrease >3.8) and backward deletion ($p < 0.001$, OFV increase >10.8), it was justified to include the covariate in the final model.

Internal model validation was performed using prediction corrected visual predictive checks (pcVPC) and bootstrap resampling analysis [27,28]. More details of the used methods for model development and internal validation can be found in the supplementary material.

Model-based simulations to guide drug dosing

Using the final model, Monte Carlo simulations were performed in 10.000 patients in a weight range of 50-215 kg for different dose regimens, which included 5 and 7 mg/kg TBW, 5 and 8 mg/kg LBW, 5 mg/kg ABW and a novel dose nomogram based on the final PK-model. In every simulation, gentamicin was administered intravenously over 30 minutes with 24 hours follow up. Values for LBW, IBW and ABW were obtained by resampling data stratified on TBW from the National Health and Nutrition Examination Survey (NHANES) database containing demographic data from a large representative cohort of adults from the USA from 1999-2016 [29]. Simulations aimed to target a similar exposure ($AUC_{0\text{-}24h}$) in comparison to non-obese individuals (<100 kg) receiving gentamicin in the standard dose of 5 mg/kg TBW and non-toxic C_{min} values (<1 mg/L) in obese individuals.

RESULTS

Patients and data

Table 1 shows the patients characteristics of the twenty morbidly obese patients (median body weight 148.8 kg, ranging 109 to 221 kg) and eight non-obese individuals (median body weight 72.9 kg, ranging 53 to 86 kg) that were included in this study. For each individual, ten samples were obtained, yielding 280 gentamicin plasma concentrations in total. Figure 1 shows the measured plasma concentrations versus time after start of infusion. Both $AUC_{0\text{-}24h}$ and C_{max} were lower in morbidly obese individuals dosed 5 mg/kg LBW compared to non-obese individuals dosed 5 mg/kg TBW ($AUC_{0\text{-}24h}$: 43.7 ± 9.7 vs 68.7 ± 9.5 mg/L*h, p <0.001. C_{max}: 8.6 ± 2.2 mg/l vs 17.8 ± 2.6 mg/l, p <0.001). C_{min} values of all individuals were <0.5 mg/L.

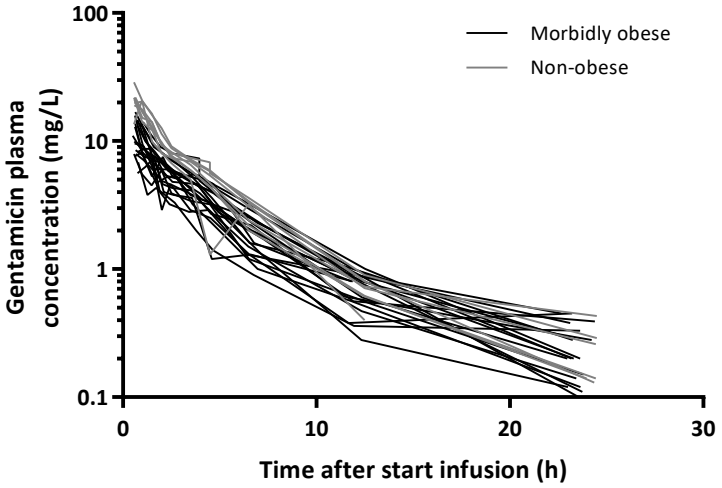


Figure 1. Observed gentamicin plasma concentrations (mg/L) versus time after start of infusion (h) for morbidly obese (receiving 5 mg/kg lean body weight, black lines) and non-obese (receiving 5 mg/kg total body weight, grey lines). Each line represents one individual.

Population pharmacokinetic model and validation

A two-compartment model with a combined residual error model best described the data, with inter-individual variability on central volume of distribution and clearance (Table 2).

The covariate analysis showed that TBW was the most predictive covariate for both central volume of distribution and clearance (p <0.001 for both). Figure 2 shows the individual estimates for clearance and volume of distribution versus TBW of the included obese and non-obese individuals. Plots for the other covariates are shown in the supplementary material (Figure S1). Implementation of TBW with a power function on central volume of distribution

and clearance led to a reduction in unexplained inter-individual variability from 49.6% to 18.5% for central volume of distribution and from 32.2% to 17.4% for clearance. In addition, OFV was found to reduce by 44.4 (p <0.001) and 30.2 (p <0.001) points for central volume of distribution and clearance, respectively. Implementation of LBW or ABW on central volume of distribution was inferior to TBW, even though these covariates significantly improved the base model as well, albeit less convincing than TBW with smaller OFV drops (-19.1 and -17.3 for LBW on central volume of distribution and clearance, -18.8 and -21.2 for ABW on central volume of distribution and clearance, respectively) and poorer goodness of fit diagnostics (data not shown). While no influence of MDRD or CG was visible, GFR seemed to slightly influence clearance although this correlation disappeared after inclusion of TBW on clearance.

Table 1. Patient characteristics.

	Morbidly obese (n = 20)	Non-obese (n = 8)	P value
Sex (% male)	50%	50%	1.00
Total body weight (kg)	148.8 ± 25.9 [109-221]	72.9 ± 7.9 [53-86]	<0.001
Lean body weight (kg)	76.5 ± 25.4 [55-99]	54.0 ± 17.9 [37-68]	0.003
Body mass index (kg/m²)	44.4 ± 8.3 [37-65]	21.8 ± 2.2 [18-24]	<0.001
Age (years)	40.5 ± 12.5 [19-54]	22.0 ± 3.5 [19-50]	0.004
Glomerular filtration rate (mL/min)	171.9 ± 70.0 [110-230]	123.7 ± 54.8 [91-170]	0.013
Gentamicin dose (mg)	380 ± 120.0 [280-480]	360 ± 30.0 [240-440]	0.466

Data are given as median ± interquartile range [range], unless stated otherwise.

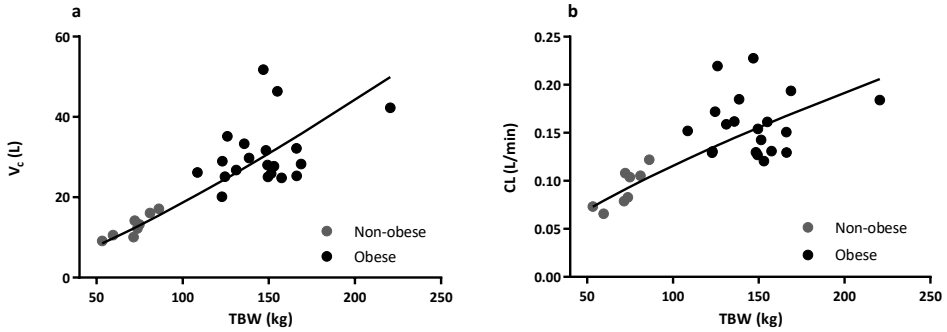


Figure 2. Individual values (n = 28) for (a) central volume of distribution (in L) and (b) clearance (in L/min) versus total body weight from the base model. Obese individuals are depicted using black dots and non-obese individuals using grey dots. The black line represents the covariate relation as implemented in the final model (Table 2). *CL* clearance, *TBW* total body weight, V_c central volume of distribution.

According to the final model (Table 2), central volume of distribution and clearance are best described using with equations (4) and (5):

$$V_{c,i} = 11.9\ [10.3 - 13.5] \times \left(\frac{TBW_i}{70}\right)^{1.25\ [1.06 - 1.46]} \quad (4)$$

$$CL_i = 0.089\ [0.082 - 0.097] \times \left(\frac{TBW_i}{70}\right)^{0.73\ [0.57 - 0.90]} \quad (5)$$

where $V_{c,i}$ and CL_i are the central volume of distribution and clearance of the i^{th} individual, respectively. TBW_i is the total body weight of the i^{th} individual. 95% confidence intervals based on the bootstrap resampling (Table 2) are shown in brackets.

The parameter estimates of the final model are shown in Table 2. Goodness of fit plots of the final model are presented in the supplementary material (Figure S2).

For internal validation, stratified pcVPCs for obese and non-obese individuals are shown in Figure 3 and show good predictive performance for both groups where confidence intervals for the median, 2.5^{th} and 97.5^{th} percentiles of observed and model simulated data are in good agreement. The results of the bootstrap analysis confirmed the model parameters and robustness of the model and are presented in Table 2.

Model-based simulations with different dose regimens

Figure 4 shows the median and 95% confidence interval for $AUC_{0\text{-}24h}$ (upper panel) and C_{min} (lower panel) upon different dosing regimens for individuals with a weight range of 50 to 215 kg based on Monte Carlo simulations. As target for gentamicin exposure, the median $AUC_{0\text{-}24h}$ in non-obese individuals (<100 kg) receiving gentamicin in a commonly prescribed dose of 5 mg/kg TBW is taken (depicted as box with horizontal dashed line, upper panel Figure 4).

Figure 4 (upper panel) illustrates that a dose based on LBW (i.e. 5 or 8 mg/kg LBW) leads to a decrease in $AUC_{0\text{-}24h}$ upon increasing body weight. In contrast, dosing on TBW (depicted for 5 and 7 mg/kg) leads to higher $AUC_{0\text{-}24h}$ with increasing body weight. The use of ABW (5 mg/kg) results in similar $AUC_{0\text{-}24h}$ across body weight compared to the reference <100 kg group, with a slight trend towards a decreased $AUC_{0\text{-}24h}$ with increasing body weight. When a dose regimen based the equation for clearance of the final model (i.e. an allometric 'dose weight' which is calculated as 70 x (TBW / 70)$^{0.73}$, Table 3) is used, similar $AUC_{0\text{-}24h}$ compared to the reference group is yielded across all weight ranges up to 215 kg.

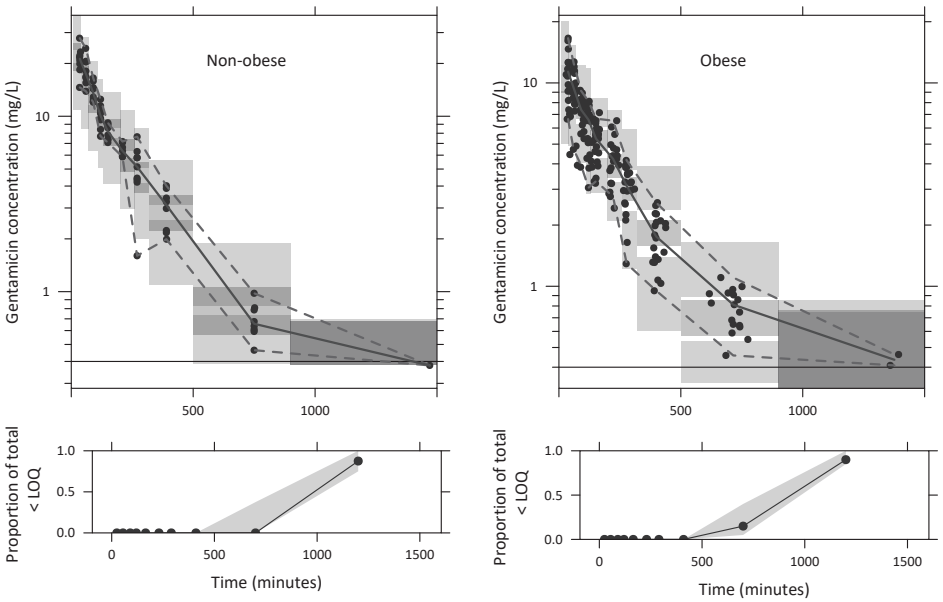


Figure 3. Prediction corrected visual predictive checks (pcVPC) of the final model for non-obese (upper left panel) and obese (upper right panel) individuals. The observed concentrations are shown as black circles, median, 2.5th and 97.5th percentiles of the observed data are shown as solid and the lower and upper dashed lines. The grey shaded area's show the 95% confidence intervals of the median (dark grey) and 2.5th and 97.5th percentiles (light grey) of the simulated concentrations (n = 1000) based on the original dataset. Lower panels show the observed proportion below the LOQ (black dots), where shaded areas represent the 95% confidence interval of these proportion based on the simulated concentrations (n = 1000). *LOQ* limit of quantification.

For all dose regimens and weight ranges, C_{min} were below the limit of 1 mg/L (Figure 4, lower panel). Results for peak concentrations (C_{max}) are shown in Figure S3 in the supplementary material, showing that a TBW-based dose regimen yield similar peak levels across body weights.

Table 2. Population pharmacokinetic parameters of the base model and final model.

Parameter	Base model (%CV)		Final model (%CV)		Bootstrap final model (n = 939/1000 successful runs) Mean (95% CI)
Fixed effects					
V_c (L)	23.3	(10.0)	-		
$V_c = Vc_{70kg} * (TBW/70)^X$					
$V_{c\ 70\ kg}$ (L)	-		11.9	(8.8)	11.9 (10.3 -13.5)
X	-		1.25	(10.8)	1.26 (1.06 – 1.46)
CL (L/min)	0.130	(5.7)	-		
$CL = CL_{70kg} * (TBW/70)^Z$					
$CL_{70\ kg}$ (L/min)	-		0.0892	(5.6)	0.0892 (0.0815 – 0.0969)
Z	-		0.729	(9.6)	0.735 (0.572 – 0.898)
V_p (L)	7.06	(8.0)	7.29	(5.7)	7.33 (6.32 – 8.35)
Q (L/min)	0.0812	(17.4)	0.0848	(8.2)	0.0873 (0.0541 – 0.121)
Inter-individual variability					
V_c [a] (%)	49.6	(11.6)	19.2	(16.6)	18.9 (7.98 – 25.7)
CL[a] (%)	32.0	(16.4)	18.1	(5.0)	17.6 (11.3-22.2)
Covariance IIV V_c-CL	-		0.0316		0.0302 (0.00894 – 0.0514)
Residual variability					
Proportional error [b]	0.156	(10.8)	0.159	(8.2)	0.157 (0.125 – 0.190)
Additive error (mg/L) [b]	0.221	(10.2)	0.206	(8.4)	0.204 (0.160 – 0.247)
OFV	329.4		232.9		223.0

Parameter estimates are shown with standard error of estimate reported as %CV (coefficient of variation)

[a] h-shrinkage for inter-individual variability in the final model is 4% (CL) and 7% (V_c)

[b] Estimates of residual error terms are reported as standard deviation

CI confidence interval, *CL* clearance from the central compartment, CL_{70kg} clearance from the central compartment for an individual weighing 70 kg, *CV* coefficient of variation, *OFV* objective function value, *Q* intercompartmental clearance, *TBW* total body weight, V_c central volume of distribution, $V_{c\ 70kg}$ central volume of distribution for an individual weighing 70 kg, V_p peripheral volume of distribution.

Table 3. Proposed dose nomogram (based on a 5 mg/kg 'dose weight', calculated as 70 x (TBW / 70)$^{0.73}$) for selecting the gentamicin dose in obese individuals with normal renal function (>60 mL/min).

TBW (kg)	Gentamicin dose (mg)
<100	Dose on TBW
100 - 120	480
120 - 140	560
140 - 160	600
160 - 180	680
180 - 200	760
200 - 220	800

TBW total body weight.

DISCUSSION

In this study, we have successfully developed a population pharmacokinetic model for gentamicin based on full PK curves obtained in individuals with body weights ranging from 53 to 221 kg. Our study shows that in obese individuals, both gentamicin clearance and central volume of distribution are significantly influenced by body weight. These findings can be used as guide for dosing in the ever-increasing group of (morbidly) obese patients.

Our study shows that gentamicin clearance increases with total body weight. From the studies investigating the pharmacokinetics of aminoglycosides in obesity [12,14–17,30,31], four papers reported an increase in clearance in obese patients [12–14,16], and two studies found ABW as a predictive covariate [13,14]. In these studies participants were only moderately obese (average body weights around 80 to 100 kg with standard deviations around 15 to 20 kg). Moreover, at the time these studies were conducted, aminoglycosides were typically dosed in regimens up to 3 times daily, and as such many studies obtained samples up to eight hours post infusion only thereby limiting the estimation of gentamicin clearance and the prediction of 24-hour exposure and minimum (trough) concentrations. In this respect, we believe that our study is an important addition to the existing literature, since we were able to sample up to 24-hour post infusion (instead of 8 hours) in a wide range of body weights (53 to 221 kg) and, combined with using state of the art modelling techniques, we could for the first time accurately assess gentamicin clearance and its covariates in the obese population.

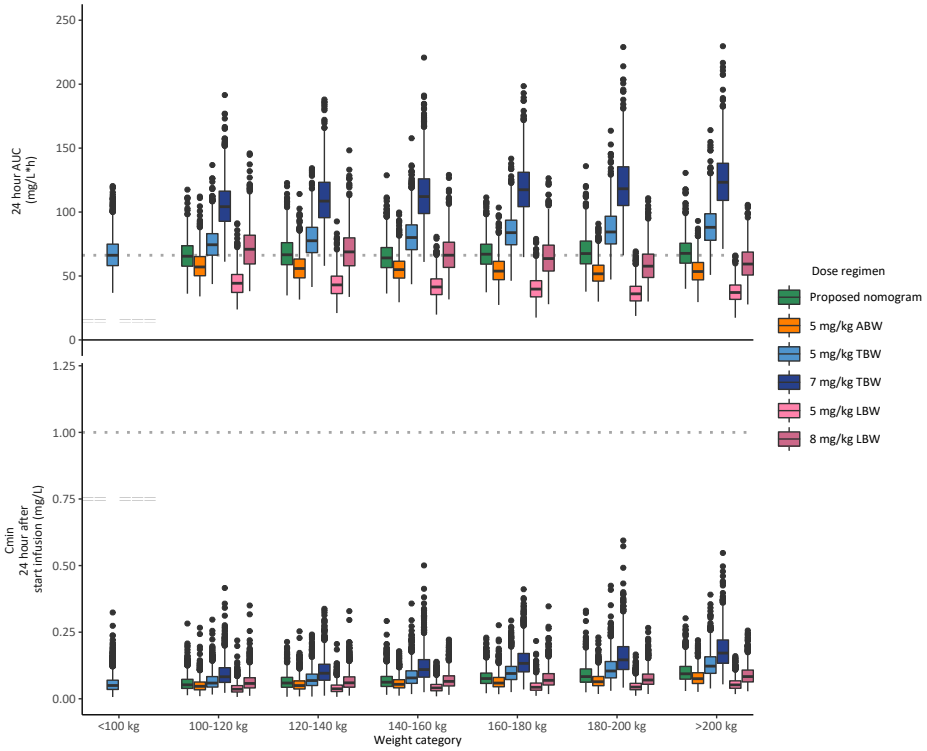


Figure 4. Boxplots (median and 95% confidence interval) representing gentamicin $AUC_{0\text{-}24h}$ (upper panel) and C_{min} (lower panel) for different weight categories based on Monte Carlo simulations with six different TBW-, LBW- (calculated with the Janmahasatian formula [18]) and ABW (calculated as IBW + 0.4 x [TBW – IBW])-based dosing regimens (n = 10.000 per regimen). The proposed nomogram is based on a 'dose weight' calculated as 70 x (TBW / 70)$^{0.73}$ (shown in Table 3). The dashed line represents the median value of 5 mg/kg TBW in the <100 kg group as a target reference for $AUC_{0\text{-}24h}$ (upper panel) or 1 mg/L as a target reference for C_{min} (lower panel). *ABW* adjusted body weight, *AUC* 24-h area under the concentration–time curve from time zero to 24 h, C_{min} minimum (trough) concentration, *LBW* lean body weight, *TBW* total body weight.

An important question is how the finding that in obese individuals clearance changes with bodyweight can be explained. The exponent we identified for the change with weight of 0.73 (95% confidence interval 0.57-0.90) is comparable to the value of 0.75 which has been reported as a value that describes the influence of size on clearance in allometry theory [32]. However, it is debatable whether an increase in weight resulting from obesity can be compared to an increase in weight because of an increase in size [32]. For other drugs that were studied in the obese, many show unchanged clearance with increasing weight, even when morbidly obese patients were included [33–35]. The increase in gentamicin clearance with body weight we identify in this study could potentially be explained by a larger GFR in obese individuals and/or by an increase in Organic Cation Transporter 2 (OCT2) activity as gentamicin was

reported to be a substrate for OCT2 [36]. With respect to GFR, it is emphasized that in our study only individuals with a GFR >60 mL/min were included. In our study, weight was the most important covariate, and after implementation of weight, no additional influence of GFR could be identified even though the range in GFR in our population was large (110-230 mL/min). While this does not preclude GFR being the explanation for the observed increase in gentamicin clearance in the obese, also for other renally excreted drugs like cefazoline, no increase in clearance with increasing weight was found when studied in morbidly obese and non-obese individuals [35,37]. As such, perhaps the increased activity in OCT2 that was reported in overfed rats and that led to increased gentamicin uptake in renal tubular cells [36], may be considered as an explanation for the findings of our study. In line with this hypothesis, for metformin, which is known to be secreted by OCT2 in the tubulus, a larger clearance was found in obese adolescents (1.17 L/min) compared to that in non-obese children (0.55 L/min), which was also explained by a higher OCT2-mediated tubular secretion of metformin in the obese [38]. From these results it seems that more basic research is needed to identify the exact cause of our findings.

Furthermore, our study demonstrates that central volume of distribution best correlates with body weight. Earlier studies with aminoglycosides in obese patients found ABW or LBW to correlate with volume of distribution [12–14,17,30]. In our study we obtained a large number of samples over a 24-hour window including samples that were taken shortly after infusion (i.e. 5, 30, 60 and 90 minutes after infusion). This study design allows us to fully describe the pharmacokinetics of gentamicin in detail. Most of the previously published studies were done with sparse (therapeutic drug monitoring) data with only few samples taken shortly after infusion and consequently analysed by non-compartmental analysis, thereby complicating exact estimation of volume of distribution. While the detailed information resulting from our sampling scheme and advanced modelling strategy justifies the conclusions on changes of volume of distribution with weight, the results challenge the common assumption that only limited changes in volume of distribution are to be expected for hydrophilic drugs like gentamicin. It therefore seems that lipophilicity alone is a poor predictor of how volume of distribution changes with increasing body weight as was demonstrated in several recent reviews [9,39].

Based on the results of our study, we propose to dose gentamicin using a practical dose nomogram (Table 3), that is based on a body weight-derived allometric 'dose weight' (i.e. 70 x (TBW / 70)$^{0.73}$) and is derived from the allometric relationship between clearance (driving AUC) and TBW (Table 2, equation 5). Considering $fAUC_{0\text{-}24h}$/MIC as primary pharmacodynamic index for aminoglycoside treatment, our dosing nomogram yields similar gentamicin exposure ($AUC_{0\text{-}24h}$) across all weights with all trough concentrations (C_{min}) <1 mg/l (Figure 4). In clinical practice, the nomogram can be easily implemented to select the initial gentamicin

dosage, after which dose individualization may be employed by estimating the individual's gentamicin clearance. This is typically done using therapeutic drug monitoring (where one or two samples are taken during the b-elimination phase, for instance between 2 and 8 hours post infusion) in combination with Bayesian software employed with a suitable population PK model. The population PK-model presented in the current paper could be used for this purpose. Alternatively, for example when such software is unavailable, other approaches have been suggested to individualize gentamicin drug treatment [7].

Figure 4 also illustrates that ABW and LBW-based dose regimens show trends towards a lower exposure with increasing body weight. Despite these trends across weight, it seems that 8 mg/kg LBW and 5-6 mg/kg ABW could be considered as alternative for our nomogram because using these doses in the median range of the morbidly obese population leads to rather similar $AUC_{0\text{-}24}$. Implementation of LBW and to a lesser extend of ABW has however been hampered by the complexity of the calculations which is why we came up with our nomogram as depicted in Table 3.

Some limitations may apply to our results. First, individuals in our study were, besides (some) being overweight, otherwise healthy, relatively young and had no renal impairment. As a consequence, renal dysfunction in the obese could not be studied, while in non-obese patients gentamicin clearance has been reported to be dependent on renal function [40]. Also, drug pharmacokinetics have been shown to be influenced by critical illness [41]. Therefore, further refinement of our model is warranted for use in obese patients with renal impairment, critical illness and/or older age. Still, we believe that the dose recommendations from the current study can be a valuable starting point for dosing of obese patients with renal impairment or critical illness. Second, in the current study we did not study the pharmacokinetics of gentamicin after significant reduction in body weight following bariatric surgery. It has been shown for the benzodiazepine midazolam that the pharmacokinetics in these individuals is different in comparison to individuals having the same body weight without a history of obesity [42]. Third, we did not include individuals with BMI 25-35 kg/m^2. However, based on the relationship between TBW and CL and V_c, as depicted in figure 2, we think it is justified to conclude that the pharmacokinetics will not be any different in these individuals. Last, the obese individuals in our study underwent bariatric surgery during the study procedures, which in theory might influence pharmacokinetics. In our hospital, bariatric surgery is performed laparoscopically, with a short procedure (usually 30-45 minutes) with minimal blood loss (usually <50 mL). Also, during surgery, hemodynamics were tightly monitored and regulated. No major hemodynamic instability was recorded for any of the included individuals in our study. For this reason, we expect that the influence of surgery on the pharmacokinetics is negligible.

CONCLUSION

In conclusion, we show that gentamicin clearance increases with body weight according to a power function with an exponent of 0.73. As we found that the current worldwide deployed dosing strategy of dosing on LBW or ABW may lead to lower exposure upon increasing bodyweight, we propose to use a dose nomogram which is based on an allometric 'dose weight' (calculated as 70 x (TBW/70)$^{0.73}$, Table 3) for dosing gentamicin in (morbidly) obese patients >100 kg to obtain similar exposure across all body weights up to 215 kg.

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Compliance with ethical standards

All participants provided written informed consent. The study was registered in the Dutch Trial Registry (NTR6058), approved by the local human research and ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki.

Conflict of interest

R.J.M. Brüggemann declares that he has no conflicts of interest with regards to this work. Outside of this work, he has served as consultant to and has received unrestricted research grants from Astellas Pharma Inc., F2G, Gilead Sciences, Merck Sharpe and Dohme Corp., and Pfizer Inc. All payments were invoiced by the Radboud University Medical Center. All other authors declare no conflicts of interest.

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SUPPLEMENTARY MATERIAL

Model development and validation

Measured gentamicin concentrations in both obese and non-obese individuals were analysed using non-linear mixed effect modelling (NONMEM, version 7.3, ICON Development Solutions, Hanover, USA [25]), Pirana (version 2.9.7, Pirana Software & Consulting BV [24]), Pearl-speaks-NONMEM (PsN, version 4.6.0) and visualized using R (Version 3.4.4 [23]), RStudio (version 1.0.136), Xpose (4.6.1) and Graphpad Prism (version 6.0).

For concentrations below LLOQ, the M3 method was employed as described elsewhere, where instead of a predicted value, a likelihood was estimated that this point was indeed <LLOQ [26]. For visual model diagnostics (such as goodness-of-fit plots) these values were discarded.

Model development was done in three stages: (1) defining the structural model, (2) development of the statistical (variability) model and (3) a covariate analysis, where steps (1) and (2) were performed simultaneously.

Discrimination between different models was made by comparing the objective function value (OFV, i.e., -2 log likelihood [-2LL]), as generated in the NONMEM output. Between nested models, a p-value of <0.05, representing a decrease of 3.84 in the OFV value, was considered statistically significant. Furthermore, goodness-of-fit plots (observed versus population predicted values, observed versus individual predicted values, individual weighted residuals (IWRES) versus time, IWRES versus population predicted values) were visually inspected to assess the performance of the model. In addition, differences in parameter estimates coefficients of variation, h-shrinkage and individual observed versus predicted plots were evaluated to discriminate between models.

Structural and statistical model development

A 1, 2 and 3-compartment model (ADVAN 1, 3 and 11) were evaluated as structural models. For the statistical model, inter-individual variability on the individual parameter estimate of the ith individual (θ_i) was modelled according to equation (1):

$$\theta_i = \theta_{mean} \times \exp(\eta_i) \quad (1)$$

where θ_{mean} is the population mean parameter value, and η_i is a random variable for the ith individual with a mean of zero and variance of ω^2, assuming log-normal distribution in the population. Correlation between eta's was visually assessed with eta-eta scatterplots and when present and not resolved by implementation of covariates, correlation was added to the model in the $OMEGABLOCK section of the NONMEM control stream.

For residual variability, resulting from assay errors, model misspecifications and other unexplained sources a combined error model was investigated, according to equation (2):

$$Y_{ij} = C_{pred,ij} + (C_{pred,ij} \times \varepsilon_1) + \varepsilon_2 \quad (2)$$

where Y_{ij} is the observed concentration, $C_{pred,ij}$ the predicted concentration for the jth observation in the ith individual and ε1 and ε2 the proportional and additive errors, respectively, with a mean of zero and variance of s^2. In addition, a proportional and additive error model was investigated by fixing ε_2 or ε_1 to zero, respectively.

Since we had only information from a single occasion, no inter-occasion variability was implemented in the statistical model.

Covariate analysis

Potential relevant relations between covariates (TBW, LBW, ABW, BMI, sex, age, GFR, duration of obesity) and pharmacokinetic parameters were inspected by plotting individual covariate values independently against the individual parameter estimates or the inter-individual variability estimates. Continuous covariates were implemented using the following equation (3):

$$P_i = P_p \times (COV / COV_{standard})^X \quad (3)$$

Where P_i and P_p represent individual and population parameter estimates, COV represents the covariate, $COV_{standard}$ represents a population standardized (e.g. 70 kg for TBW) or median value for the covariate and X represents the exponential scaling factor for a power function. A linear function was testing by fixing the scaling factor to 1. When TBW was tested as a covariate, COV_{median} was substituted for 70 kg. Potential covariates were separately entered into the model and statistically tested using the OFV. In addition, if applicable, it was evaluated whether the inter-individual variability in the concerning parameter decreased upon inclusion of the covariate and whether the plot of the eta vs. covariate was improved. Finally, using forward inclusion ($p < 0.05$, OFV decrease >3.8) and backward deletion ($p < 0.001$, OFV decrease >10.8), it was justified to include the covariate.

Model validation

Prediction corrected visual predictive checks (pcVPC) were generated using PsN by simulating 1000 datasets stratified on group (obese/non-obese) with prediction and variability correction. Internal robustness of the model was evaluated with a bootstrap re-sampling using 1000 replicates. 95% confidence intervals of parameter estimates were obtained with all runs except when minimization was unsuccessful due to boundary errors.

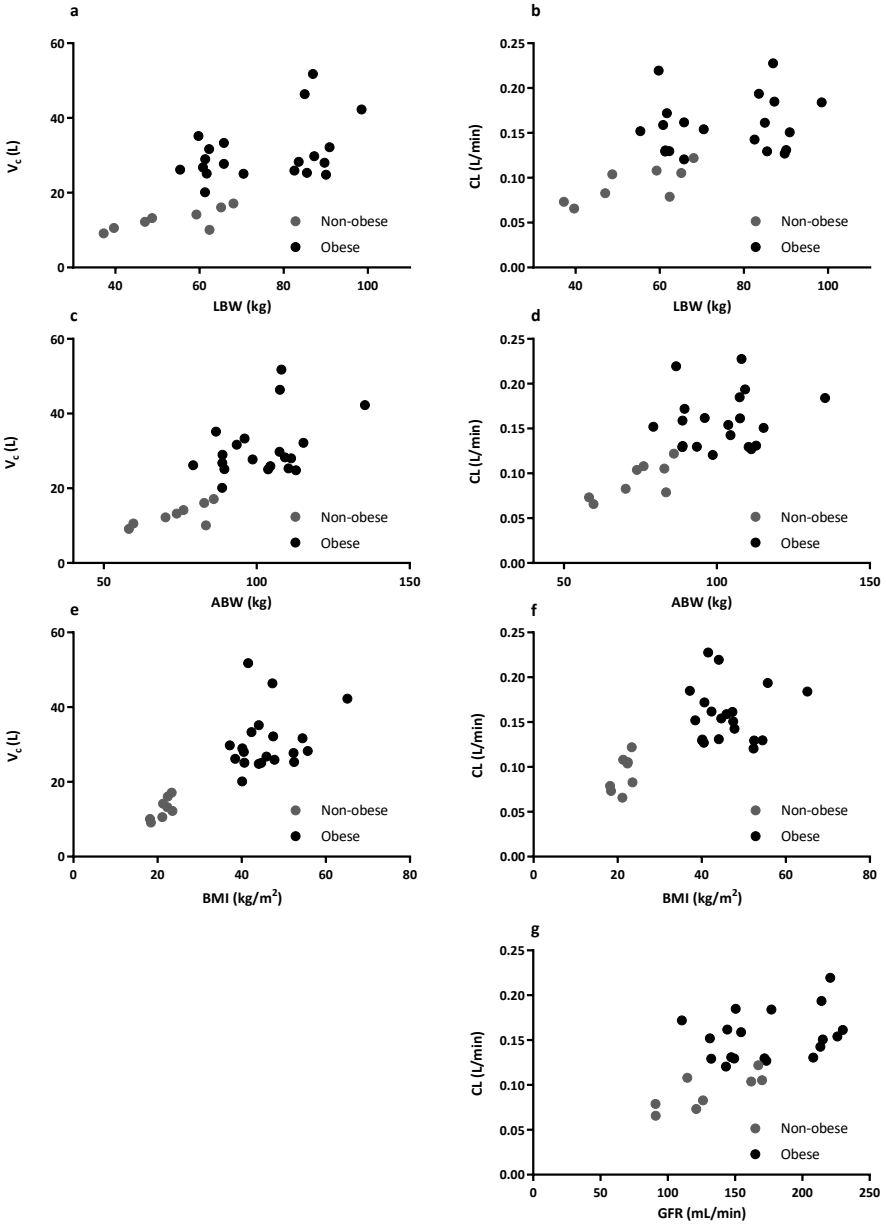


Figure S1. Individual values (n = 28) for (a, c and e) for central volume of distribution (L) and (b, d, f and g) clearance from the central compartment (in L/min) versus lean body weight, adjusted body weight, body mass index and glomerular filtration rate from the base model. Obese individuals are depicted using black dots and non-obese individuals using grey dots. *ABW* adjusted body weight, *BMI* body mass index, *CL* clearance from the central compartment, *GFR* glomerular filtration rate, *LBW* lean body weight, *Vc* central volume of distribution.

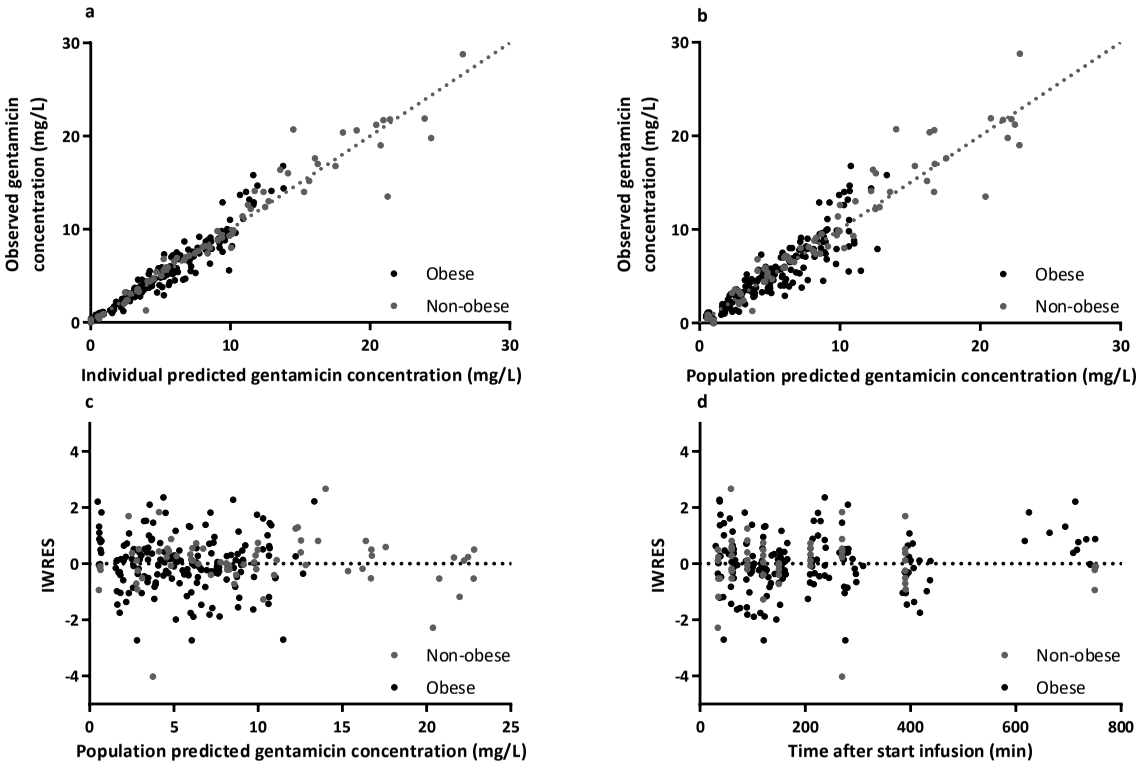


Figure S2. Goodness-of-fit plots of the final model for morbidly obese individuals (n = 20, black dots) and non-obese individuals (n = 8, grey dots): observed versus individual predicted gentamicin concentrations (a), observed versus population predicted gentamicin concentrations (b), individual weighted residuals versus population predicted gentamicin concentrations (c) and individual weighted residuals versus time after start of infusion (d). Plots (c) and (d) only show observations above the lower limit of quantification. The dashed line represents the line of identity (x = y). *IWRES* individual weighted residuals.

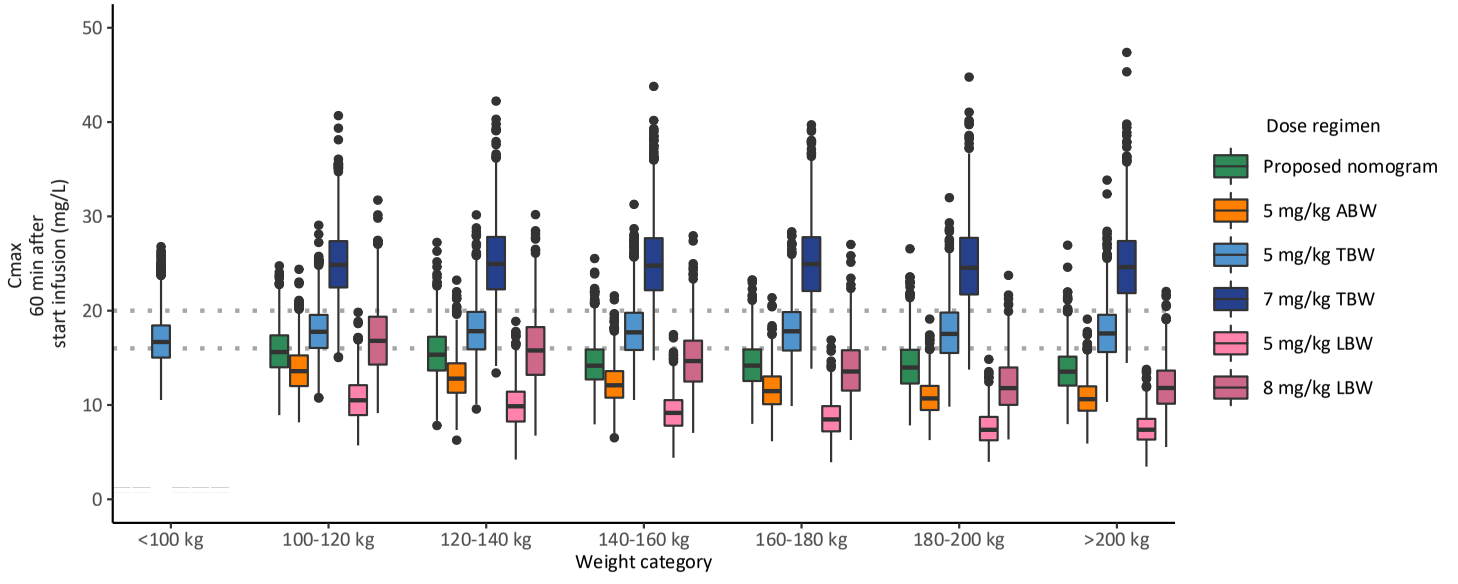


Figure S3. Boxplots (median and 95% confidence interval) representing gentamicin C_{max} for different weight categories based on Monte Carlo simulations with six different TBW-, LBW- (calculated with the Janmahasatian formula [18]) and ABW (calculated as IBW + 0.4 x [TBW – IBW])-based dosing regimens (n = 10.000 per regimen). The proposed nomogram is based on a 'dose weight' calculated as 70 x (TBW / 70)$^{0.73}$ (shown in Table 3). The dashed lines depict 16 and 20 mg/L (respectively 8 and 10 times MIC of 2 mg/L) as a lower and upper target reference for C_{max}. *ABW* adjusted body weight, C_{max} maximum (peak) concentration, *LBW* lean body weight, *TBW* total body weight.

NONMEM CONTROL STREAM FOR THE FINAL MODEL


```
$PROBLEM GENTA
$INPUT ID        TIME    AMT     RATE    DV      LNDV    MDV     GFR     WT
LBW     BMI      IBW     ABW     AGE     BSA     SEX     RACE    HIST    PHASE
SURG    GRP      LLOQ    BATCH   CREAT   MDRD    CG      EGFR
;
$DATA nonmem_all.prn IGNORE=#
$SUBROUTINE ADVAN3 TRANS4

$PK
TVCL = THETA(1)*((WT/70)**THETA(6)); TVCL
TVV1 = THETA(2)*((WT/70)**THETA(5)); TVV1
TVQ = THETA(3); TVQ
TVV2 =    THETA(4); TVV2
;
CL = TVCL*EXP(ETA(1))
V1 = TVV1*EXP(ETA(2))
Q = TVQ*EXP(ETA(3))
V2 = TVV2*EXP(ETA(4))
;
S1 = V1
;
ET1=ETA(1)
ET2=ETA(2)
ET3=ETA(3)
ET4=ETA(4)
;
$THETA
(0, 0.1) ; TVCL
(0, 20) ; TVV
(0,0.1) ; Q
(0,20) ; V2
(0, 1) ; exp v1
(0, 0.75); EXP CL

(0,0.1) ; SD PROPORTIONAL ERR
(0, 0.1) ; SD ADD
```

```
$OMEGA BLOCK(2)
0.032 ; CL ETA 1
0.03 0.031 ; COVAR ET1-ET2, V1 ETA 2
$OMEGA
0 FIX;ETA 3
0 FIX ;ETA 4
;
$ERROR
IPRED = F
PROP=THETA(7)*F ; proportional part
ADD=THETA(8) ; additive part
SD=SQRT(PROP*PROP + ADD*ADD)
;
IF(DV.GE.LLOQ)THEN
F_FLAG=0
Y=F+SD*ERR(1) ; COMBINED ERROR MODEL
ELSE
F_FLAG=1
Y=PHI((LLOQ-F)/SD)
ENDIF
;
IRES = DV - IPRED
IWRES = IRES/SD
;
$SIGMA
1 FIX ; ERR 1
;
$ESTIMATION METHOD=1 INTER MAXEVAL=9999 NOABORT NUMERICAL SLOW
POSTHOC LAPLACIAN;
$COVARIANCE SLOW PRINT=E;
$TABLE ID TIME IPRED IWRES CWRES AMT TVCL CL TVV1 V1 TVV2 V2 ET1 ET2 MDV GFR
WT LBW BMI IBW ABW AGE SEX RACE HIST PHASE SURG GRP LLOQ BATCH MDRD CG
EGFR NOPRINT ONEHEADER
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4



Tobramycin clearance is best described by renal function estimates in obese and non-obese individuals: results of a prospective rich sampling pharmacokinetic study

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ABSTRACT

Purpose Tobramycin is an aminoglycoside antibiotic of which the 24h exposure correlates with efficacy. Recently, we found that clearance of the aminoglycoside gentamicin correlates with total body weight (TBW). In this study, we investigate the full pharmacokinetic profile of tobramycin in obese and non-obese individuals with normal renal function.

Methods Morbidly obese individuals (n = 20) undergoing bariatric surgery and non-obese healthy volunteers (n = 8), with TBW ranging 57-194 kg, received an IV dose of tobramycin with plasma concentrations measured over 24 hours (n = 10 per individual). Statistical analysis, modelling and simulations were performed using NONMEM.

Results In a two-compartment model, TBW was the best predictor for central volume of distribution ($p < 0.001$). For clearance, MDRD (de-indexed for body surface area) was identified as best covariate ($p < 0.001$), and was superior over TBW ($p < 0.05$). Other renal function estimates (24h urine GFR and de-indexed CKD-EPI) led to similar results as MDRD (all $p < 0.001$).

Conclusions In obese and non-obese individuals with normal renal function, renal function estimates such as MDRD were identified as best predictors for tobramycin clearance, which may imply that other processes are involved in clearance of tobramycin versus gentamicin. To ensure similar exposure across body weights, we propose a MDRD-based dosing nomogram for obese patients.

INTRODUCTION

The global prevalence of obesity and morbid obesity, which is commonly defined as a body mass index (BMI) over 30 and 40 kg/m^2, respectively, is rapidly rising. In 2015, over 600 million adults were obese worldwide, accounting for 12% of the entire adult population [1]. Due to physiological changes associated with obesity, such as an increase in fat and other tissue, differences in liver size, liver flow, liver enzyme activity and glomerular filtration rate (GFR), obesity-related changes in pharmacokinetic (PK) and/or pharmacodynamic (PD) parameters of drugs may be expected [2]. However, the exact quantification of these changes in PK and PD is lacking for many drugs. This is of particular relevance for drugs for which a target concentration and/or exposure related to efficacy or safety has been identified, like in the case of aminoglycosides. These antibiotics, such as gentamicin and tobramycin, are used for the treatment of severe infections, with their efficacy being closely related to a (timely) attainment of an adequate plasma exposure (depicted by the 24 hour area under the curve (AUC_{24}) over the minimal inhibitory concentration (MIC) of the microbiological target [3–5]. Since in the general population AUC_{24} closely correlates with the maximum plasma concentration (C_{max}) and measurement of an AUC puts substantial burden to the treated patient, the C_{max} is often used as measure of efficacy with target values between 15-20 mg/L. Despite this approach that is used in clinical practice, the AUC_{24} is still considered the cornerstone PD-index for aminoglycoside effectivity and toxicity [5–7], with 75 mg*h/L being proposed as a pharmacodynamic target with an optimal effect and acceptable risk for toxicity [5]. However, this is based on the assumption that MICs are not higher than 1 mg/L, whereas the wild-type population of most gram-negatives extend to 2 mg/L [5,8].

To date, in clinical practice tobramycin is dosed on a mg/kg basis. Clinicians may however be reluctant to use mg/kg dosing in (morbidly) obese patients, since high trough levels (i.e. >1 mg/L 24 hours after dosing) are associated with side effects such as nephro- or ototoxicity [9,10]. Therefore, over the past decades, several alternative body size descriptors to guide aminoglycoside dosing have been proposed, such as adjusted body weight (ABW) and lean body weight (LBW) [11–16]. These dosing measures were mainly proposed to compensate for a body weight-related increase in volume of distribution (V_d) which was found in these studies [11–16], with V_d being the parameter that determines C_{max}. However, since not V_d, but drug clearance drives the AUC, it is essential to clarify what body size descriptor or parameter best predicts clearance with increasing body weight. For the aminoglycoside gentamicin, we recently found that in obese individuals, TBW was the most predictive descriptor for clearance, albeit in a nonlinear manner [17]. In the current prospective rich sampling study, we investigate the pharmacokinetics of tobramycin in (morbidly) obese and non-obese individuals with normal renal function (eGFR >60 mL/

min), in order to investigate how tobramycin clearance and other PK parameters change in obesity. In line with our previous study on gentamicin PK in the obese, beside weight measures, other measures like renal function estimates were investigated as covariates. The results are used to guide dosing of tobramycin in (morbidly) obese individuals.

MATERIALS AND METHODS

This prospective observational study was registered in the Dutch Trial Registry (NTR6058), approved by the local human research and ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki.

Participants

Morbidly obese patients (BMI >40 kg/m^2 or >35 kg/m^2 with comorbidities) scheduled for bariatric surgery (laparoscopic gastric sleeve or gastric bypass) were considered for inclusion. In addition, a group of non-obese healthy volunteers (body mass index (BMI) 18-25 kg/m^2) were included.

Participants were excluded when they had a known allergy to aminoglycosides, used potentially nephrotoxic medication in the week before surgery (such as lisdiuretics, vancomycin, ACE-inhibitors, non-steroid anti-inflammatory drugs), had a known renal insufficiency (eGFR <60 mL/min, using the Modification of Diet in Renal Disease (MDRD) (non-obese) or LBW in the Cockcroft Gault formula (obese) [18]), were pregnant or breastfeeding. Before inclusion, all participants provided written informed consent.

Study procedures

Twenty morbidly obese patients received 5 mg/kg LBW (calculated according to Janmahasatian [19]) tobramycin on the day of surgery as a single dose infused over 0.5 h, after which venous blood samples were collected at t = 5 minutes after end of infusion, followed by collections at t = 1, 1.5, 2, 2.5, 3.5, 4.5, 6, 12 and 24 hours after start of infusion. 3 mL blood samples were collected in lithium-heparin tubes, centrifuged at 1900 g for 5 minutes, and plasma was stored at -80 ^{o}C until analysis. Eight non-obese healthy volunteers received a single dose of 5 mg/kg TBW tobramycin, infused over 0.5 h, after which the same sampling scheme was employed.

In order to measure the glomerular filtration rate (GFR), urine was collected over 24 hours on the study day and before and 24 hours after administration of tobramycin, a blood sample was collected to measure serum creatinine. In addition, GFR was estimated (eGFR) as follows: (1) using the Cockcroft-Gault formula with LBW without correction for gender for obese and with TBW for non-obese individuals (CG-LBW) [18], (2) using the Modification of Diet in

Renal Disease (MDRD) which was de-indexed for body surface area (BSA) by multiplying with individual BSA/1.73, and (3) Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, also de-indexed for body surface area (BSA) by multiplying with individual BSA/1.73 [18]. Equations for the different renal function estimates are shown in the supplementary material (Table S1).

Total tobramycin plasma concentrations were measured using a commercially available, validated immunoassay kit (Cobas® TOBR2, Roche Diagnostics GmbH, Mannheim), with a lower limit of quantification (LLOQ) of 0.3 mg/L.

Pharmacokinetic analysis

For each individual, AUC_{24} was calculated using the trapezoidal rule. C_{max} was defined as the measured concentration 1 hour after start of the 0.5-hour infusion. Categorical data was analysed using Fischer Exact test, where continuous data is compared using the Wilcoxon Rank test.

Using all data, population pharmacokinetic modelling was performed with NONMEM 7.3 (ICON Development Solutions, Hanover, USA), Pearl-speaks-NONMEM (PsN) 4.6.0 and visualized using Pirana 2.9.7 (Pirana Software & Consulting BV), R 3.4.4 and GraphPad Prism 6.0 (GraphPad Software, La Jolla, USA) [20–22]. Concentrations below LLOQ were retained in the dataset and analysed using the M3 method, where a likelihood for being below LLOQ was estimated for these concentrations [23]. Discrimination between nested models was done by comparing the objective function value (OFV, -2 log likelihood) as obtained from the NONMEM output. A difference in OFV of 3.84, corresponding with a p-value <0.05 for one degree of freedom, was considered statistically significant. In addition, goodness-of-fit plots (GOF, observed versus population and individual predicted values, individual weighted residuals versus time or population predicted values), prediction-variability corrected visual predictive checks (pvcVPC), precision of parameter estimates, shrinkage, and individual plots were examined for diagnostic purposes. One-, two- and three-compartment models were evaluated as structural models. Inter-individual variability (IIV) on the individual parameter estimate of the *i*th individual (θ_i) was modelled according to equation (1):

$$\theta_i = \theta_{mean} \times e^{\eta_i} \quad (1)$$

where θ_{mean} is the population mean parameter value, η_i is a random variable for the *i*th individual with a mean of zero and variance of ω^2, assuming log-normal distribution in the population. For residual variability a combined, proportional and additional error model was investigated, according to equation (2):

$$Y_{ij} = C_{pred,ij} + \left(C_{pred,ij} \times \varepsilon_1\right) + \varepsilon_2 \quad (2)$$

where Y_{ij} is the observed concentration, $C_{pred,ij}$ the predicted concentration for the *j*th observation in the *i*th individual and ε_1 and ε_2 the proportional and additive errors, respectively, with a mean of zero and variance of s^2.

Covariate analysis

The influence of covariates was explored by plotting individual posthoc parameter estimates or the IIV estimates against individual covariate values. Covariates were TBW, LBW (calculated using the Janmahasatian formula [19]), ABW (calculated as ideal body weight (IBW) + 0.4 * (TBW-IBW) [11]), BMI, GFR, de-indexed MDRD, de-indexed CKD-EPI, CG-LBW, sex and age. Equations are summarized in the supplementary material. Continuous covariates were implemented using the following equations:

$$P_i = P_p \times \left(\frac{COV}{COV_{standard}}\right)^X \quad (3)$$

$$P_i = P_p \times \left(1 + Z \times \left(COV - COV_{standard}\right)\right) \quad (4)$$

where P_i and P_p represent individual and population parameter estimates, COV represents the covariate, $COV_{standard}$ represents a population standardized (e.g. 70 kg for TBW) or median value for the covariate, X represents the exponent for a power function and Z represents the relative change of the parameter in a linear covariate relationship. Linear covariate relationships were tested with a slope parameter Z using equation (4) or by fixing the exponent X in equation (3) to 1. In addition, the recently described function characterising the influence of TBW on gentamicin clearance [17], was evaluated for its performance for tobramycin (i.e. equation (3) using TBW as covariate with an exponent of 0.729), which is an approach that was applied before on aminoglycosides in neonates and children [24,25]. Categorical covariates were entered into the model by calculating a separate pharmacokinetic parameter for each category of the covariate. After entering covariates separately into the model, their added value was statistically tested using the OFV. In addition, if applicable, it was evaluated whether the IIV for the parameter decreased upon inclusion of the covariate and whether the trend in the IIV versus covariate disappeared. In general, a forward inclusion ($p < 0.05$, OFV decrease >3.8) and backward deletion ($p < 0.001$, OFV decrease >10.8) strategy was employed for inclusion of covariate. Finally, earlier mentioned general diagnostics were taken into account.

Internal model validation

pvcVPC's were generated using PsN (n = 1000 datasets split for obese and non-obese) with prediction and variability correction. Bootstrap re-sampling (n = 1000, stratified on weight group, i.e. obese and non-obese) was performed to obtain confidence intervals for the parameters, as well as to assess the robustness of the model.

Model-based simulations

Using the final PK model, Monte Carlo simulations were performed with interindividual and residual variability in 9.993 individuals with body weights uniformly distributed between 60-190 kg. Values for de-indexed MDRD were assigned to each individual using a normal distribution with separate mean and standard deviation (SD) for obese (mean: 137 mL/min, SD: 34) and non-obese (mean: 112 mL/min, SD: 23) groups, based on the distributions found in the ongoing AMIGO trial (Dutch Trial Registry NTR6058, n = 60 obese, n = 32 non-obese individuals,). Four dosing scenarios were simulated: (1) tobramycin 5 mg/kg TBW, (2) de-indexed MDRD based dosing using the relationship between clearance and MDRD as was found a-posteriori in the final PK-model, with 75 mg*h/L as target for the AUC_{24} [5] and (3) 5 mg/kg ABW. For comparison, (4) simulations using a dosing strategy based on the best function identified for TBW (Table 3) were also performed. All infusions were simulated as single intravenous administrations given in 0.5 hour.

RESULTS

Demographics and data

A total 20 obese and 8 non-obese participants were included in this study. Obese patients had a median TBW of 137.8 kg (range 103 – 194) versus 66.3 kg (range 57 – 91) in the non-obese group. Patient characteristics are shown in Table 1. For each individual, 10 samples were obtained resulting in 280 tobramycin plasma concentrations in total. Of these, 23 (8.2%) were below LLOQ of 0.3 mg/L.

The mean measured tobramycin plasma concentrations for each timepoint are shown in Figure 1. The AUC_{24} was significantly lower in the obese group receiving tobramycin as a single 5 mg/kg LBW dose compared to the non-obese control group receiving a 5 mg/kg TBW dose (mean 56.1 ± 16.3 mg*h/L vs. 70.0 ± 12.0 mg*h/L, p = 0.039). Also C_{max} levels were significantly lower in the obese individuals (mean 11.8 ± 2.8 mg/L vs. 18.3 ± 2.7 mg*h/L, p < 0.001). No nephrotoxicity (based on the RIFLE criteria [26]) was observed in any participant.

Pharmacokinetic analysis

A two-compartmental model with first-order elimination from the central compartment and a combined additional and proportional residual error model best described the data. IIV was implemented on clearance and central volume of distribution. Parameters of the structural model without covariates (base model) are shown in Table 2.

Table 1. Summary of patient characteristics.

	Morbidly obese (n = 20)	Non-obese (n = 8)	P value
Male/female	9/11	4/4	0.57
Age (years)	43.0 [27-54]	22.5 [20-25]	<0.001
Total body weight (kg)	137.8 [103-194]	66.3 [57-91]	<0.001
Lean body weight [19] (kg)	69.3 [51-107]	49.7 [38-69]	0.0029
Body mass index (kg/m^2)	41.9 [36-53]	22.2 [19-25]	<0.001
Glomerular filtration rate measured using 24-h urine collection (mL/min)	163.3 [85-230]	124.7 [98-141]	0.031
Estimated glomerular filtration rate			
De-indexed Modification of Diet in Renal Disease (MDRD, mL/min)	127.5 [77-171]	102.6 [91-120]	0.031
De-indexed Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI, mL/min)	138.0 [78-171]	109.4 [101-129]	0.050
Cockcroft Gault with lean body weight (obese) or total body weight (non-obese) (CG-LBW, mL/min)	116.4 [69-148]	119.8 [101-138]	0.40
Tobramycin dose (mg)	340 [240-480]	320 [280-440]	0.75

Data shown as median [range], unless otherwise specified.

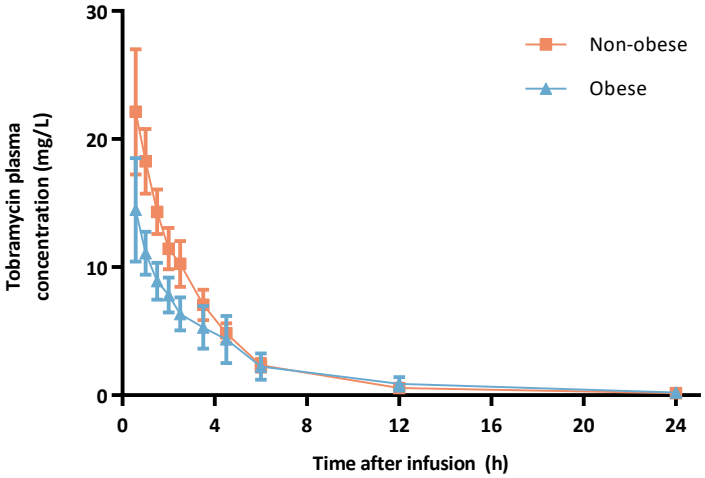


Figure 1. Mean ± SD tobramycin plasma concentrations versus time after end of infusion for obese (blue triangles, n = 20, dose: 5 mg/kg lean body weight) and non-obese individuals (orange squares, n = 8, dose: 5 mg/kg total body weight).

Exploration using scatter plots of individual posthoc parameter estimates and IIV against different covariates indicated TBW, ABW and LBW as candidate covariates for central volume of distribution, and de-indexed MDRD, de-indexed CKD-EPI, CG-LBW, GFR, TBW and LBW for clearance. Figure 2 shows the individual posthoc parameter estimate for clearance versus the different candidate covariates, showing particularly clear relationships for GFR, MDRD and CKD-EPI.

For central volume of distribution, TBW in a power function, LBW and ABW as linear covariates resulted in significant OFV drops (-25.9, -23.9 and -29.2, respectively, all $p < 0.001$). As TBW gave the best GOF (populations predicted versus observed concentrations) with the least bias especially in higher concentrations (i.e. >12 mg/L), TBW was selected over ABW ($p > 0.05$). Inclusion of TBW on central volume of distribution resulted in a reduction of IIV from 42.9 % to 24.9 % (Table 2).

The results of the covariate implementation on CL are shown in Table 3. Table 3 shows that implementation of de-indexed MDRD, de-indexed CKD-EPI, and GFR resulted in the largest reduction in OFV, i.e. -36.3, -32.8 and -32.3, respectively (all $p < 0.001$). GOF plots for all covariates were comparable, although all models seemed to slightly underpredict tobramycin concentrations below 10 mg/l in the non-obese individuals (data not shown). The addition of TBW to de-indexed MDRD as covariate for clearance improved this underprediction, however the limited reduction in OFV (i.e. -3.4 in OFV, $p > 0.05$) and only moderate improvement of GOF did not justify to include this extra parameter. Inclusion of de-indexed MDRD resulted in a reduction in IIV on clearance from 25.2% to 12.0% (Table 2). Implementation of TBW instead of de-indexed MDRD, resulted in a power function on clearance with an estimated exponent of 0.42, and was inferior to implementation of de-indexed MDRD (i.e. -10.3 versus -36.3 in OFV drop, $p < 0.05$, and a resulting drop in IIV on CL of 25.2 % to 20.6% versus 12.0%, respectively). Implementation of the covariate relationship between TBW and clearance as found for gentamicin in similar study [17], i.e. a power relationship with an exponent of 0.729, resulted in an even smaller drop in OFV (i.e. -4.0, $p < 0.05$), with inferior GOF and only a very modest reduction in IIV from 25.2 % to 23.4%. As final model, de-indexed MDRD was selected as covariate on clearance, since MDRD gave a significantly larger OFV reduction ($p < 0.05$) and better GOF compared to CKD-EPI, and since in clinical practice a serum creatinine based eGFR such as MDRD is more readily available than 24-h urine based GFR.

The GOF plots of the final covariate model are shown in Figure S1 in the supplementary material and show that the model described the data well. The parameters of the final model with confidence intervals based on the bootstrap analysis are shown in Table 2 together with final equations for clearance and central volume of distribution. The results from the boostrap analysis (Table 2) indicate a good precision and stability of the final model. The prediction-variability corrected visual predictive check (pvcVPC) shown in Figure 3 indicates good validity of the final model, with median and 5^{th} and 95^{th} percentile of the observations being in concordance with the 95% confidence intervals of the simulations.

Table 2. Population pharmacokinetic parameters of the base and final tobramycin model and results of the bootstrap analysis.

	Base model (%RSE)		Final model (%RSE)		Bootstrap final model (n = 1000)		
						95% Confidence interval	
					Mean	Lower	Upper
Fixed effects							
V_c (L)	17.2	(7.3)	-				
$V_c = Vc_{70kg} * (TBW/70)$							
$V_{c\ 70\ kg}$ (L)	-		10.6	(11)	10.6	8.94	12.4
CL (L/h)	6.42	(4.3)	-				
$CL = CL_{MDRD\ 115} * (1 + Z * [MDRD-115])$							
$CL_{MDRD\ 115}$ (L/h)	-		6.33	(2.6)	6.33	6.02	6.63
Z	-		0.00990	(10)	0.0100	0.0880	0.0122
V_p (L)	4.24	(15)	4.34	(18)	4.41	2.84	5.98
Q (L/h)	6.4	(5.1)	6.69	(12)	6.77	2.63	10.91
Inter-individual variability							
V_c [a] (%)	42.9	(9.3)	24.9[a]	(17)	24.1	14.9	30.8
CL [a] (%)	25.2	(14)	12.0[a]	(13)	11.7	7.90	14.5
Residual variability							
Proportional error	0.112	(12)	0.116	(12)	0.115	0.0880	0.141
Additive error (mg/L)	0.369	(13)	0.346	(12)	0.342	0.239	0.445
OFV	351.7		289.6		276.6	185.9	367.2

Parameter estimates are shown with standard error of estimate reported as %RSE

[a] h-shrinkage in the final model is 8% for inter-individual variability on CL and 6% for IIV on V_c

CL clearance from the central compartment, $CL_{MDRD\ 115}$ clearance from the central compartment for a person with a MDRD of 115 mL/min, *MDRD* de-indexed Modification of Diet in Renal Disease (in mL/min), *OFV* objective function value, *Q* intercompartmental clearance between V_C and V_P, *RSE* relative standard error, *TBW* total body weight in kg, V_c central volume of distribution, $V_{c70\ kg}$ central volume of distribution for a 70 kg person.

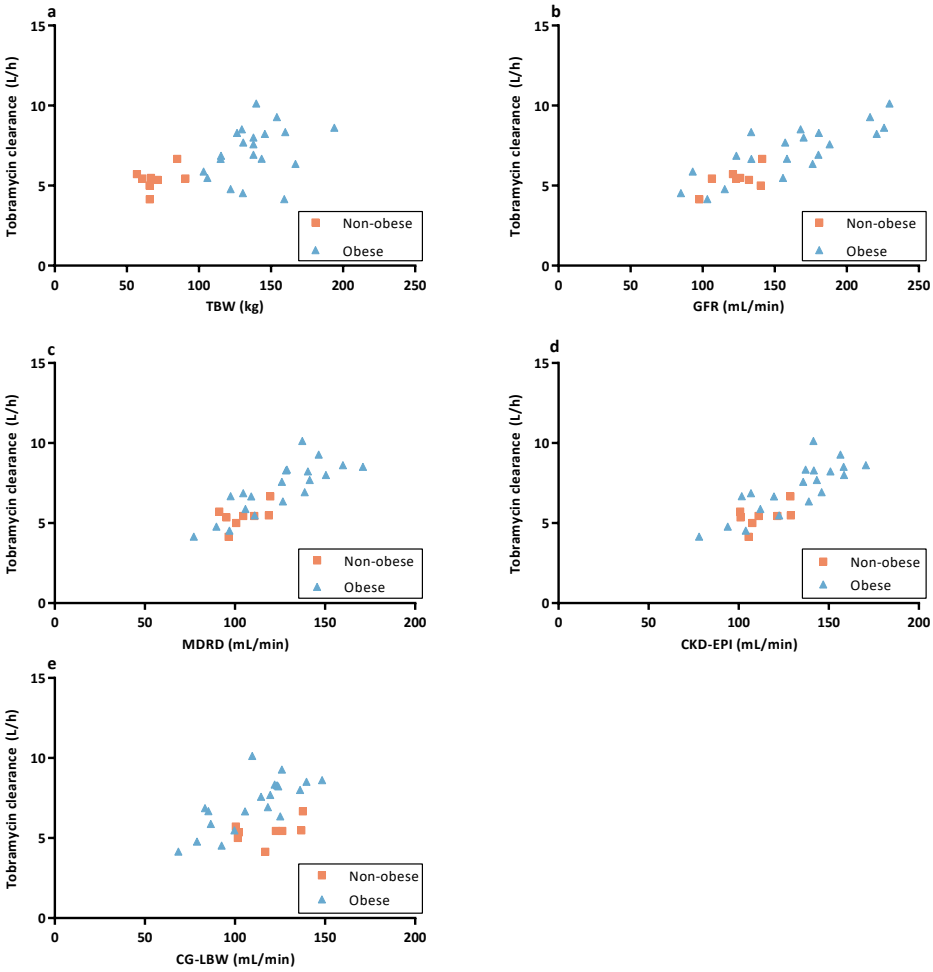


Figure 2. Individual posthoc clearance values for tobramycin (n = 28, in L/h) versus (a) total body weight (TBW), (b) 24-h urine glomerular filtration rate (GFR), (c) eGFR based on de-indexed Modification of Diet in Renal Disease, (d) de-indexed Chronic Kidney Disease Epidemiology Collaboration and (e) Cockcroft-Gault using LBW in obese and TBW in non-obese. Obese individuals are shown in blue triangles, non-obese individuals in orange squares. *CG-LBW* Cockcroft-Gault with lean body weight (obese) or total body weight (non-obese) (CG-LBW, mL/min), *CKD-EPI* de-indexed Chronic Kidney Disease Epidemiology Collaboration (in mL/min), *GFR* glomerular filtration rate, *MDRD* de-indexed Modification of Diet in Renal Disease (in mL/min), *TBW* total body weight.

Model-based simulations

Figure 4 shows the individual (dots), median and interquartile range (boxplots) AUC_{24} values as obtained in the Monte Carlo simulations. Quantitative results are shown in Table S2 in the supplementary material. For individuals up to 100 kg (non-obese population), tobramycin was dosed as 5 mg/kg TBW. For obese individuals 100-190 kg, tobramycin was dosed using the nomogram depicted in Figure 5, which is based on the relationship between clearance and MDRD as found in the final covariate model. The figure shows that when tobramycin is dosed as 5 mg/kg TBW, exposure increases with increasing body weight, with higher AUC_{24} values being observed in individuals with relatively low MDRD-values (<100 mL/min, dark blue dots). Median AUC_{24} per weight subgroup of non-obese individuals when receiving 5 mg/kg TBW increases from around 50 to 80 mg*h/L with increasing body weight. For individuals >100 kg, Figure 4 shows that when a de-indexed MDRD-based dosing strategy is employed (using the nomogram in Figure 5), no trend is visible with increasing body weight, with a median AUC_{24} tightly around 75 mg*h/L. In case the 5 mg/kg TBW dosing strategy was employed in obese individuals, an increase in both the mean and variability (range) of exposures is observed, with a median of around 150 mg*h/L for obese individuals weighing around 190 kg (Figure S2B in supplementary material). When the MDRD-based dosing strategy is used in non-obese individuals as well, no remaining trend in this population is found (<100 kg, Figure S2A in supplementary material). Finally, when dosing was performed based on scaled body weight (i.e. using 0.42 as exponent for TBW [Table 3]) or ABW, no clear trends are visible in median exposure across body weights similar to MDRD-based dosing (Figure S2C and D in supplementary material). However, in contrast to MDRD-based dosing, these do yield a substantial reduction in exposures within target in individuals with increased and decreased renal functions, respectively (Figure S2C and D, Table S2).

Table 3. Impact of different covariates on tobramycin clearance.

Model	Parameter relationship (subpopulation)	X (exponential) / Z (linear)	Number of parameters	OFV	ΔOFV[a]
TBW on V_c	-	-	8	325.8	(reference)
TBW on CL	Exponential (all)	0.42	9	315.6	-10.3
TBW on CL[b]	Exponential (all)	0.729 FIX	9	321.8	-3.96
MDRD on CL	Linear (all)	0.0099	9	289.6	-36.2
CKD-EPI on CL	Linear (all)	0.0089	9	293.0	-32.8
GFR on CL	Linear (all)	0.0055	9	293.5	-32.3
CG-LBW on CL	Linear (obese)	0.0069	9	315.9	-9.88

[a] OFV drop relative to reference model (base model with TBW on V_c)

[b] Covariate relationship for clearance and TBW as reported for gentamicin in similar study [17]

CG-LBW Cockcroft-Gault using lean body weight for obese and total body weight for non-obese individuals, *CKD-EPI* de-indexed Chronic Kidney Disease Epidemiology collaboration, *CL* clearance, *GFR* glomerular filtration rate based on 24-h urine collection, *OFV* objective Function Value, *MDRD* de-indexed modification of Diet in Renal Disease, *TBW* Total body weight, V_c central volume of distribution.

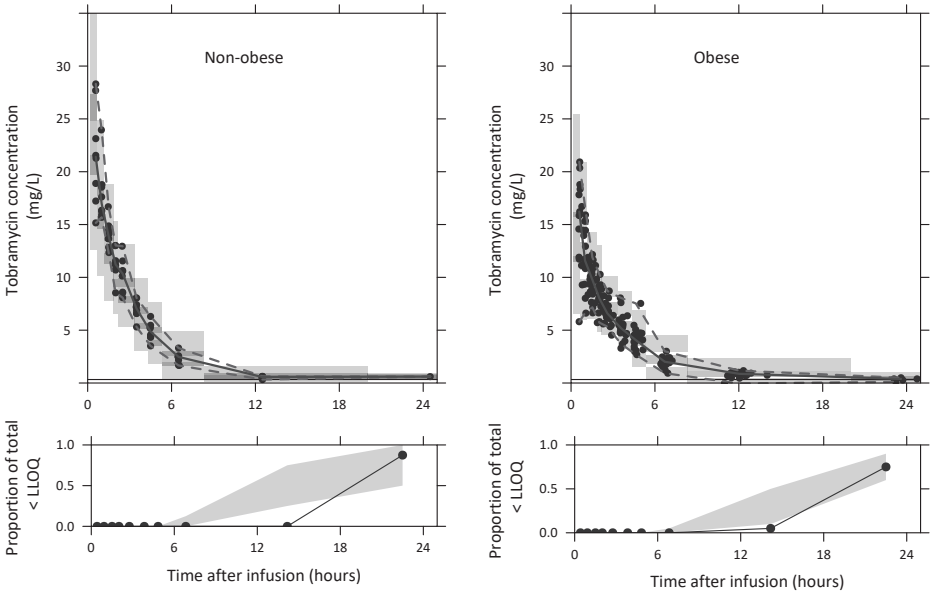


Figure 3. Prediction- and variability-corrected visual predictive checks (pvcVPC) of the final model for non-obese (upper left panel) and obese (upper right panel) individuals (n = 1000 simulations). The observed concentrations are shown as black circles, with median, 2.5th and 97.5th percentiles of the observed data as solid line, lower dashed line and upper dashed line, respectively. The grey shaded areas depict the 95% confidence intervals of the median (dark grey) and 2.5th and 97.5th percentiles (light grey) of predicted concentrations. Lower panels show the observed proportion below LLOQ (black dots), where shaded areas depict the 95% confidence interval of these proportion based on the simulated concentrations. *LLOQ* lower limit of quantification.

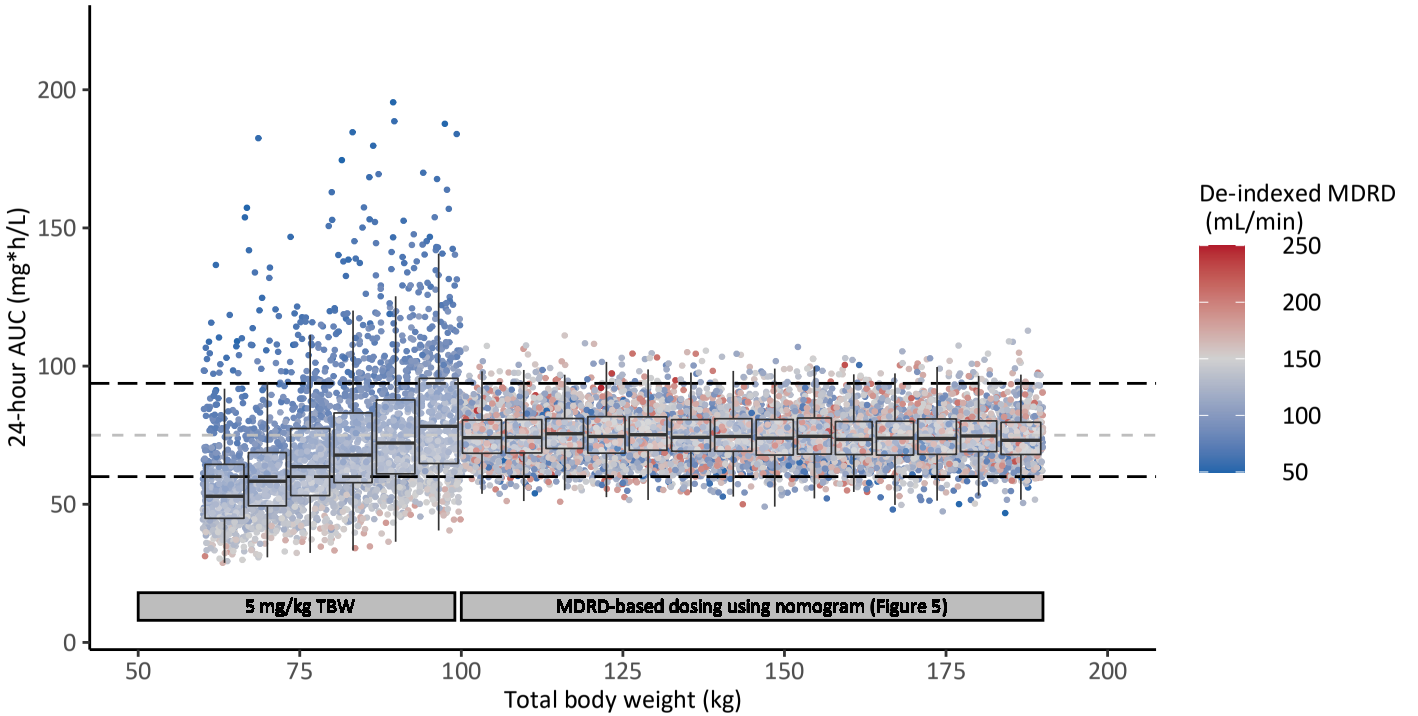


Figure 4. Monte Carlo simulations (n = 9.993) for individuals <100 kg receiving one IV dose of 5 mg/kg total body weight tobramycin, and individuals >100 kg received a MDRD-based tobramycin dose using the nomogram in Figure 5. Each dot represents the AUC_{24} (in mg*h/L) of one individual in the dataset, where the colour shows the de-indexed MDRD in mL/min (calculated as MDRD * body surface area/1.73) of this individual (ranging from dark blue to dark red with increasing MDRD). The boxplots represent median and interquartile range of AUC_{24} values within a specific total body weight subgroup. The grey dashed line shows the target AUC_{24} of 75 mg*h/L, black dashed lines show the 80%-125% range (EMA acceptance criteria for bio-equivalence studies [27]) relative to this target value. *AUC* Area under the curve, *MDRD* Modification of Diet in Renal Disease.

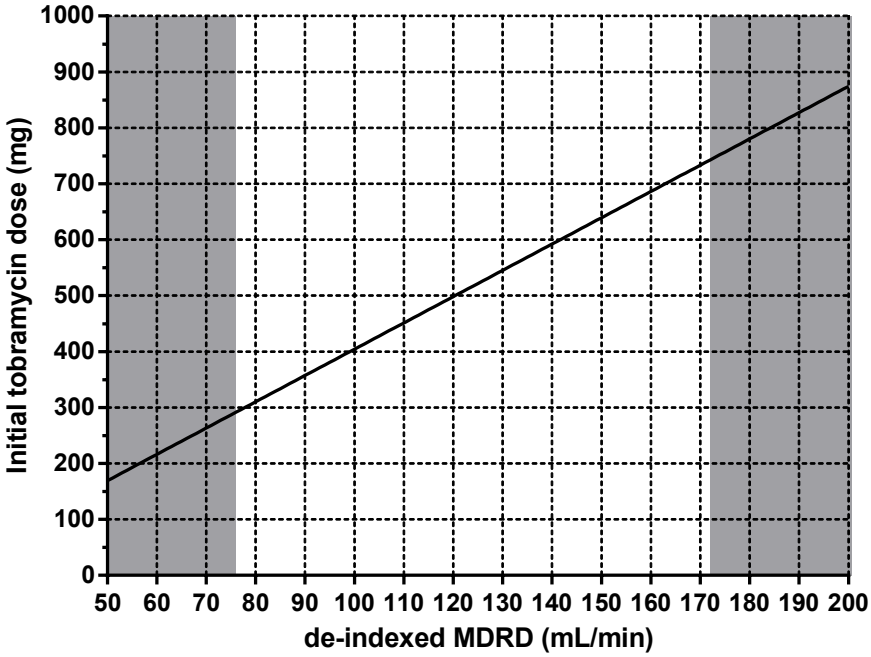


Figure 5. Dosing nomogram for tobramycin dose (in mg) based on the final tobramycin population PK model in non-obese and obese patients with body weights ranging from 57–194 kg and de-indexed MDRD values (calculated as MDRD * body surface area (BSA)/1.73) ranging from 77 to 171 mL/min, aiming for an AUC_{24} of 75 mg*h/L. The recommended tobramycin dose is calculated using equation: Dose (mg) = $AUC_{24, target}$ * 6.33 * (1 + 0.099 * [MDRD – 115]), where $AUC_{24, target}$ is the target AUC_{24} in mg*h/L of 75 and MDRD represents the de-indexed MDRD in mL/min. Since the PK data consists of MDRD values from 77 to 171 mL/min, dose recommendations extrapolation to values outside these should be interpreted with caution (grey area in the nomogram). *MDRD* Modification of Diet in Renal Disease.

DISCUSSION

In this report we studied the population pharmacokinetics tobramycin across body weights from 57-194 kg in individuals with a normal renal function. We show that with increasing body weight, tobramycin clearance is best predicted using a renal function estimate. In our data, this relationship between clearance and renal function was best described using de-indexed MDRD, although de-indexed CKD-EPI or GFR based on 24-hour urine collection seem to lead to similar results. In order to reach the target exposure of 75 mg*h/L in individuals of varying weights, model-based simulations (Figure 4) were performed showing that in obese individuals >100 kg tobramycin should be dosed using the proposed nomogram (shown in Figure 5) based on the individuals de-indexed MDRD. Strong aspects of our study design are (1) the wide range of TBW in our study, including non-obese individuals and obese individuals up to 194 kg, (2) the rich sampling procedure up to 24 hour post-infusion and, (3) the use of a modelling and simulation strategy that is nowadays seen as the gold standard by regulatory authorities for approval of new dose regimens [28].

The influence of obesity on aminoglycoside clearance has been reported in some studies over the years [11–13,15,16,29]. Although in general these studies found an increase in clearance with increasing body weight, their results have to be interpreted with caution since individuals in most of these studies were only moderate obese compared to present-day standards with average body weights around 85-105 kg with standard deviations of ±12-18 kg [12,13,16]. Moreover, analyses were often performed with sparse data collected up to only 8 hours [11–13,15,16]. These study designs limit the ability to properly assess drug clearance, particularly in view of the once every 24 hours dosing that is currently in practice. Only few studies report on covariates that can be used to adequately predict aminoglycoside clearance in obese individuals. One clinical study by Pai et al. in 497 subjects (with 91 obese patients), report that both gentamicin and tobramycin clearance could be best predicted using unadjusted eGFR formula (either MDRD or CKD-EPI) rather than de-indexed eGFR functions or the CG formula [15]. Our study found better predictions for eGFR over the CG-formula as well, although we found that de-indexed eGFR is preferred over the unadjusted estimates. A possible explanation for this difference might be that Pai et al. had to rely on sparse data, potentially making it more difficult to estimate individual tobramycin clearances. In addition, the authors used Mosteller's equation for estimating BSA instead of the Dubois and Dubois formula as employed in our analysis, which may result in some differences. However, our results did not change significantly when the Mosteller's equation was employed (data not shown). Lim et al. found in a retrospective study with 342 patients with ~30% being obese, that de-indexed eGFR outperformed their unadjusted counterparts in predicting aminoglycoside clearance [29]. Leader et al. reported that ABW used in the CG equation is the best predictor for gentamicin clearance. Since this is an older study,

no information is available on the performance of the eGFR formulas [12]. Some other papers looked directly into predicting GFR in the obese population. These studies might be of relevance for our study, since in healthy adults, tobramycin clearance is shown to be primarily mediated through glomerular filtration [30]. These papers generally agree that GFR can be best predicted using the de-indexed form of MDRD or CKD-EPI [31,32], or the CG formula with LBW or ABW [18,33,34]. These conclusions are in line with our results, but should be translated to tobramycin clearance with caution since other (active) processes might be involved besides glomerular filtration when using GFR to predict clearance of a drug. In summary, it appears that most literature point to a renal function estimate to be most predictive for tobramycin clearance in obese individuals, although results from previous studies are conflicting as to how these renal function estimates should be corrected in obese individuals. The current study, with rich data collected in a wide range of body weights and (unimpaired) renal functions, in our opinion now definitively shows that de-indexed MDRD or CKD-EPI outperform body weight, the CG formula (using either TBW or LBW) and unadjusted renal function estimates in predicting tobramycin clearance in obese individuals.

Our results on tobramycin differ from results that we have found for gentamicin in a recently performed prospective pharmacokinetic study that studied a similar patient population in a similar study design [17]. This study showed that the increase in gentamicin clearance was best described by TBW with an estimated allometric exponent of 0.73. In contrast to tobramycin, renal function estimates (eGFR or GFR based on 24-hour urine collection) were inferior to TBW in predicting gentamicin clearance, despite the fact that in both studies individuals with a similar distribution in body weights and renal function (all >60 mL/min) were included. Interestingly, this finding has been reported before by other studies, describing stronger correlations between eGFR and drug clearance for tobramycin than gentamicin [15,29]. To explain this difference between tobramycin and gentamicin, it could be hypothesized that transporters play a role. For gentamicin an increase in renal organic cation transporter 2 (OCT2) activity and consequently enhanced renal uptake has been reported that may contribute to increased gentamicin clearance in the obese. In an obese overfed mouse model, OCT2 activity increased with obesity, leading to increased renal accumulation of gentamicin [35]. In addition, it is well established from studies with metformin, which is a well-known OCT2 substrate, that for OCT2 substrates drug clearance is influenced by altered OCT2 function. A human study showed that OCT2 genotypes associated with impaired activity led to a reduced apparent metformin clearance (CL/F) [36]. Moreover, an increase in metformin CL/F was seen in obese adolescents compared to non-obese children, possibly due to an increase in renal OCT2-activity [37]. In this light, the contrasting results on gentamicin and tobramycin clearance might be explained by a relatively higher dependence of gentamicin on OCT2-mediated renal uptake in favour of

glomerular filtration. Although to our best knowledge, this never has been properly studied, this hypothesis is further substantiated by the observation that tobramycin accumulates less in the kidney compared to gentamicin and therefore might be less nephrotoxic [38]. Further (preclinical) research seems warranted to clarify these differences between tobramycin and gentamicin PK based on the current study results.

An important question is what the target AUC_{24} is when treating patients with tobramycin. An AUC_{24} of 75 mg*h/L for pathogens with a MIC of 0.25 – 1 mg/L has been shown to be have the best balance between effectiveness and toxicity for aminoglycosides [5]. Therefore, we provided a nomogram that can be used to determine the initial tobramycin dose for obese individuals based on the patient's de-indexed MDRD targeting an AUC_{24} of 75 mg*h/L (Figure 5). When this dose strategy is employed in the obese, a stable median AUC_{24} up to 190 kg without trends can be expected. In addition, outer ranges lie around ~75% to ~125% relative to the target of 75 mg*h/L (absolute 95% confidence interval of 57.4 – 93.5 and 56.9 – 92.8 mg*h/L for non-obese and obese individuals, respectively, visualized in Figure 4). This is acceptable, considering the acceptance range of 80-125% as specified by the European Medicines Agency (EMA) for bio-equivalence studies [27]. In contrast, when a 5 mg/kg TBW dose regimen is employed in obese individuals, the 95% confidence intervals lie between 22.2 mg*h/L and 184.1 mg*h/L, corresponding to 30% to 246% relative to the target AUC_{24}. This high variability, which is most pronounced for the highest body weights of the obese population, can be explained by the fact that renal function is not taken into account in this strategy. Moreover, median AUC_{24} steadily increases with increasing body weight. In current daily practice, tobramycin is mostly dosed using ABW as is recommended by several papers, in order to maximize peak levels in obese individuals [11,39,40]. However, like with TBW-based dosing, this approach does not consider variation in renal function. As such, our simulations show that this approach leads to a substantial reduction in the proportion of patients having an AUC within the target AUC_{24} compared to using the dose nomogram for the obese population (43.9% versus 93.6%). Therefore, even though inadequate target concentrations can be picked up by therapeutic drug monitoring that is usually performed after a one or more dosages, we do not recommend to use TBW or ABW-based dose regimens in obese individuals.

A few remarks should be made regarding the proposed nomogram. First, the dose nomogram shows dose recommendations for de-indexed MDRD values ranging from 30 to 250 mL/min. However, our PK-model is based on a dataset with MDRD values of 77 to 171 mL/min. Dose recommendations outside of this MDRD-range should therefore be interpreted with caution in clinical practice. Second, the AUC-target of 75 mg*h/L used in the nomogram is based on an AUC/MIC ratio of 75, with a corresponding MIC ≤1 mg/L, as has been proposed earlier [5]. However, it is known that the wild-type population of most gram-negatives extends to 2 mg/L [8]. Therefore, higher dosages might be necessary to cover the whole range of pathogens

with MIC values up to 2 mg/L. Third, our study was specifically designed to obtain dose recommendations for obese individuals. A mg/kg-based dosing is already a widely accepted strategy for non-obese individuals. The proposed nomogram is expected to lead to an adequate exposure in the non-obese population as well (as shown in Figure S3B in the supplementary material). Despite this, our simulations of a 5 mg/kg TBW dose (Figure 4) show that in non-obese individuals, this strategy generally results in considerable variability. Last, after determining the initial tobramycin dose, we recommend that subsequent dosages should always be individualized by therapeutic drug monitoring, preferably with a limited sampling strategy in combination with model informed precision dosing based on Bayesian PK-software that is capable of translating the measured tobramycin concentrations to an individualized dose prediction [41].

Several limitations may apply to our study. First, we only included relatively healthy obese and non-obese individuals with an estimated renal function >60 mL/min/1.73 m^2. Therefore, extrapolation of our study results to critically-ill patients with or without renal impairment should be done with caution, since critical illness can have an additional impact on PK. Secondly, obese study participants underwent bariatric surgery during the PK study, which might influence the PK results. However, since these surgeries in our hospital are very short (<1 hour), and performed laparoscopically with minimal blood loss (<50 mL), we expect this impact to be negligible.

CONCLUSION

In conclusion, we found that in non-obese and obese patients up to 194 kg, tobramycin clearance shows an important relation with renal function estimates. In obese individuals, de-indexed MDRD was superior over TBW in predicting tobramycin clearance. In order to yield similar exposure across body weights, we therefore propose that the tobramycin dose in individuals >100 kg should be based on de-indexed MDRD. To aid the clinician in finding the optimal dose, we provide a dose nomogram that can be used to determine the correct initial tobramycin dose by integrating MDRD and target AUC.

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SUPPLEMENTARY MATERIAL

Table S1. Equations for different covariates used in this study.

Covariate	Equation
Body weight descriptors	
TBW (total body weight)	Total body weight (kg)
BMI (body mass index, kg/m^2)	TBW (kg)/((Length (m)^2)
BSA (body surface area, m^2)	TBW (kg)$^{0.425}$ * (Length (cm)$^{0.725}$ * 0.007184
IBW (kg)	50 (or 45.5 if female) + 2.3 * (Length (cm) * 0.3937-60)
ABW (kg)	IBW (kg) + (0.4 * TBW-IBW)
	If TBW<IBW, TBW is used as ABW
LBW (kg)	9270 * TBW / (6680+216 * BMI) if male
	9270 * TBW / (8780+244 * BMI) if female
Renal function estimates	
MDRD (mL/min/1.73m^2)	186.3 * (creatinine (mcmol/l)/88.4)$^{-1.154}$ * AGE (years) $^{-0.203}$ * 0.742 (if female) * 1.210 (if black)
De-indexed MDRD (mL/min)	MDRD * BSA/1.73
CKD-EPI (mL/min/1.73 m^2)	141 * min(creatinine (mg/dl)/k,1)^a * max(Scr/k,1)$^{-1.209}$ * 0.993^{age} * 1.018 (if female) * 1.159 (if black) k = 0.7 (females) or 0.9 (males) a = -0.329 (femfales) or -0.411 (males) min = minimum of creatinine/k or 1 max = maximum of creatinine/k or 1
De-indexed CKD-EPI (mL/min)	CKD-EPI * BSA/1.73
CG-LBW (mL/min)	(140 – age (years)) * LBW (kg) / (0.82 * creatinine (mcmol/l))
CG-TBW (mL/min)	(140 – age (years)) * total body weight (kg) / 0.82 * creatinine (mcmol/l) * F F = 0.85 (females) or 1 (males)
GFR (mL/min)	(1000 * creatinine$_{urine}$ (mmol/l) / creatinine$_{serum}$ (mcmol/l)) * (volume$_{urine}$ (mL) / collection time (hours))

Table S2. Results of Monte Carlo Simulations (n = 9.993) with different dose regimens.

Simulated dose	Within target[b] (%)		AUC_{24h} (mg * h/L)					
			Median		95% CI lower limit		95% CI upper limit	
	Non-obese[c]	Obese[c]	Non-obese[c]	Obese[c]	Non-obese[c]	Obese[c]	Non-obese[c]	Obese[c]
Nomogram (MDRD-based)	93.4	93.6	75.0	74.2	57.4	56.9	93.5	92.8
5 mg/kg TBW	48.0	40.4	65.0	94.6	23.3	22.2	116.8	184.1
5 mg/kg $TBW^{0.42}$ [a]	44.6	41.8	60.9	61.6	24.1	18.8	105.7	115.5
5 mg/kg ABW	40.2	43.9	58.8	63.5	23.3	18.4	102.3	120.3

[a] $TBW^{0.42} = 70 * (TBW/70)^{0.42}$

[b] Target is defined as 80%-125% relative to 75 mg*h/L (EMA acceptance criteria for bio-equivalence studies [27])

[c] Non-obese individuals: subgroup with total body weight 60 – 100 kg, Obese individuals: subgroup with total body weight 100 – 190 kg

ABW Adjusted body weight AUC_{24} 24 hour Area under the curve, *CI* confidence interval, *MDRD* Modification of Diet in Renal Disease *TBW* Total body weight.

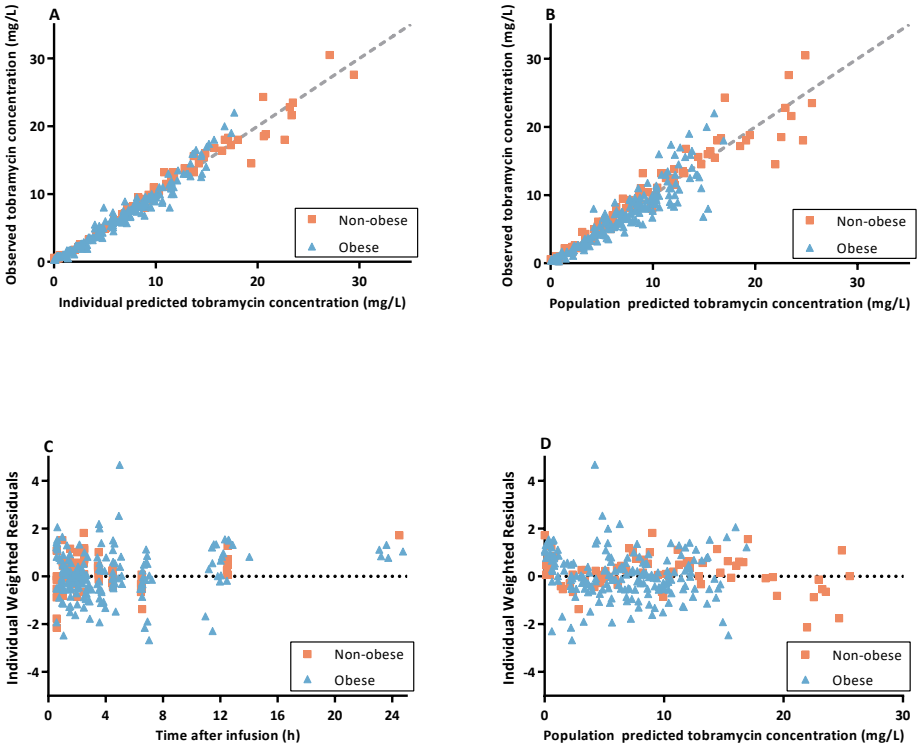


Figure S1. Goodness-of-fit plots of the final model for morbidly obese individuals (n = 20, blue triangles) and non-obese individuals (n = 8, orange squares), with (a) observed versus individual predicted tobramycin concentrations, (b) observed versus population predicted tobramycin concentrations, (c) individual weighted residuals versus time after start of infusion and (d) versus population predicted tobramycin concentrations. The dashed lines in plots (a) and (b) represent the line of identity (x = y).

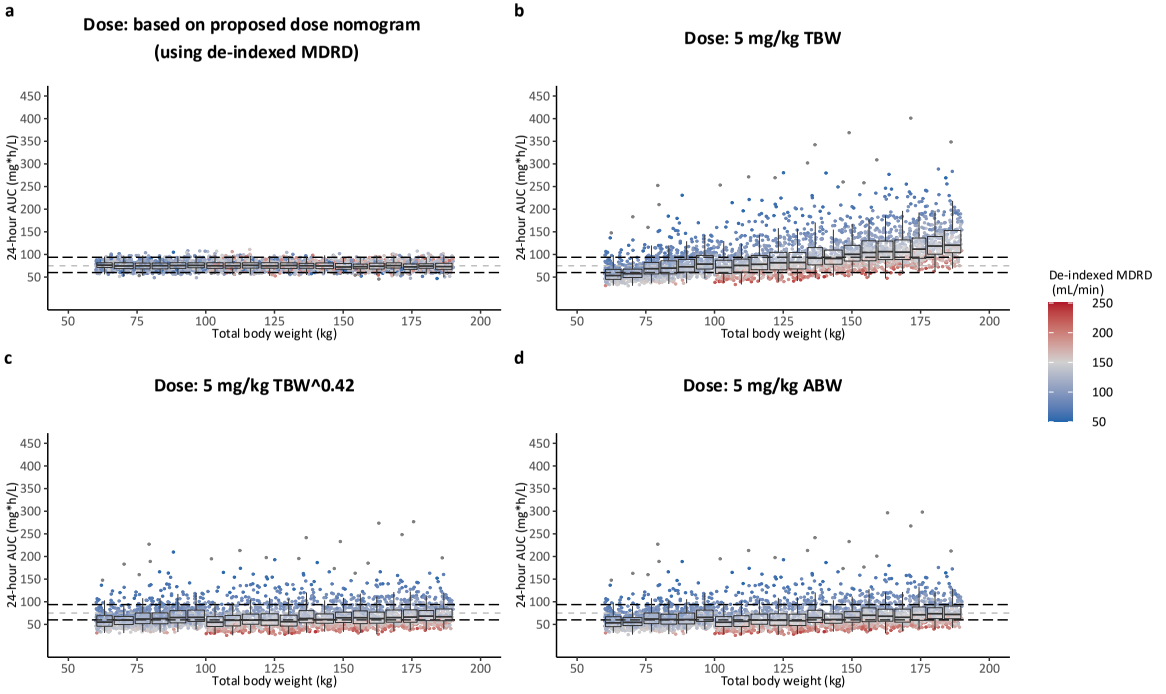


Figure S2. Monte Carlo simulations (n = 9.993) for individuals receiving (a) a MDRD-based tobramycin dose using the nomogram in Figure 5, (b) 5 mg/kg total body weight (TBW), (c) 5 mg/kg TBW scaled with exponent 0.42 (dose weight = 70 * (TBW/70)$^{0.42}$) or (d) 5 mg/kg adjusted body weight (ABW = Ideal Body Weight (IBW) + 0.4 * [TBW-IBW]) tobramycin. Each dot represents the AUC_{24} (in mg*h/L) of one individual in the dataset, where the color shows the de-indexed MDRD in mL/min (calculated as MDRD * body surface area (BSA)/1.73) of this individual (ranging from dark blue to dark red with increasing MDRD). The boxplot represents median and interquartile range of AUC_{24} values within a specific total body weight subgroup. The grey dashed line shows the target AUC_{24} of 75 mg*h/L, black dashed lines show the 80%-125% range (EMA acceptance criteria for bio-equivalence studies [27]) relative to this target value. *ABW* adjusted body weight, *AUC* area under the curve, *MDRD* Modification of Diet in Renal Disease, *TBW* total body weight.

NONMEM CONTROL STREAM FOR THE FINAL MODEL

```
$PROBLEM TOBRA
$INPUT ID        TIME    AMT     RATE    DV      LNDV    MDV     GFR     WT
LBW     BMI     IBW     ABW     AGE     BSA     SEX     RACE    HIST    PHASE
SURG    GRP     LLOQ    CG      EGFR    MDRD    MDRD_M          CREAT   CGTBW
CKD     CKD_M
$DATA nonmem_all_h.prn IGNORE=#
$SUBROUTINE ADVAN3 TRANS4
$PK
TVCL = THETA(1)*(1+THETA(7)*(MDRD-115)); TVCL
TVV1 = THETA(2)*(WT/70); TVV1
TVQ =    THETA(3); TVQ
TVV2 =   THETA(4); TVV2
;
CL = TVCL*EXP(ETA(1))
V1 = TVV1*EXP(ETA(2))
Q = TVQ*EXP(ETA(3))
V2 = TVV2*EXP(ETA(4))
;
S1 = V1
;
ET1=ETA(1)
ET2=ETA(2)
ET3=ETA(3)
ET4=ETA(4)
;
$THETA
(0, 10) ; TVCL
(0, 15) ; TVV1
(0,8) ; TVQ
(0,5) ; TVV2
(0, 0.2) ; SD PROPORTIONAL ERR
(0, 0.5) ; SD ADD
(0,0.01) ;factor MDRD on CL
;
$OMEGA
0.01 ; CL ETA 1
```

```
0.1 ; V1 ETA 2
0 FIX ; Q ETA 3
0 FIX      ; V2 ETA 4
;
$ERROR
IPRED = F
PROP=THETA(5)*F ; proportional part
ADD=THETA(6) ; additive part
SD=SQRT(PROP*PROP + ADD*ADD) ;
IF(DV.GE.LLOQ)THEN ;
F_FLAG=0
Y=F+SD*ERR(1) ; COMBINED ERROR MODEL
ELSE ;
F_FLAG=1
Y=PHI((LLOQ-F)/SD)
ENDIF
;
IRES = DV - IPRED
IWRES = IRES/SD
;
$SIGMA
1 FIX ; ERR 1
$ESTIMATION METHOD=1 INTER MAXEVAL=9999 POSTHOC LAPLACIAN;
$COVARIANCE PRINT=E;
$TABLE ID TIME IPRED CWRES AMT TVCL CL TVV1 TVV2 TVQ V1 Q V2 ET1 ET2 ET3 ET4
IWRES MDV GFR WT LBW BMI ABW IBW AGE SEX RACE HIST PHASE SURG GRP LLOQ
CREAT CG MDRD EGFR SD CKD CKD_M MDRD_M NOPRINT ONEHEADER
```



5



Population pharmacokinetics of vancomycin in obesity: finding the optimal dose for (morbidly) obese individuals

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ABSTRACT

Aims For vancomycin treatment in obese patients, there is no consensus on the optimal dose that will lead to the pharmacodynamic target (AUC 400 – 700 mg*h L^{-1}). This prospective study quantifies vancomycin pharmacokinetics in morbidly obese and non-obese individuals, in order to guide vancomycin dosing in the obese.

Methods Morbidly obese individuals (n = 20) undergoing bariatric surgery and non-obese healthy volunteers (n = 8) (total body weight (TBW) 60.0 – 234.6 kg) received a single vancomycin dose (obese: 12.5 mg kg^{-1}, maximum 2500 mg; non-obese: 1000 mg) with plasma concentrations measured over 48 hours (11 – 13 samples per individual). Modelling, internal validation, external validation using previously published data and simulations (n = 10.000 individuals, TBW 60 – 230 kg) were performed using NONMEM.

Results In a three-compartment model, peripheral volume of distribution and clearance increased with TBW (both p <0.001), which was confirmed in the external validation. A dose of 35 mg kg^{-1} per day (maximum 5500 mg/day) resulted in a >90% target attainment (AUC >400 mg*h L^{-1}) in individuals up to 200 kg, with corresponding trough concentrations of 5.7 – 14.6 mg L^{-1} (twice daily dosing). For continuous infusion, a loading dose of 1500 mg is required for steady state on day 1.

Conclusions In this prospective, rich sampling pharmacokinetic study, vancomycin clearance was well predicted using TBW. We recommend that in obese individuals without renal impairment, vancomycin should be dosed as 35 mg kg^{-1} per day (maximized at 5500 mg/day). When given over two daily doses, trough concentrations between 5.7 – 14.6 mg L^{-1} correspond to the target exposure in obese individuals.

INTRODUCTION

Over the past decades, the worldwide prevalence of obesity (defined as a body mass index (BMI) ≥30 kg m^{-2}) has dramatically increased [1]. Since 1975, the percentage of obese men and women increased from 3.2 and 6.4 % to 10.8 and 14.9 %, respectively. This corresponds with 641 million individuals being obese worldwide. If this trend continues, global obesity prevalence will reach 18 – 21% in 2025 [1]. Evidence suggests that these individuals are more prone to infections [2]. As a consequence, clinicians are increasingly facing (severely) obese patients requiring antibiotic treatment. It has been well established that due to pathophysiological changes that are associated with overweight, such as an increased cardiac output, increase in adipose tissue, changes in renal function and impacted metabolic enzyme activity, the pharmacokinetics (PK) of drugs can be significantly impacted, often requiring dose adaptations [3,4].

Vancomycin is a glycopeptide antibiotic, introduced in clinical practice over 60 years ago. Since then vancomycin has become a widely used agent predominantly for serious gram-positive infections and is considered first line treatment in methicillin-resistant *Staphylococcus aureus* (MRSA) infections [5]. For these indications the drug is administered intravenously using intermittent or continuous infusion regimens, preceded by a loading dose in the latter setting [6,7]. Around 80% is excreted unchanged renally, mostly by glomerular filtration but other (active) excretion pathways might also play an important role [6]. In *S. Aureus* infections, vancomycin efficacy closely correlates with a total 24-hour area-under-the-curve (AUC_{24h}) over the minimal inhibitory concentration (MIC). Target AUC_{24h} of vancomycin for efficacy for this indication have been well defined in the clinical setting, with thresholds of ≥345 – ≥451 mg*h L^{-1} found over the years, based on MICs up to 1 mg L^{-1} [8–12]. A comprehensive practice guideline published in 2009 advocated an efficacy target of AUC_{24h}/MIC ≥400 mg*h L^{-1} [13]. To reach this target with intermittent dose regimens, a target steady state trough concentration of 15-20 mg L^{-1} was advised [13]. There is however substantial evidence from other populations that lower trough concentration ranges might also be effective to reach the AUC_{24h} target [14,15]. To date, this has not been studied for the obese population. Regarding vancomycin toxicity, 700 mg*h L^{-1} was recently proposed as an AUC_{24h} upper limit for the first 48 hours of treatment [16]. Another study found an increasing risk of nephrotoxicity with steady state AUC_{24h} values over 1300 mg*h L^{-1} [17].

With respect to dosing guidelines, according to the FDA drug label, vancomycin should be given as a fixed dose of 2000 mg per day in adults with a normal renal function, without specific recommendations for obese patients [18]. Since the FDA-regimen has been shown to result in suboptimal exposure (AUC_{24h} around 100-250 mg*h L^{-1}) in normal weight adults, more recent guidelines recommend 15 – 20 mg kg^{-1} every 8-12 hours [13]. This rather broad dosing regimen is also recommended for obese patients, thereby resulting in a large variability of

dose regimens used for obese individuals in clinical practice [13] and is based on studies that are mostly performed with sparse data based on routine TDM peak and trough levels [19–24]. Most of these studies show that both volume of distribution and clearance increase in obese patients. Initially, total body weight (TBW) was shown to be the best predictor for vancomycin clearance [20,21]. However, these findings have been challenged by other studies in obese patients, including the most recent [19,22,24].

As a consequence, the exact dosing strategy for vancomycin in obese patients still remains to be established. This study aims to quantify the pharmacokinetics of vancomycin in morbidly obese and non-obese individuals. Using prospectively collected, rich data gathered over 48 hours after a single dose in individuals over a wide range in body weight, we aim to identify covariates that best predict changes in vancomycin clearance and volume of distribution in obesity. The model is externally validated using independent data and is ultimately applied to guide vancomycin dosing in the (morbidly) obese thereby optimizing target attainment.

METHODS

Subjects

Morbidly obese patients with an indication for bariatric surgery (BMI ≥40 kg m^{-2} or ≥35 kg m^{-2} with comorbidities), i.e. laparoscopic sleeve gastrectomy or gastric bypass, and non-obese healthy volunteers (BMI 18 – 25 kg m^{-2}) were considered for inclusion in this study. Participants were excluded when they were known to have an allergy to glycopeptides, were pregnant or breastfeeding, were renally impaired (defined as estimated glomerular filtration rate (eGFR) of <60 mL min^{-1} 1.73 m^{-2} (calculated using the Cockcroft-Gault (CG) formula with lean body weight (LBW) for obese [25] or CG with TBW for non-obese) or had used potentially nephrotoxic drugs (for example aminoglycosides, loop diuretics, or non-steroid anti-inflammatory drugs) in the week before surgery. All participants provided written informed consent prior to inclusion. This clinical trial was approved by the local human research and ethics committee (Medical Research Ethics Committees United, Nieuwegein, The Netherlands, NL52260.100.16) and registered in the Dutch Trial Registry (NL5885/NTR6058), and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Study design

Participants received a single intravenous infusion of vancomycin (obese patients: 12.5 mg kg^{-1}, maximum 2500 mg; non-obese 1000 mg as fixed dose, all infused in 10 mg min^{-1}). Obese patients received the infusion during or immediately after bariatric surgery. Blood samples were collected 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 12 hours after end of infusion. In the obese group, samples were also drawn during infusion, at 2 and 0.25 hours before end of infusion. Additional samples

were drawn around 24 hours and, if the individual was still admitted, 48 hours after start of infusion. Blood samples were collected in lithium-heparin tubes, centrifuged at 1900 g for 5 minutes, after which plasma was stored at -80 ^{o}C until analysis. For safety assessment, serum creatinine was measured before and 24 hours after administration of vancomycin. Estimated glomerular filtration rate (eGFR) was calculated using Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas, either the conventional Cockcroft-Gault (CG-TBW) formula or CG calculated with LBW instead of TBW for obese (CG-LBW). MDRD and CKD-EPI were corrected for body surface area (BSA) by multiplying the result (in mL min^{-1} 1.73 m^{-2}) by BSA/1.73. Lastly, 24-hour urine was collected on the study day to measure 24-hour creatinine clearance as marker for the glomerular filtration rate (GFR).

Sample assay

Vancomycin plasma concentrations were measured using a validated, commercially available immune-assay method (VANC3, Cobas® System, Roche Diagnostics GmbH, Mannheim, Germany) with a limit of detection (LOD) of 1.5 mg L^{-1}, lower limit of quantification (LLOQ) of 4 mg L^{-1} and upper limit of quantification (ULOQ) of 80 mg L^{-1}. Measured concentrations below LOD or LLOQ were reported in the dataset. Within-run and inter-day variability was 3.7% and 4.4%, respectively.

Pharmacokinetic analysis

Pharmacokinetic parameters were analysed using non-linear mixed-effects modelling (NONMEM 7.4, ICON Development Solutions, Hanover, USA) and Pearl-speaks-NONMEM 4.8.1 [26] using Pirana 2.9.7 (Certara USA, Inc, Princeton, USA) [27,28]. One-, two- and three-compartmental models were evaluated with the ADVAN 1, 3 or 11 routine, respectively, using the first order conditional estimation method with interaction (FOCE-I) and addition of the LAPLACIAN method. Interindividual variability and residual variability were assumed to be respectively log-normally and normally distributed. NONMEM output was visualized with R 3.5.1 (Xpose package 4.6.1) [29] and GraphPad Prism 6.0 (GraphPad Software, La Jolla, USA). Values below LOD were analysed using the M3 method as described elsewhere [30]. Model building was performed in three stages: (1) selection of the structural model, i.e. a one-, two- or three-compartmental model, (2) selection of the statistical error model (additive, proportional or a combined error model) and (3) a covariate analysis. Nested models were compared using the drop in objective function value (OFV, -2 log likelihood function), where a difference of 3.84 corresponds with a p-value <0.05 with one parameter difference. In addition, goodness of fit plots (GOF), such as observed versus population and individual predictions, or conditional weighted residuals versus time after dose or population predictions were used for diagnostic purposes. Lastly, parameter estimate precision, shrinkage, individual fits, and prediction-corrected visual predictive checks (pcVPC) [31] were evaluated to identify the best model.

Potential covariates were identified by assessing trends in plots of the individual *post-hoc* parameter or the unexplained variability against the specific covariate. Covariates that were present in the dataset included TBW, LBW (calculated using the Janmahasatian formula [32]), adjusted body weight (ABW, calculated with correction factor 0.4 as described elsewhere [33]), BMI, ideal body weight (IBW, using the Devine formula [34]), sex, age, GFR (based on collection of 24-hour urine) and serum creatinine-based estimations of GFR such as CG-TBW, CG-LBW, MDRD or CKD-EPI (the latter two both normalized for BSA 1.73 m^2 and de-indexed for BSA by multiplying the original value by BSA/1.73). Covariates were implemented in the model using linear and power functions, standardized for a typical individual of 70 kg or median value of the covariate [35]. Inclusion was considered when step-by-step inclusion resulted in a drop in OFV of at least -3.84 ($p < 0.05$) and backward deletion gave an OFV increase of at least 10.8 points ($p < 0.001$). Furthermore, the contribution of a covariate was judged based on the reduction in interindividual variability and diagnostics described earlier.

Internal validation

The final model was internally validated by pcVPC based on 1000 simulations, split for obese and non-obese individuals. Parameter precision and robustness of the structural and final model were analysed by the sampling importance resampling (SIR) procedure [36].

External validation

Data from a previously published prospective study in which six obese (111 – 226 kg) and four non-obese (66 – 89 kg) individuals with normal renal function received a single infusion of 1000 mg vancomycin in 40 minutes, [21] were used to externally validate our pharmacokinetic (covariate) model. In the external validation study, vancomycin concentrations were measured using a validated immuno-assay with a LLOQ of 0.5 mg L^{-1}. External validation was done using pcVPC based on 1000 simulations, split for obese and non-obese individuals. Bias and precision of the model was quantified by calculation of the median prediction error (MPE) and root mean squared error (RMSE) according to equations (1) and (2),

$$PE_i(\%) = \frac{C_{pred,i} - C_{obs,i}}{C_{obs,i}} \times 100\% \quad (1)$$

$$RMSE\ (mg\ L^{-1}) = \sqrt{\frac{\sum\left(C_{pred,i} - C_{obs,i}\right)^2}{N}} \quad (2)$$

where PE_i and RMSE are the prediction error for the ith observation and root mean squared error of all observations, where $C_{pred,i}$ and $C_{obs,i}$ represent the predicted and observed vancomycin concentration for the ith observation and N is total number of observations. MPE under 20% and RMSE under 5 mg L^{-1} were considered accurate.

Simulation based comparison of dosing strategies

To guide the optimal dosing strategy in the obese, simulations using the final model with interindividual variability were performed with different dose regimens in 10,000 obese individuals (BMI >35 kg m^{-2}) with a uniform weight distribution between 90 and 230 kg. AUC_{24h} was calculated by implementing an AUC compartment equal to the central compartment in the NONMEM $DES subroutine. Based on literature, we chose a target for the probability of target attainment (PTA) and probability of toxicity (PTOX) an AUC_{24h} of >400 mg*h L^{-1} and AUC_{24h} >700 mg*h L^{-1}, respectively, both assessed at day 3 (when in steady state). We aimed for a PTA of at least 90% in obese individuals (BMI >35 mg kg^{-2}) with the lowest possible PTOX, as recommended by the European Medicine Agency. Simulated dose regimens consisted of continuous infusion regimens of 20, 25, 30, 35, 40 and 45 mg kg-1 per day (with or without a dose cap for the 24-hour dose) and 2000, 3000, 4000, 5000 and 6000 mg per day as fixed doses. In combination with the selected dose, loading doses of 500, 1000, 1500, 2000 or 2500 mg were evaluated. The loading doses, given as single infusions at a rate of 10 mg min^{-1}, were followed by a continuous infusion starting two hours after start of the loading dose. Different loading dose strategies were evaluated by comparing the mean and 95% confidence intervals of the AUC_{24h}-ratio per weight group, which is calculated by dividing the AUC_{24h} at day 1 by the AUC_{24h} at day 3. Ideally, the 95% confidence intervals of these ratios should contain 1, meaning that steady state is reached at day 1 and the loading dose is adequate.

Correlation of trough concentrations with achievement of target AUC_{24h}

For the selected vancomycin dose, trough concentrations related to the optimal target attainment (AUC_{24h} within the target of 400 – 700 mg*h L^{-1}) were investigated by simulations using the same weight distribution (n = 10,000). Administration of the dose over two or three administrations per day or a continuous infusion were investigated. At day 3, trough concentrations that corresponded to the 2.5-95 percentiles of the AUC_{24h} within the target of 400 – 700 mg*h L^{-1} were identified. This target AUC_{24h} was chosen since the current consensus guideline describes that the recommended target trough concentrations correspond to AUC_{24h} >400 mg* h L^{-1} [13]. Correlation between trough concentrations and AUC_{24h} at day 3 was assessed by linear regression using R 3.5.1.

RESULTS

In total, 20 obese individuals with a median weight of 139.0 kg (range 110.6 – 234.6 kg) and 8 non-obese individuals with a median weight of 69.5 kg (range 60.0 – 84.7 kg) were included. Participant demographics are shown in Table 1. A total of 326 samples was collected (238 in obese and 88 in non-obese individuals), with a median of 12 samples (range 11 – 13) per participant. 24 samples (7%) were below LOD and handled according to the M3 method [30]. Samples were collected up to 24 hours in all cases. For two obese patients and all non-obese individuals, vancomycin concentrations were obtained until 48 hours after dosing. Measured vancomycin concentrations versus time are shown in Figure S1 in the supplementary file.

Table 1. Summary of baseline characteristics.

Parameter	Morbidly obese group (n = 20)	Non-obese group (n = 8)
Weight (kg)	139.0 (110.6 - 234.6)	69.5 (60.0 - 84.7)
Height (cm)	173.5 (159 - 189)	182.5 (166 - 190)
Body mass index (kg m^{-2})	45.5 (40.8 - 65.7)	21.2 (20.4 - 25.0)
Age	38.0 (23 - 54)	25.5 (20 - 55)
Serum creatinine (mmol L^{-1})[a]	72 (41 - 101)	70 (60 - 86)
Glomerular filtration rate measured using 24-h urine collection (mL/min^{-1})	141.4 (80.7 - 260.7)	117.9 (88.1 - 147.0)
De-indexed Modification of Diet in Renal Disease (MDRD, mL min^{-1})	138.3 (89.5 - 220.6)	115.4 (72.8 - 144.7)
De-indexed Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI, mL min^{-1})	148.1 (95.5 - 221.6)	125.3 (77.1 - 139.3)
Cockcroft-Gault (conventional, (mL min^{-1})	249.2 (166.0 - 431.8)	140.1 (87.9 - 157.3)
Cockcroft Gault with lean body weight for obese (CG-LBW, mL min^{-1})	122.0 (83.1 - 191.0)	140.1 (87.9 - 157.3)

Data shown as median (range)

[a] Serum creatinine as measured before administration of vancomycin.

Pharmacokinetic analysis

A 3-compartment model with first order elimination and a combined proportional and additive residual error model with interindividual variability for clearance, V1 and V2 best described the data. Parameters of the structural model are shown in Table 2.

Implementation of TBW with a linear relationship on V2 gave the largest reduction in OFV (-24.5 [p <0.001]) and interindividual variability (from 37.1% to 5.8%). In the model with TBW on V2, interindividual variability on V2 was omitted from the model since this did not impact

the OFV (+0.11). In the following step, the best results were obtained by inclusion of (1) TBW with a power function on clearance using an estimated exponent, (2) ABW and (3) LBW, both with linear functions. This resulted in OFV reductions of -17.4 (1), -18.9 (2) and -15.5 (3) ($p < 0.001$ for all), resulting in a reduction in interindividual variability from 29.3% to 21.2, 20.5 and 21.9%, respectively. No significant differences were visible in goodness-of-fit plots between TBW, LBW and ABW-models. Since TBW is more readily available in clinical practice and is therefore preferable in the light of model-informed dose recommendations, we chose to include TBW on clearance. Inclusion of MDRD, CKD-EPI, CG-TBW, CG-LBW or GFR (based on 24-hour creatinine clearance) did not significantly improve the model ($p > 0.001$). After inclusion of TBW on clearance, no remaining covariates could be identified for this parameter. Lastly, introduction of age as covariate on V1 and V2 resulted in a decrease of OFV with -19.4 points and improved GOF ($p < 0.001$).

Since interindividual variability for clearance appeared to be significantly higher in the obese group, we estimated separate IIV values for both groups, resulting in an OFV drop of -11.8 and a resulting interindividual variability on clearance of 5.3% and 24.7% for non-obese and obese subpopulations, respectively. While the interindividual variability on clearance in the non-obese showed a high uncertainty and significant shrinkage, we decided to fix this parameter to 5.3% in the final model, since removing it from the model resulted in a penalty of 4 points increase in OFV. The final PK parameters of the resulting model are shown in Table 2. Goodness-of-fit plots for the final model are shown in Figure S2 in the supplementary file.

Internal validation

The pcVPC, shown in Figure 1 shows that the median and 2.5th and 97.5th percentiles of the prediction intervals correspond with the observations. The lower panel in Figure 1 shows that the model performs well in predicting the portion of observations that are below LOD. Confidence intervals of the model parameters based on the SIR procedure are presented in Table 2.

External validation

pcVPC of the external validation using data of the study from Blouin and colleagues (6 obese and 4 non-obese individuals) are shown in Figure 2. The VPC shows a good predictive performance of our model in the obese population without significant bias and good precision, while the model seems to slightly underpredict observations in non-obese individuals, mostly in higher concentrations (>20 mg L^{-1}). This is shown by MPE and RMSE, where acceptance criteria (MPE <20 %, RMSE <5 mg L^{-1}) are met only in the obese population (MPE for non-obese subgroup: -20.1 %, obese subgroup: -0.171 %, corresponding RMSE values 7.24 mg L^{-1} for the non-obese and 3.27 mg L^{-1} for the obese population).

Table 2. Pharmacokinetic parameter estimates of the structural and final (covariate) model.

Parameter	Structural model (RSE %) [95% CI]	Final model (RSE %) [95% CI]
Fixed effects		
CL (L h^{-1})	7.32 (14.0) [6.13 – 8.33]	-
$CL = CL_{70kg} \times \left(\frac{TBW}{70}\right)^{\theta_1}$		
CL_{70kg} (L h^{-1})	-	5.72 (5.0) [5.34 – 6.10]
θ_1	-	0.535 (20) [0.36 – 0.67]
V1 (L)	15.8 (27) [11.2-20.4]	-
$V1 = V1_{36.5yr} \times (1+ \theta_2 \times [age-36.5])$		
$V1_{36.5yr}$ (L)	-	16.7 (18) [12.9 – 21.2]
θ_2	-	0.0136 (31) [0.00575 – 0.0211]
Q_{V1-V2} (L h^{-1})	16.2 (20) [13.0 – 21.4]	15.8 (23) [11.6 – 21.7]
V2 (L)	13.2 (26) [9.48 – 17.2]	-
$V2 = V2_{70kg;36.5yr} \times \left(\left[\frac{TBW}{70}\right] \times (1+ \theta_2 * [age-36.5])\right)$		
$V2_{70kg;36.5yr}$ (L)	-	6.98 (17) [5.78 – 8.67]
θ_2	-	0.0136 (31) [0.00575 – 0.0211]
Q_{V1-V3} (L h^{-1})	4.37 (25) [2.88 – 6.07]	5.21 (21) [3.83 – 6.63]
V3 (L)	19.7 (21) [14.9 – 26.3]	19.5 (13) [15.0 – 24.1]
Inter-individual variability		
CL[a,b] (%)	31.9 (22) [25.3 – 41.6]	-
$CL_{non-obese}$[a,b] (%)	-	5.28 FIX
CL_{obese}[a,b] (%)	-	24.7 (19) [18.4 – 32.3]
V1[a,b] (%)	56.8 (44) [40.1 – 83.9]	45.3 (24) [34.9 – 62.0]
V2[a,b] (%)	37.1 (37) [23.4 – 50.9]	-
Residual variability		
Proportional error[c,d]	0.0401 (21) [0.0253 – 0.0568]	0.0392 (21) [0.0246 – 0.0541]
Additive error (mg L^{-1})[d]	1.03 (5.0) [0.923 – 1.13]	1.07 (5.0) [0.960 – 1.16]
OFV	682.82	609.89

Parameter estimates are shown with standard error of estimate reported as %RSE with 95% CI based on sampling importance resampling (SIR) procedure

[a] Shrinkage of inter-individual variability in the final model are below 20 % for all estimates

[b] Calculated by $\sqrt{(e^{\omega^2} - 1)}$

[c] Proportional error is shown as σ

[d] Epsilon shrinkage for the final model is 8%

CI confidence interval obtained from sampling importance resampling (SIR) procedure, *CL* clearance, CL_{70kg} clearance from the central compartment for an individual weighing 70 kg, *OFV* objective function value, Q_{V1-V2} inter-compartmental clearance between V1 and V2, Q_{V1-V3} inter-compartmental clearance between V1 and V3, *RSE* relative standard error based on covariance step in NONMEM, *TBW* total body weight, *V1* volume of distribution of the central compartment, $V1_{36.5yr}$ volume of distribution of the central compartment for an individual aged 36.5 years, *V2* volume of distribution of the second peripheral compartment, $V2_{70kg;36.5yr}$ volume of distribution of the second peripheral compartment for an individual aged 36.5 years and weighing 70 kg, *V3* volume of distribution of the third peripheral compartment.

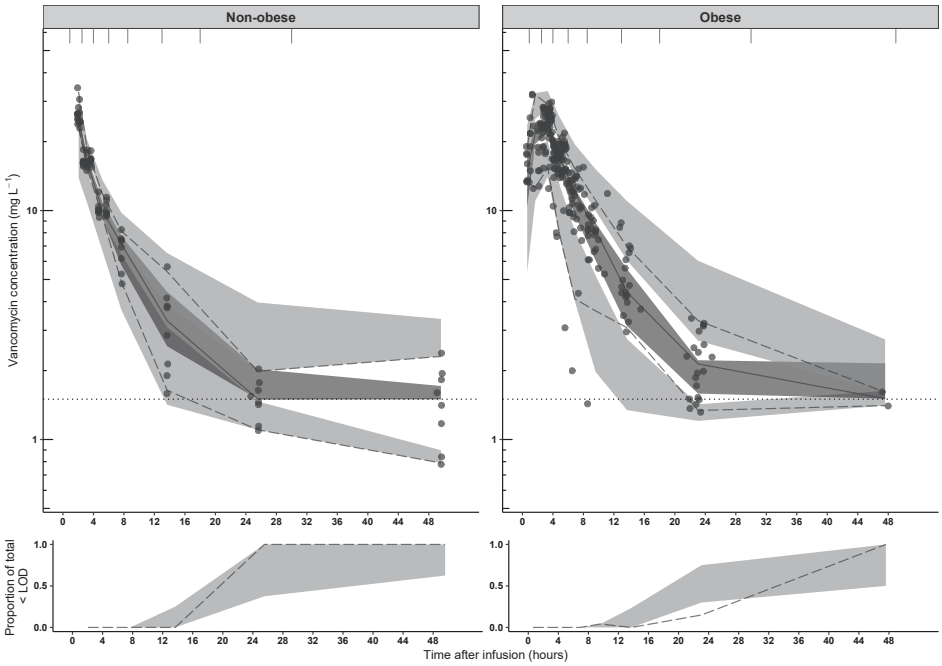


Figure 1. Prediction corrected visual predictive checks (pcVPC) of the final model split for non-obese (upper left panel) and obese (upper right panel) subgroups of the current study. The observed concentrations are shown as black circles, median, 2.5th and 97.5th percentiles of the observed data are shown as solid, lower and upper dashed lines. Grey shaded areas represent the 95% confidence intervals of the median (dark grey) and 2.5th and 97.5th percentiles (light grey) of simulated concentrations (n = 1000) based on the original dataset. The lower limit of detection (LOD) is depicted by the dotted grey line. Intervals of the bins are shown by the vertical ticks on the top of the plot. Lower panels show the observed proportion below the LOD (dashed line), where shaded areas represent the 95% confidence intervals based on simulated concentrations (n = 1000). *LOD* limit of detection.

Simulation based comparison of dosing strategies

Figure 3 shows the results of simulations in obese individuals ranging 90 – 230 kg upon weight-based dose regimens. In Figure 3, the left column shows the resulting mean AUC_{24h} with 95% percentiles, while in the right column PTA (AUC_{24h} >400) and PTOX (AUC_{24h} >700) at day 3 are presented. Figure S3 in the supplementary file shows the same plot for fixed dose regimens. Figure 3 shows that when the vancomycin dose is increased from 25 mg kg^{-1} per day to 45 mg kg^{-1} per day, both chances of achieving an AUC_{24h} >400 and >700 increase for all individuals. A high PTA could be achieved for all body weights using a dose regimen of 35 mg kg^{-1} per day, maximized at 5500 mg per day. For some weight categories where the PTA (AUC_{24h} >400) was below 90% (i.e. individuals under 110 kg and over 210 kg), PTA was still above 80%, and in all cases the probability of reaching an AUC_{24h} >350 mg*h L^{-1} was above 90% (data not shown). The highest PTOX (AUC >700) with this dose regimen is seen in individuals weighting around

150 – 160 kg. Notably, in this group still 94% of the individuals have an AUC_{24h} <900 mg*h L^{-1}. A fixed dose of 2000 mg per day, the recommended dose in the FDA drug label, results in unacceptably low PTA for both non-obese and obese individuals (Figure S3, supplementary file). All weight-based dosages evaluated in Figure 3 were maximized at 5500 mg per day, based on Monte Carlo simulations with fixed dosages (Figure S3 in the supplementary file) where a suboptimal PTA (AUC >400) is seen with dosages ≤5000 mg per day, and considerable PTOX (AUC >700) is seen with high body weights with 24-hour dosages ≥6000 mg. Figure 4 shows simulations with increasing loading doses in combination with a maintenance dose of 35 mg kg^{-1} per day illustrating that a loading dose of 1500 mg yields similar exposure at day 1 compared to day 3 without significant trends across body weights, with all mean AUC-ratio's close to 1 and all corresponding 95% confidence intervals containing 1. No clinically significant influence of age on simulated vancomycin concentrations was found for four typical individuals with age ranging 20–50 years and a TBW of 130 kg (Figure S4 in supplementary file).

Correlation of trough concentrations with achievement of target AUC_{24h}

A daily dose of 35 mg kg^{-1}, maximized at 5500 mg per day, was selected for simulation of trough concentrations at day 3 when given as intermittent or continuous infusion regimens. Figure 5 shows the AUC_{24h} versus trough concentrations for obese individuals at day 3. There is a strong relationship between AUC at day 3 and trough concentrations, with R^2 values of 0.92, 0.93 and 1.00 when the dose is given in two- or three-times dosages or as continuous infusion, respectively. Trough concentrations corresponding to 95% AUC_{24h} within target (400 – 700) are 5.70 – 14.6 (dose divided over two administrations), 7.8 – 17.8 (dose divided over three administrations) and 17.5 – 28.3 (continuous infusion) mg L^{-1}, as depicted by the red lines in Figure 5.

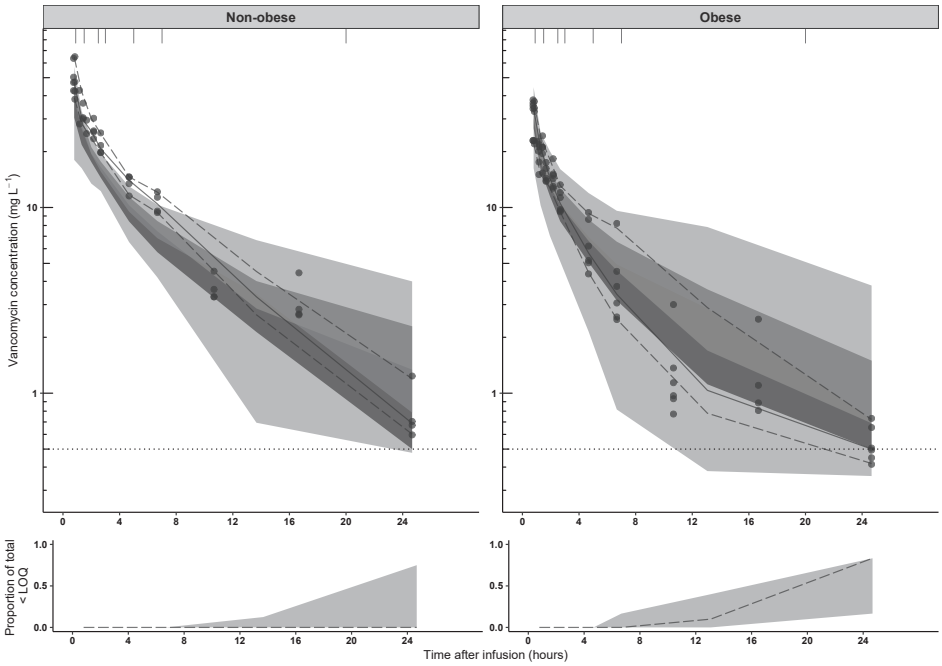


Figure 2. Prediction corrected visual predictive checks (pcVPC) of the final model split for non-obese (upper left panel) and obese (upper right panel) subgroups for the external dataset published by Blouin et al. [21]. The observed concentrations from the Blouin study are shown as black circles, median, 2.5th and 97.5th percentiles of the observed data are shown as solid, lower and upper dashed lines. Grey shaded areas represent the 95% confidence intervals of the median (dark grey) and 2.5th and 97.5th percentiles (light grey) of simulated concentrations (n = 1000) based on the original dataset. The lower limit of quantification (LOQ) is depicted by the dotted grey line. Intervals of the bins are shown by the vertical ticks on the top of the plot. Intervals of the bins are shown by the vertical ticks on the top of the plot. Lower panels show the observed proportion below the LOQ (dashed line), where shaded areas represent the 95% confidence intervals based on simulated concentrations (n = 1000). *LOQ* limit of quantification.

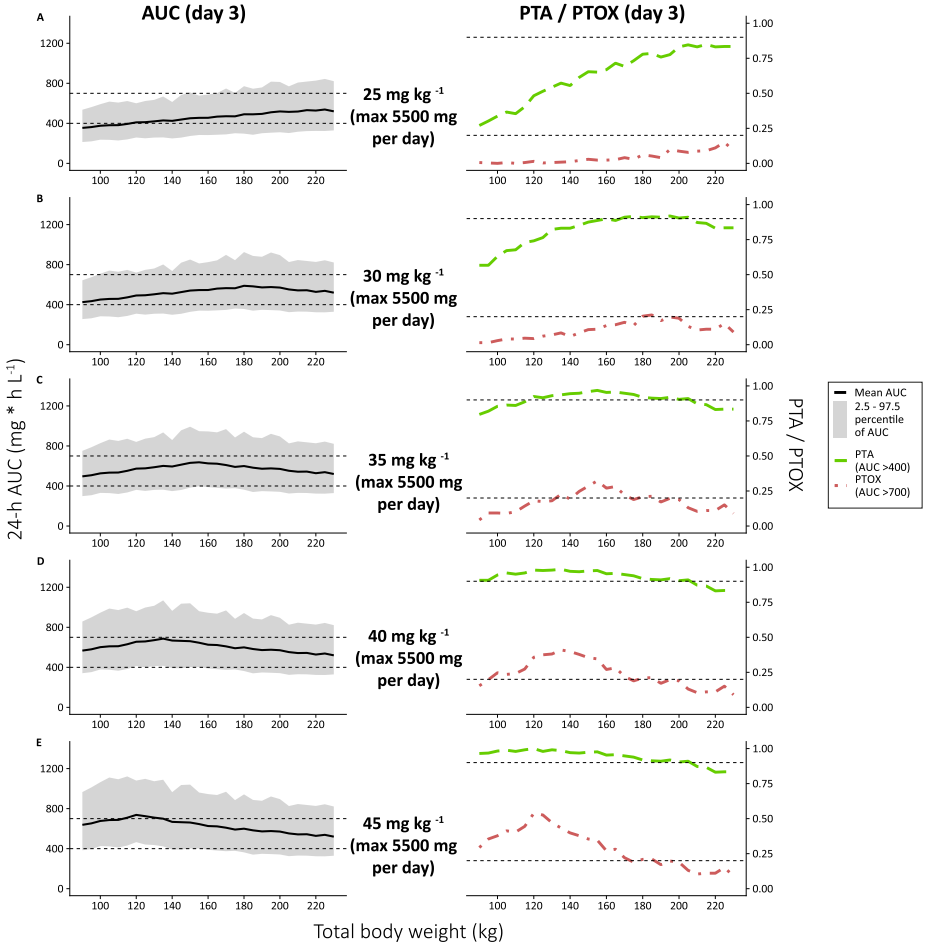


Figure 3. 24-hour area under the curve (AUC) values at day 3 (left column) and probability of target attainment (PTA, AUC_{24h} >400) or toxicity (PTOX, AUC_{24h} >700) (right column), shown versus weight (90 – 230 kg) for several dose regimens (n = 10.000 per dose regimen). Panels A – E show increasing dose regimens from 25 mg kg^{-1} per day to 45 mg kg^{-1} per day, all maximized at 5500 mg per day. In the left plots, the solid black line and grey area indicate mean observed AUC with 2.5 – 97.5 percentiles. Dashed grey line represents target AUC levels (400 and 700 mg*h L^{-1}). In the right plots, the dashed green line and dot-dashed red line indicate PTA and PTOX, respectively. Dashed grey lines represent the threshold for PTA (0.9) and, for reference, 20% PTOX (0.2). *AUC* 24-hour area under the curve at day 3, *PTA* Probability of Target Attainment (AUC >400) at day 3, *PTOX* Probability of Toxicity (AUC >700) at day 3.

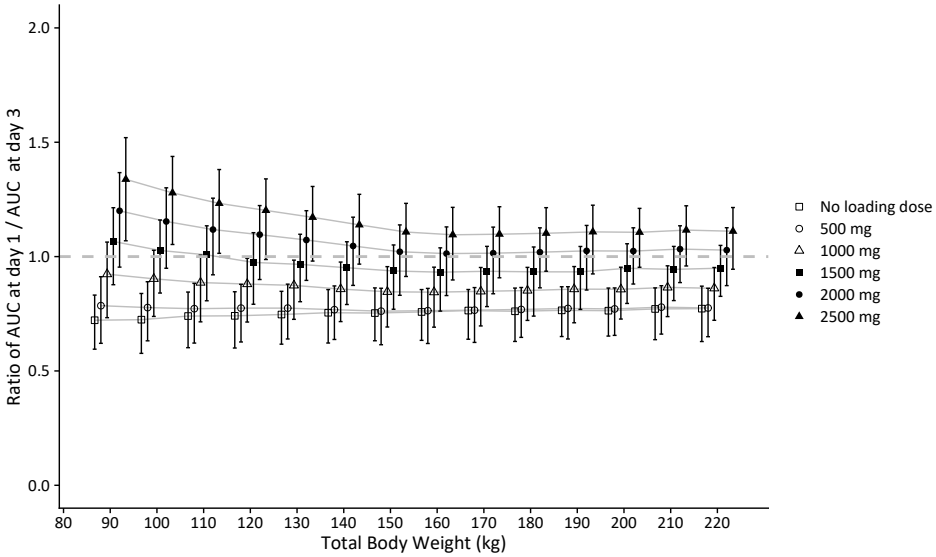


Figure 4. Mean ratio of AUC_{24h} at day 1/AUC_{24h} at day 3 with 95% confidence intervals, shown for different loading doses versus body weight (90–230 kg), based on Monte Carlo Simulations (n = 10.000 per loading dose). Each line represents one loading dose regimen. All individuals received 35 mg kg^{-1} continuous infusion started 2 hours after the loading dose (maximised at 5500 mg per day). Grey dashed line represents a ratio of 1. *AUC* 24-hour area under the curve.

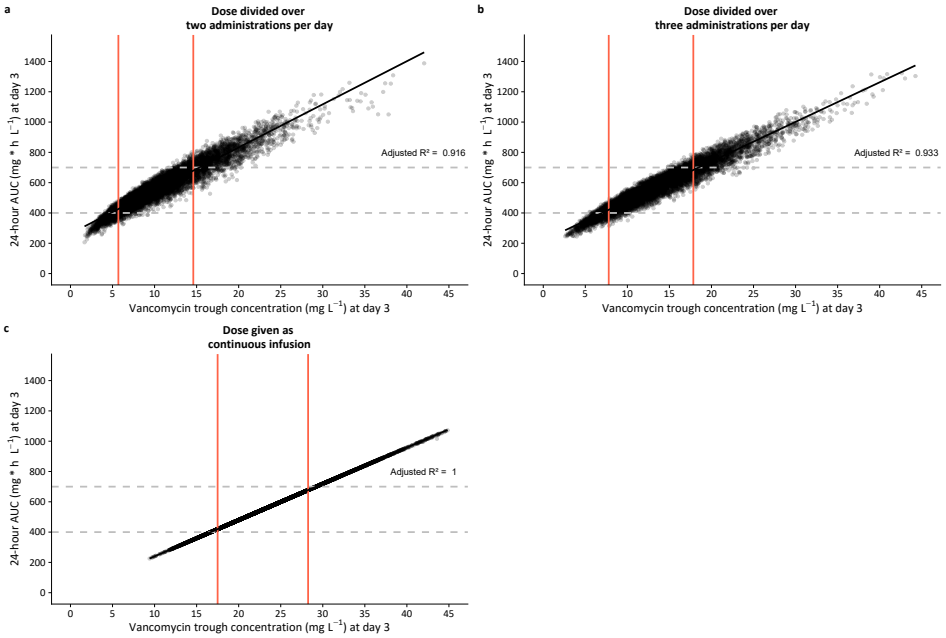


Figure 5. 24-hour area under the curve (AUC_{24h}) at day 3 versus individual trough concentrations at day 3 (measured 0.5 hour prior to the second dose) based on Monte Carlo Simulation in obese patients (n = 10,000, weight ranging 90 – 230 kg), using the final model. Vancomycin dose was 35 mg kg^{-1} per day, maximized at 5500 mg per day, (a) given over two infusions per day, (b) three infusions per day or (c) as a continuous infusion regimen. Each dot represents one simulated individual. Dashed horizontal lines show the target AUC window (400 - 700 mg*h L^{-1}). Trough concentrations corresponding to 95% of AUC_{24h} within this target are shown with red vertical lines. The black line represents the linear regression line, with corresponding adjusted R^2 value shown in the graph. *AUC* area under the curve.

DISCUSSION

Our study shows that vancomycin PK is significantly altered by obesity. We found that in obese individuals up to 235 kg without renal impairment, vancomycin clearance could be predicted by TBW (Table 2) using a power function with estimated exponent of 0.54, which was confirmed by the external validation. Monte Carlo simulations incorporating inter-individual variability showed that in obese individuals, the target exposure (at least 90% AUC_{24h} >400) could be attained when vancomycin is dosed as 35 mg kg^{-1} per day, maximized on 5500 mg per day. Using this regimen, PTOX (AUC_{24h} >700) was <20% for most individuals, despite a slight trend in increasing exposure with increasing body weight. In theory, a dose regimen based on TBW scaled to 0.54 (in accordance with the relationship found between CL and TBW) would result in an equal exposure across body weights, but is in our opinion less suitable for use in daily practice. For continuous infusion regimens of 35 mg kg^{-1} per day, a loading dose of 1500 mg is

sufficient for reaching steady at day 1 for all weight categories. A fixed dose regimen of 2000 mg per day as dictated by the FDA drug label, leads to unacceptable low PTA under 25% across the whole population, as was described earlier [13].

A strong aspect of our study is the prospective study design with intensive pharmacokinetic sampling in adults with a wide range of body weights across the included cohort from 60 to 235 kg, allowing for the characterisation of a three-compartment model. This is in contrast with other reports on vancomycin PK in obesity, that fully rely on TDM data, that consist mostly of peak and trough concentrations, making it difficult to estimate more than one compartment, thereby limiting the ability to adequately assess individual pharmacokinetic parameters [19,22]. Moreover, we used data from a previously performed study to externally validate our model [21]. Our model showed a high precision without bias in describing the data in the obese subgroup. Therefore, taken these results together with our internal validation, we can conclude that our PK-model shows an excellent performance in predicting vancomycin PK in the (morbidly) obese population up to 235 kg.

Our results on vancomycin clearance and volume of distribution in obese individuals puts forward what was known on vancomycin PK in obesity. Regarding clearance, predominantly retrospective studies also found a larger vancomycin clearance in obese compared to non-obese individuals [19,20,22,24]. One prospective rich sampling PK study in healthy obese individuals, similar to our study design but with only six obese individuals included, found a linear relationship of TBW with vancomycin clearance, in contrast to the power relationship as found in our study [21]. One retrospective study in 108 obese and 596 non-obese patients, found no difference in absolute vancomycin clearance between both groups [23]. This might be explained by the relatively low body weight in the obese group (mean TBW 94.3 kg). Other reports in which obese patients were included, show conflicting results on the best predictive covariate for vancomycin clearance, varying from CG with TBW [19], serum creatinine [24], or a combination of serum creatinine, age, TBW and gender [22]. These results might be explained by differences in studied body weights or employed sampling schedules (i.e. use of TDM data versus intensive sampling). Considering the fact that vancomycin is predominantly excreted renally, it is interesting that we found TBW to be a better predictor than any of the renal function estimates including GFR based on 24-hour urine clearance. This might be explained by the lack of individuals with renal impairment in our study. In addition, in our PK model vancomycin clearance of a typical individual of 70 kg is 5.72 L h^{-1}, corresponding to 95 mL min^{-1}, which is slightly below the average GFR in our relatively young population. This is in line with what has been reported in other studies and suggests that other processes besides glomerular filtration also play a role [6]. There is substantial evidence that obesity can influence both passive and active processes in the kidney's [37], which might explain why body weight is a better predictor for vancomycin clearance than renal function estimates in obese individuals without renal failure.

Results on vancomycin volume of distribution in obese seem to be more consistent across literature. Five studies reported on changes in volume of distribution, all describing an increase of volume of distribution with body weight in a linear fashion [19–21,23,24]. No study reported age as a covariate for volume of distribution. In our study we found age as covariate for volume of distribution, even though its impact was limited. As a consequence, increasing age does not impact the proposed dose regimen.

It is well known that vancomycin pharmacokinetics exhibits large inter-individual variability and has a small therapeutic window, and therefore the 2009 consensus guideline recommends that TDM is routinely applied when treating patients with vancomycin [13]. Our results further substantiate this recommendation for the obese populations, since our final PK model still shows considerable unexplained inter-individual variability for both clearance (25% in the obese subgroup) and volume of distribution (45% on V1). To obtain an adequate AUC_{24h} between 400 and 700 mg*h L^{-1}, guidelines recommend to target trough concentrations between 15 – 20 mg L^{-1} [13]. We show that in obese individuals, steady state trough concentrations of 5.7 – 14.6 mg L^{-1} (when dosed two times daily) are sufficient to assure adequate exposure. This discrepancy with the guideline recommendation has been reported for several other special populations as well [14,15]. Plots with individual *post-hoc* clearance and volume of distribution values visualized by colour (shown in Figure S5 in the supplementary file) point out that the variability in volume of distribution explains why we see this range in trough concentrations with similar AUC_{24} values. To circumvent this problem in translating trough concentrations to exposure, it might be preferable to measure the AUC directly using a limited sampling strategy (for example with peak-and-trough concentrations) along with the employment of Bayesian forecasting software. This recommendation has also been incorporated in the revision of the 2009 vancomycin TDM guideline, which is currently under development [38]. If resources or knowledge is unavailable, clinicians should be aware that in obese individuals, trough concentrations below 15 mg L^{-1} do not necessarily correspond to a subtherapeutic exposures and therefore do not always require dose adjustments.

Some limitations apply to our study. First, our participants received only a single vancomycin infusion. Therefore, extension of our PK model to simulate continuous infusions should be done with caution. Yet, the maintenance dose is merely dependent on vancomycin clearance which can be adequately estimated in the current study design. Second, in interpreting the simulations, we chose a target PTA of 90% for selection of the best dose regimen, as advocated by the EMA [39]. However, certain situations may call for a higher target PTA and therefore a higher dosage, for example in serious life-threatening infections [39,40]. In addition, the target for PTA (AUC_{24} >400 mg h L^{-1}), has only been established for *S. Aureus* infections. We still remain fairly ignorant as to the appropriate targets for other infections where vancomycin is indicated. Third, obese individuals underwent bariatric surgery during

the PK study, which could theoretically interfere with the results. However, the concerning operations are performed laparoscopically, with a short duration (<1 h), and minimal blood loss (<50 mL). Therefore, we consider this influence to be negligible. Last, the participants in our study were, besides being obese, otherwise healthy individuals with adequate renal function. Therefore, one should apply caution in extrapolating of our results to individuals with renal impairment or critical illness and always perform TDM in these populations.

In conclusion, our study shows that in order to obtain optimal exposure with minimal risk on toxicity, vancomycin should be dosed as 35 mg kg^{-1} per day in obese individuals without renal impairment. For continuous infusion regimens, a loading dose of 1500 mg is sufficient for the whole population to obtain steady state at day 1.

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Contributors

C.S., M.J.W., E.P.A.D., J.W.M., R.J.M.B, and C.A.J.K. designed the study, C.S., R.E.W and E.P.A.D. performed the study, C.S., R.E.W., S.C.G., C.A.J.K. analysed the data and C.S., R.E.W., S.C.G., M.J.W., E.P.A.D., J.W.M., R.J.M.B. and C.A.J.K. wrote the manuscript.

Data sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPLEMENTARY FILE

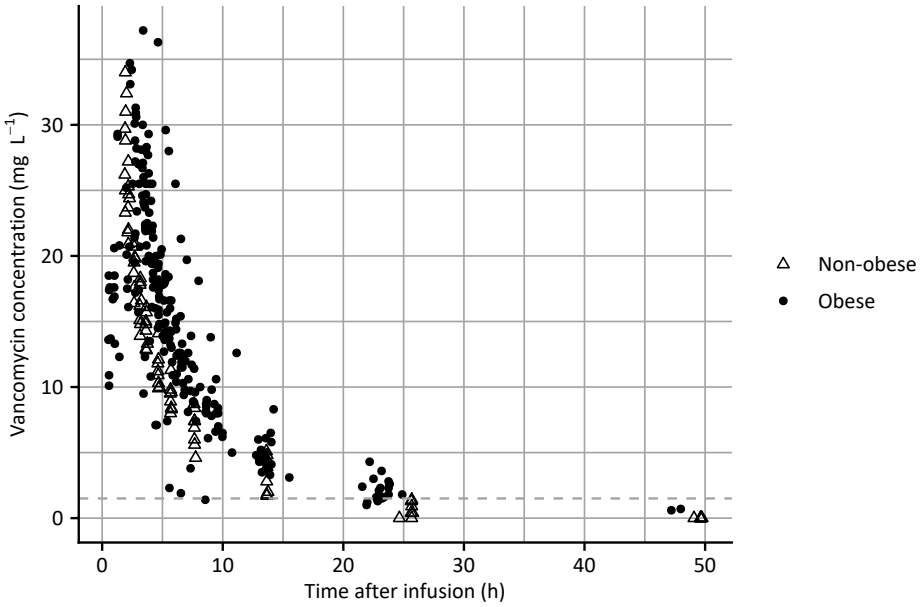


Figure S1. Measured vancomycin concentration versus time after infusion. Non-obese participants (n = 8 individuals, dose 1000 mg) are shown as triangles, obese participants as circles (n = 20 individuals, dose 12.5 mg kg^{-1}, maximum 2500 mg)). The limit of detection (LOD) of 1.5 mg L^{-1} is shown with the grey dashed line.

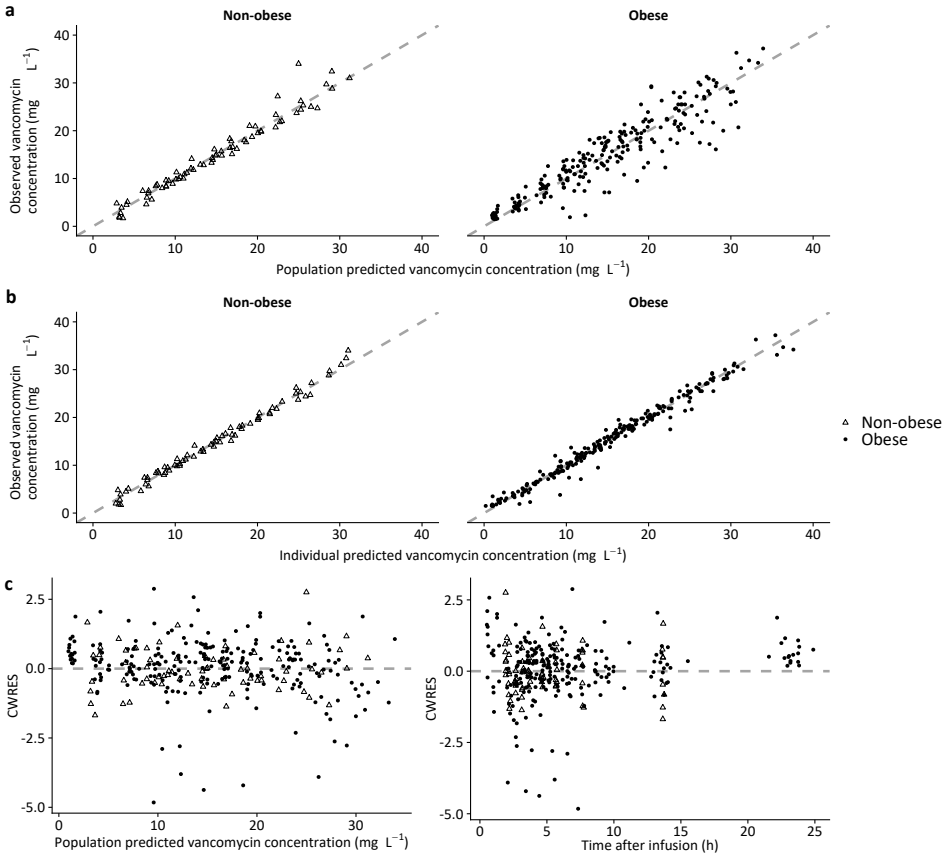


Figure S2. Goodness-of-fit plots of the final pharmacokinetic model for non-obese individuals (n = 8, white triangles) and morbidly obese individuals (n = 20, black dots). (a) Observed versus population predicted vancomycin concentration, (b) observed versus individual predicted vancomycin concentration and (c) conditional weighted residuals (CWRES) versus population predicted vancomycin concentration (left panel) and CWRES versus time after start of infusion (right panel). Grey dashed lines in plots (a) and (b) represent the line of identity (x = y), grey dashed lines in (c) represent a CWRES of 0. *CWRES* conditional weighted residuals.

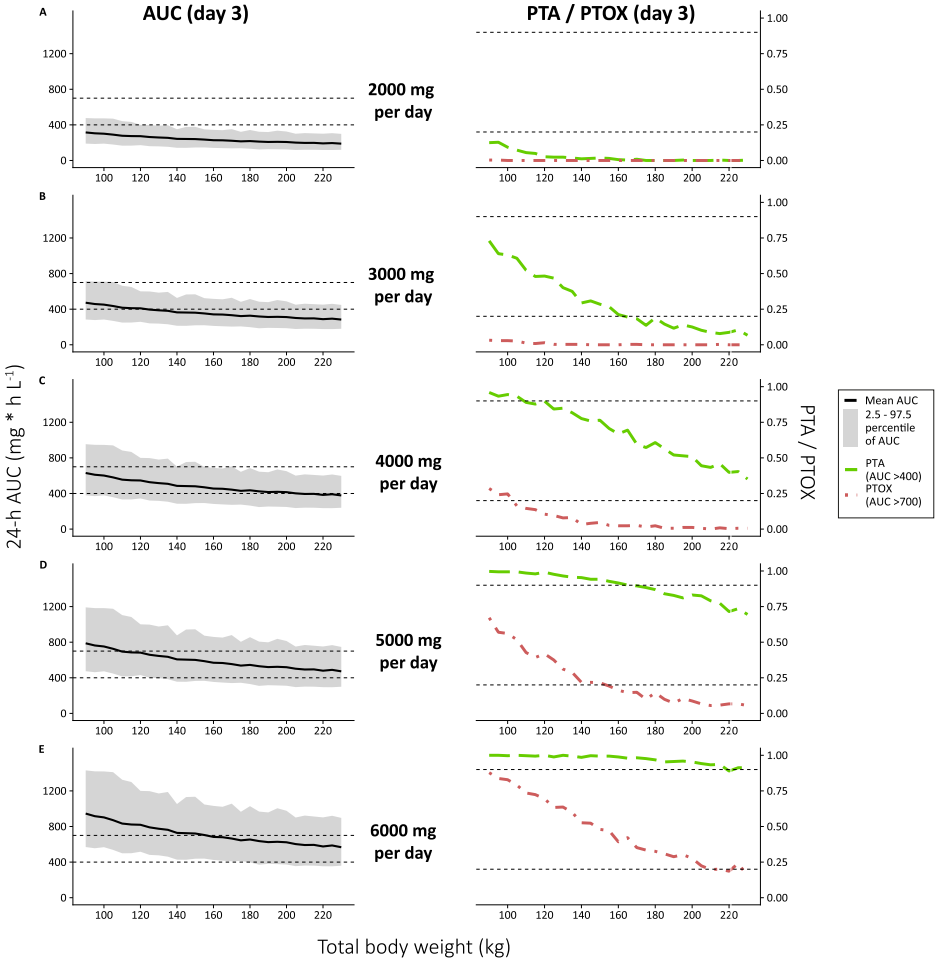


Figure S3. 24-hour area under the curve (AUC) values at day 3 (left column) and probability of target attainment (PTA, AUC_{24h} >400) or toxicity (PTOX, AUC_{24h} >700) (right column), shown versus weight (90 – 230 kg) for several fixed dose regimens (n = 10.000 per dose regimen). Panels A – E show increasing dose regimens from 2000 mg per day to 6000 mg per day. In the left plots, the solid black line and grey area indicate mean observed AUC with 2.5 – 97.5 percentiles. Dashed grey line represents target AUC levels (400 and 700 mg*h L-1). In the right plots, the dashed green line and dot-dashed red line indicate PTA and PTOX, respectively. Dashed grey lines represent the threshold for PTA (0.9) and, for reference, 20% PTOX (0.2). *AUC*, 24 hour area under the curve at day 3; *PTA*, Probability of Target Attainment (AUC >400) at day 3; *PTOX*, Probability of Toxicity (AUC >700) at day 3.

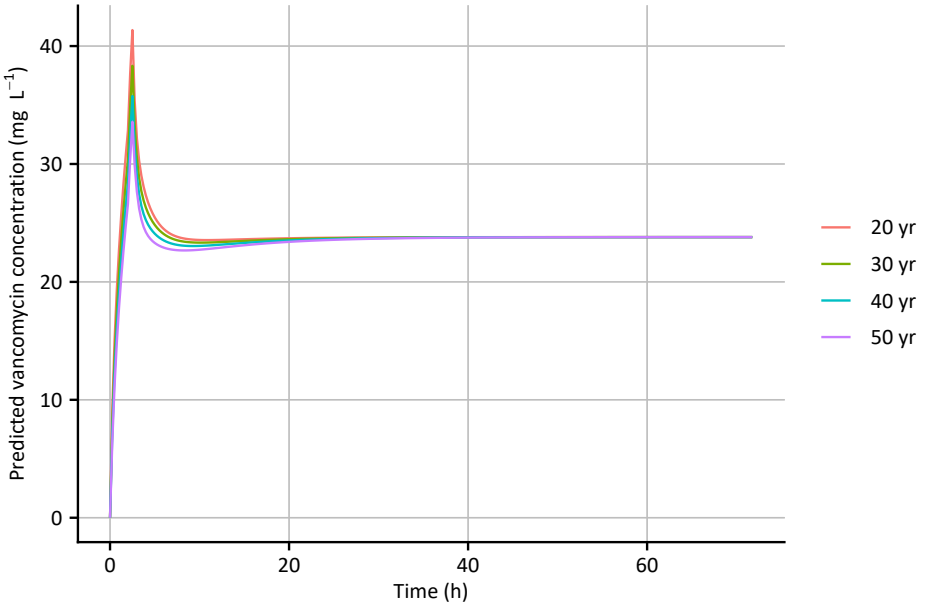


Figure S4. Predicted vancomycin concentrations when administered to 4 individuals weighing 130 kg with varying age after administration of a vancomycin dose of 1500 mg (infusion rate 10 mg min^{-1}) followed after 2 hours by a continuous infusion of 35 mg kg^{-1} per day (maximized at 5500 mg per day). Each line represents population predicted vancomycin concentrations over time for 1 individual.

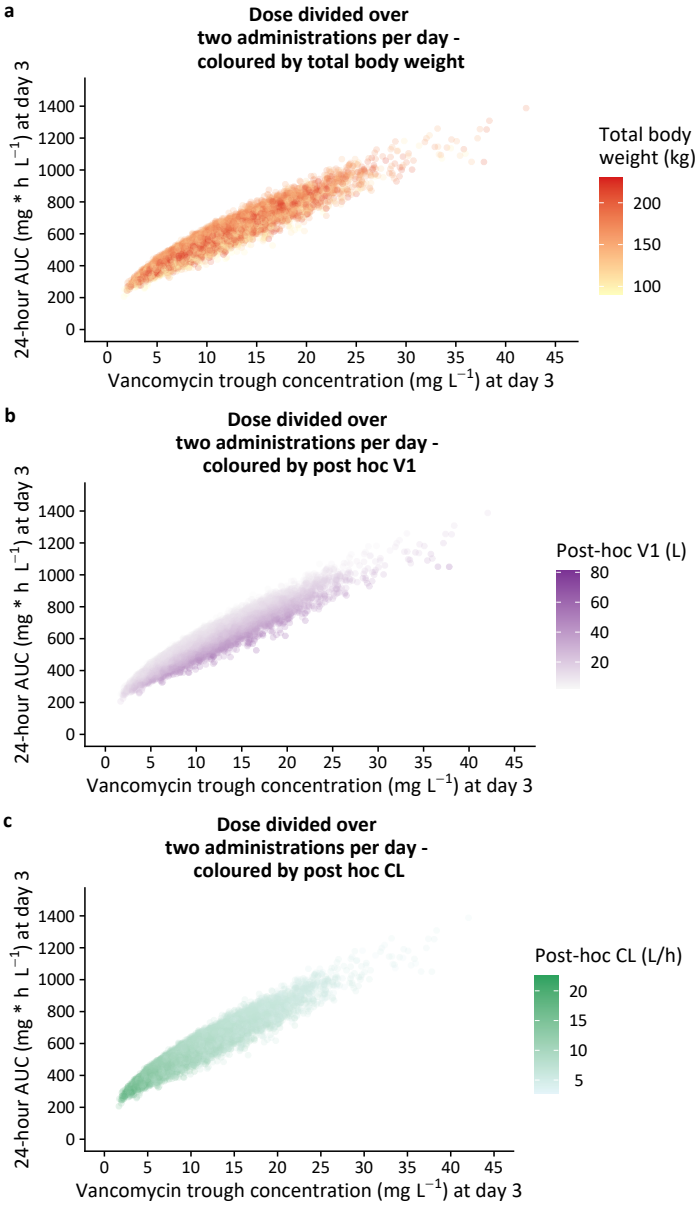


Figure S5. 24-hour area under the curve (AUC_{24h}) at day 3 versus individual trough concentrations at day 3 (measured 0.5 hour prior to the second dose) based on Monte Carlo Simulation in obese patients (n = 10.000, weight ranging 90 – 230 kg), using the final model. Vancomycin dose was 35 mg kg^{-1} per day, maximized at 5500 mg per day, given over two infusions per day. Each dot represents one simulated individual. Each dot is coloured according to the individual's (a) total body weight, (b) post-hoc volume of distribution of central compartment and (c) post-hoc clearance. *AUC* area under the curve, *CL* clearance, *V1* central volume of distribution.

NONMEM CONTROL STREAM FOR THE FINAL MODEL

```
$PROBLEM VANCO
$INPUT ID TIME AMT RATE DV LNDV=DROP MDV LLOQ
LOD DURING OK GFR WT LBW BMI IBW ABW AGE
BSA SEX RACE HIST PHASE SURG GRP CG MDRD CREAT
CKD CGTBW
$DATA nonmem_all.prn IGNORE=#
$SUBROUTINE ADVAN11 TRANS4
$PK
TVCL = THETA(1)*((WT/70)**THETA(10)); TVCL
TVV1 = THETA(2)*(1+THETA(11)*(AGE-36.5)); TVV1
TVQ2 = THETA(3); TVQ2
TVV2 = THETA(4)*((WT/70)**THETA(9))*(1+THETA(11)*(AGE-36.5)); TVV2
TVQ3 = THETA(5);TVQ3
TVV3 = THETA(6);TVV3
;
IF (GRP.EQ.0) THEN
CL = TVCL*EXP(ETA(1))
ELSE
CL = TVCL*EXP(ETA(7))
ENDIF
;
V1 = TVV1*EXP(ETA(2))
Q2 = TVQ2*EXP(ETA(3))
V2 = TVV2*EXP(ETA(4))
Q3 = TVQ3*EXP(ETA(5))
V3 = TVV3*EXP(ETA(6))
;
S1 = V1 ;
;
ET1_0=ETA(1)
ET1_1=ETA(7)
ET2=ETA(2)
ET3=ETA(3)
ET4=ETA(4)
ET5=ETA(5)
ET6=ETA(6)
```

```
;
$THETA
(0, 5.72) ; TVCL
(0, 16.7) ; TVV1
(0, 15.8) ; TVQ2
(0, 6.99) ; TVV2
(0, 5.21) ; TVQ3
(0, 19.5) ; TVV3
(0.0392) ; SD PROPORTIONAL ERR
(1.07) ; SD ADD ERROR
(1) FIX ; EXP V1 WT
(0, 0.535) ; EXP CL-WT
(-0.054, 0.0136,0.0606) ; SLOPE V1-V2-AGE
;
$OMEGA
0.00278 FIX ; CL ETA 1_0 (NON-OBESE)
0.187 ; V1 ETA 2
0 FIX ; Q2 ETA 3
0 FIX ; V2 ETA 4
0 FIX ; Q3 ETA 5
0 FIX ; V3 ETA 6
0.0593 ; CL ETA 1_1 (OBESE)
;
$ERROR
TYPE=1
IF(DV.LT.LOD) TYPE = 2
;
PROP=THETA(7)*F ; proportional part
ADD=THETA(8) ; additive part
SD=SQRT(PROP*PROP + ADD*ADD) ;
;
IPRED = F
DUM = (LOD - IPRED) / SD
CUMD = PHI(DUM)
IF (TYPE .EQ. 1.OR.NPDE_MODE.EQ.1) THEN
F_FLAG = 0
Y = IPRED + SD * ERR(1)
ENDIF
IF (TYPE .EQ. 2.AND.NPDE_MODE.EQ.0) THEN
```

```
F_FLAG = 1
Y = CUMD
MDVRES=1
ENDIF
IF(TYPE.EQ.2) DV_LOQ=LOD
;
IRES = DV - IPRED
IWRES = IRES/SD
;
$SIGMA
1 FIX ; ERR 1
;
$ESTIMATION METHOD=1 INTER MAXEVAL=9999 POSTHOC LAPLACIAN NOABORT
NUMERICAL SLOW ;
$COVARIANCE MATRIX=S PRINT=E SLOW;
;
$TABLE ID TIME IPRED CWRES NPDE AMT TVCL CL NPDE TVV1 V1 TVQ2 Q2 TVV2 V2
TVQ3 Q3 TVV3 V3 ET1_1 ET1_0 ET2 ET3 ET4 ET5 ET6 MDV GFR LLOQ WT LOD IWRES LBW
BMI IBW ABW AGE BSA SEX RACE HIST PHASE OK DURING SURG GRP CG MDRD CREAT
CKD CGTBW NOPRINT ONEHEADER
```

Part III



Extension of obesity studies to real-world adult and paediatric populations





6



Dose recommendations for gentamicin in the real-world obese population with varying bodyweight and renal (dys)function

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ABSTRACT

Objectives The impact of weight on pharmacokinetics of gentamicin was recently elucidated for (morbidly) obese individuals with normal renal function. This study aims to characterize the pharmacokinetics of gentamicin in real-world obese patients, ultimately to develop dose recommendations applicable across the entire obese population.

Patients and methods In two large Dutch hospitals, all admitted patients with BMI ≥25 kg/m^2 with ≥1 gentamicin administration, ≥1 gentamicin and ≥1 creatinine serum concentration measurement were included. Data from one hospital, obtained from electronic health records, combined with prospective data of non-obese and morbidly obese with normal renal function, served as the training dataset, and data from the second hospital as external validation dataset.

Results In the training dataset (1187 observations from 542 individuals, total body weight (TBW) 52 – 221 kg and renal function (CKD-EPI) 5.1 – 141.7 mL/min/1.73 m^2), TBW was identified as a covariate on distribution volume, and de-indexed CKD-EPI and ICU-stay on clearance (all p <0.001). Clearance was 3.53 L/h and decreased with 0.48 L/h with each 10 mL/min reduction in de-indexed CKD-EPI. The results were confirmed in the external validation (321 observations from 208 individuals, TBW 69 – 180 kg, CKD-EPI 5.3 – 130.0 mL/min/1.73 m^2).

Conclusions Based on the study, we propose specific mg/kg dose reductions with decreasing CKD-EPI values for the obese population, and extension of the dosing interval beyond 24h when CKD-EPI drops below 50 mL/min/1.73 m^2. In ICU patients, a 25% dose reduction could be considered. These guidelines can be used to guide safe and effective dosing of gentamicin across the real world obese population.

INTRODUCTION

Gentamicin is an aminoglycoside antibiotic which is commonly used for severe Gram-negative bloodstream infections. Both efficacy and toxicity closely correlate with serum concentrations, with an area-under-the-curve in the first 24 hours ($AUC_{0\text{-}24}$) relative to the MIC being paramount for its efficacy, as has been extensively reviewed in several papers during the past years [1–5]. To ensure adequate exposure, current guidelines recommend a once daily dose of 6-7 mg/kg for lean subjects with a normal renal function [4,6]. Dose interval extension is recommended with renal impairment, since trough concentrations over 1 mg/L have been shown to be associated with nephro- and ototoxicity in clinical practice [7,8]. Recently, we have characterized the influence of (morbid) obesity on the pharmacokinetics of gentamicin, based on a prospective full pharmacokinetic study in healthy non-obese and (morbidly) obese individuals with normal renal function. In this study we found that in this population of individuals without renal impairment, but with body weights up to 221 kg, gentamicin clearance could be predicted using total body weight with an allometric exponent of 0.72 [9]. Since both renal function and (critical) illness are known to influence gentamicin clearance [10], it is likely that an adaptation of this dose nomogram is required for the real-world obese patients with a varying degree of renal function. This study aims to characterize the pharmacokinetics of gentamicin in this real-world obese population, ultimately to extend the dose nomogram to be used in obese, (critically) ill patients with and without renal impairment.

METHODS

Data

Data for this study were collected in two large Dutch teaching hospitals (St. Antonius Hospital in Nieuwegein/Utrecht and the Spaarne Gasthuis in Haarlem). Over the period of October 2017 – April 2019, all patients with a BMI ≥25 mg/m² treated with gentamicin in the St. Antonius Hospital were considered for inclusion. In this cohort, peak, trough and/or mid-way concentrations were collected as standard of care as the gentamicin therapeutic drug monitoring (TDM) guideline from the Dutch Association of Hospital Pharmacists prescribes that gentamicin treatment courses should be individualized using gentamicin serum concentration measurements [11]. Patient characteristics, gentamicin administration data and gentamicin concentrations were extracted from the electronic health record system. Patients were included in the analysis if they received at least one gentamicin administration and had at least one gentamicin and creatinine serum concentration measured during the course of therapy without restrictions regarding gentamicin dose or time of sampling relative to the administration. Gentamicin was dosed at the discretion of the treating physician and usually varied between 5 and 3 mg/kg. Double entry of a single patients was allowed under

the condition that time between two gentamicin dosages was more than 14 days. Exclusion criteria were a gentamicin measurement without recorded gentamicin administrations, a documented course of extracorporeal renal replacement therapy, or absence of a body weight measurement within 6 months of the first gentamicin administration. These data were analysed in conjunction with data from a previously performed rich sampling prospective pharmacokinetic study (the AMIGO trial), that were obtained upon a single gentamicin dose in both non-obese (5 mg/kg total body weight (TBW) and morbidly obese individuals (5 mg/kg lean body weight (LBW [12]) with normal renal function and with body weights ranging from 53 – 221 kg (non-obese n = 8, obese n = 20, ten samples per patient up to 24 hours after infusion) [9], comprising the training dataset used for pharmacokinetic model development.

A second dataset using electronic health record data obtained over the period of January 2013 to December 2018 was obtained from the Spaarne Gasthuis, containing the same variables as the training dataset and using the same in- and exclusion criteria, for the external validation of the developed model (external validation dataset).

Gentamicin concentrations were measured using commercially available, validated immunoassay kits (training dataset: Roche Diagnostics GmbH, validation dataset: Abbott Laboratories), with lower limits of quantification (LLOQ) of 0.4 and 0.5 mg/L for the training and validation dataset, respectively.

Ethics

Since this study uses TDM data obtained in routine clinical care in both hospitals, the need for informed consent was waived by the Institutional Review Boards (IRB). All participants in the prospective rich data sampling study (AMIGO study, registered in the Dutch Trial Registry (NTR6058) and approved by the local research and ethics committee) provided written informed consent before inclusion. All study procedures and protocols adhered to the principles of the Declaration of Helsinki.

Pharmacokinetic analysis

Concentration-time data was analyzed using non-linear mixed effects modeling (NONMEM v7.4.3, Pirana® v2.9.7, PsN [Perl-speaks-NONMEM] v4.9.0) and visualized using R (v3.6.1) [13–16]. Measurements below LLOQ were incorporated using the M3 method [17]. Using the Laplacian method and ADVAN 1, 3 and 11 subroutines, one- two- and three-compartment models were evaluated with additive, proportional or combined error structures. Models were compared using the objective function value (OFV) and standard goodness-of-fit plots (GOF). Covariates present in the dataset (TBW, LBW, adjusted body weight (ABW, correction factor 0.4 [18]), body surface area (BSA), serum creatinine, renal function estimates such as Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology (CKD-EPI) or Cockcroft-Gault

with LBW (CG-LBW) or TBW (CG-TBW), age, gender and ICU-stay were assessed for possible correlation with inter-individual variability (IIV) or conditional weighted residuals (CWRES). Serum creatinine, renal function estimates and ICU-stay (dichotomous) were analysed as time-varying covariates with backwards (serum creatinine and renal function estimates) or forward (ICU-stay) interpolation. De-indexed values for MDRD and CKD-EPI were obtained by multiplying with BSA/1.73. Covariates were implemented in the model using power (with an allometric exponent) and linear functions (by fixing the allometric exponent to 1). The final model was internally validated using prediction- and variability corrected visual predictive check (pvcVPC [19]) and a bootstrap resampling analysis, stratified for study group, with 1000 replicates and externally validated with the validation dataset based on pvcVPC, GOF (using MAXEVAL = 0) and assessment of the median prediction error (MPE) and relative root mean square error (rRMSE). A complete list of equations used for calculating body size descriptors and renal function estimates can be found in the supplementary material (Tables S1 and S2).

Dose simulations

Using the final pharmacokinetic model, a single intravenous dose of gentamicin (given over 30 minutes) with different dose strategies was simulated in virtual subjects (n = 10.000 per dose regimen) with randomly assigned values of CKD-EPI, total body weight (both with the same ranges as the training dataset) and gender. Height was imputed as 180 cm (for males) or 167 cm (for females), corresponding to the median values in the training dataset. For ABW-based dose strategies, realistic combinations of weight, height and gender were necessary to obtain realistic ABW-values. To this end, values for these parameters were obtained by resampling combinations from the NHANES database (data from 1999 to 2016), where we stratified on TBW to ensure sufficient virtual subjects in each TBW strata [20]. CKD-EPI values were de-indexed as done in the original training dataset by multiplying with BSA/1.73. With inclusion of inter-individual variability, $AUC_{0\text{-}24}$ values were obtained for each subject using the $DES block in ADVAN6. As target for selecting the optimal dose strategy, we used the median $AUC_{0\text{-}24}$ from a reference subset of lean (non-ICU) subjects with a TBW <100 kg) and CKD-EPI > 60 mL/min/1.73 m^2 receiving 6 mg/kg TBW. This dose corresponds to the standard dose as currently recommended by the EUCAST [6]. Exposure within 80 – 125% of the target $AUC_{0\text{-}24}$ was considered equivalent, in line with the EMA guideline for bio-equivalence studies [21].

RESULTS

A total of 1187 gentamicin concentrations from 542 individuals and 321 concentrations from 208 individuals were available in the training and validation dataset, respectively (Figure S1 in the supplementary file). Median body weight was 90.0 kg (range 53 – 221 kg) in the training dataset, and 100 kg (range 69 – 180 kg) in the validation dataset. Renal function assessed by CKD-EPI ranged from 5.1 – 141.7 mL/min/1.73 m^2 (training dataset) and 5.3 – 130.0 mL/min/1.73 m^2 (validation dataset). The baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics of the training and external validation dataset.

Parameter	Training dataset	External validation dataset
Number of individuals (n)	542	208
Age (years)	69.5 (19.0 – 94.0)	70.8 (60.5 – 78.4)
Male/female (n (% male))	347/195 (64)	114/94 (55)
Patients admitted on ICU during gentamicin treatment (n (% of total))	70 (13)	35 (17)
Height (cm)	175 (150 – 198)	172 (146 – 200)
Body mass index (kg/m^2)	29.3 (18.2 – 65.1)	33.2 (26.0 – 56.8)
Total body weight (kg)	90.0 (53.3 – 220.5)	100 (68.6 – 180.4)
Adjusted body weight (kg)	78.1 (50.4 – 135.4)	80.4 (53.4 – 115.9)
Lean body weight (kg)	62.1 (36.7 – 98.5)	62.9 (39.2 – 88.1)
Body surface area (m^2)	2.1 (1.6 – 3.1)	2.2 (1.7 – 3.0)
Serum creatinine (mmol/L)	96 (24 – 763)	90 (22 – 920)
Indexed CKD-EPI (mL/min/1.73 m^2)	63.1 (5.1 – 141.7)	70.7 (5.3 – 130.0)
De-indexed CKD-EPI (mL/min)[a]	77.3 (6.0 – 215.6)	90.2 (7.1 – 180.4)
Indexed MDRD (mL/min/1.73 m^2)	61.7 (5.8 – 320.1)	72.1 (5.7 – 297.2)
De-indexed MDRD (mL/min)[a]	75.0 (6.4 – 444.1)	93.1 (8.3 – 376.3)
Cockcroft-Gault with LBW (mL/min)	54.2 (5.6 – 246.2)	60.9 (7.2 – 232.5)
Cockcroft-Gault with TBW (mL/min)	77.3 (7.9 – 404.5)	92.5 (11.3 – 380.3)
Gentamicin dose (mg, median (IQR range))	360 (280 – 440)	400 (300 – 460)
Gentamicin dose (mg/kg, median (IQR range))	4.3 (3.1 – 5.1)	3.9 (3.0 – 4.7)
No. of samples (n)	1187	321
No. of samples per individual (n (IQR range))	1 (1 – 2)	1 (1 – 2)
Time after dose (hours, median (IQR range))	19.7 (8.9 – 25.0)	17.5 (11.0 – 23.0)
No. of samples < LLOQ (n (%))	194 (16)	61 (19)

Data shown as median (range) unless otherwise specified

[a] De-indexed by multiplying the original CKD-EPI or MDRD with BSA/1.73

CKD-EPI Chronic Kidney Disease Epidemiology Collaboration, *IQR* interquartile range, *LBW* lean body weight, *MDRD* Modification of Diet in Renal Disease, *TBW* total body weight.

Pharmacokinetic analysis

A two-compartment model best described the data with both weight and renal function as important covariates for gentamicin clearance (CL). Figure 1a shows how clearance was found to change with both indexed (mL/min/1.73 m^2, left panel) and de-indexed CKD-EPI (mL/min, right panel). De-indexed CKD-EPI proved to be the most significant covariate, since inclusion of de-indexed CKD-EPI gave a larger OFV drop compared to the original, indexed CKD-EPI (-807.0 versus -775.3, p <0.001), confirming the difference in trends both covariates in Figure 1a. When indexed CKD-EPI was combined with TBW (-816.2, p >0.001), a similar goodness-of-fit and OFV drop compared to de-indexed CKD-EPI alone could be obtained, confirming that both renal function and body weight influence gentamicin CL in this population. Since these two factors are merged in de-indexed CKD-EPI as one covariate, the OFV difference was not significant and we found considerable parameter correlation and an increase in condition number when implementing both CKD-EPI and TBW, we chose to include de-indexed CKD-EPI in the final model as a covariate for simultaneously describing weight and renal function. Here, for each 10 mL/min drop in de-indexed CKD-EPI, gentamicin clearance decreases with 0.48 L/h (95% CI 0.44 – 0.51 L/h), where an individual with a de-indexed CKD-EPI of 74 mL/min has a gentamicin clearance of 3.53 L/h (95% CI 3.28 – 3.79 L/h). In addition, Figure 1b shows that CL was lower in patients admitted to the ICU. After incorporation of ICU-admission status as binary covariate in the model with de-indexed CKD-EPI on CL, CL was found to be reduced by 24.9% (95% CI: 12.9% – 34.2%) during ICU-admission (OFV drop of -20.7, p <0.001). Lastly, TBW was identified as covariate on central volume of distribution (V1) (OFV –41.8, p <0.001), using a power function with an estimated exponent of 0.91. Fixing this exponent to 1, representing a linear relationship, resulted in a similar model (OFV +0.45, p >0.05) and was entered in the final model. Finally, due to some correlation between IIV on clearance and central volume of distribution, we included this correlation in the model using an OMEGABLOCK, resulting in a further reduction in OFV of -17.4 points (p <0.001) and some improvement in GOF (data not shown).

The pharmacokinetic parameters of the final model are shown in Table 2. Covariate inclusion on the initial structural model led to a reduction in inter-individual variability from 81.0 % to 36.3% and from 38.9% to 32.4% for CL and V1, respectively. Diagnostics of the final model (pvcVPC and GOF split for renal function and ICU-admission status) are shown in Figures S2A, S3 and S4 in the supplementary file. These plots illustrate that the final model described all data, irrespective of level of renal dysfunction and ICU admission status.

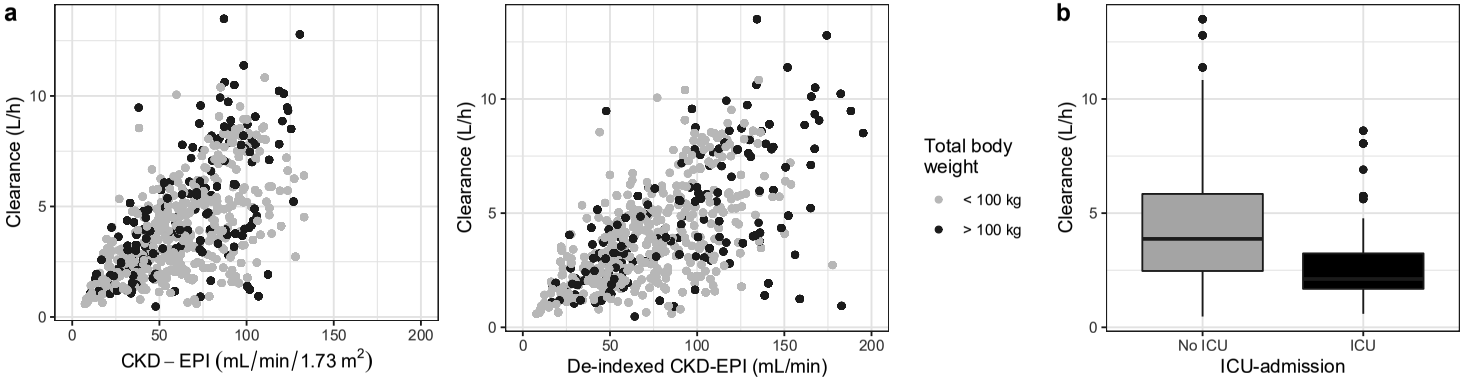


Figure 1. Individual *post-hoc* estimates of gentamicin clearance (from the structural model without covariates) versus (a) CKD-EPI (in mL/min/1.73 m2, left panel) or de-indexed CKD-EPI (in mL/min, right panel), with de-indexation being done by multiplication of CKD-EPI with BSA/1.73 and versus (b) ICU-admission. Individual estimates of CL are shown as (a) scatterplots where each dot represents one individual with grey and black dots depict individuals with total body weight < 100 kg and > 100 kg, respectively or (b) as boxplots based on the median and interquartile ranges of CL for both categories. *CKD-EPI* Chronic Kidney Disease Epidemiology.

Table 2. Pharmacokinetic parameter estimates of the final gentamicin covariate model and the bootstrap analysis.

Parameter	Final model (RSE %)	Bootstrap estimates [95% CI][a]
Fixed effects		
CL (L/h) = TVCL $\times \left(\frac{\text{CKD-EPI}_{di}}{74}\right) \times F_{IC}$ (if ICU)		
TVCL (L/h)	3.53 (2.7)	3.54 [3.29 – 3.79]
F_{IC}	0.751 (5.7)	0.76 [0.66 – 0.87]
V1 (L) = TVV1 $\times \left(\frac{\text{TBW}}{70}\right)$		
TVV1 (L)	16.6 (5.2)	16.4 [14.5 – 18.4]
Q (L/h)	1.48 (14.3)	1.72 [0.30 – 3.13]
V2 (L)	13.4 (7.6)	13.5 [9.48 – 17.5]
Inter-individual variability		
CL[b,c] (%)	36.3 (6.2)	36.7 [24.5 – 46.3]
V1[b,c] (%)	32.4 (14.4)	37.4 [0.00 – 59.7]
Covariance IIV CL – V1	0.074	0.084 [-0.043 – 0.21]
Residual variability		
Proportional error [d,e]	0.306 (4.0)	0.288 [0.155 – 0.421]
Additive error (mg/L)[e]	0.253 (7.4)	0.260 [0.133 – 0.388]

[a] Bootstrap analysis was performed with n = 1000 datasets, with 987 successful runs (ignoring rounding errors)

[b] Shrinkage of inter-individual variability in the final model: 23% (CL) and 55% (V1)

[c] Calculated by $\sqrt{(e^{\omega^2} - 1)}$

[d] Proportional error is shown as s

[e] Epsilon shrinkage for the final model is 23%

CI confidence interval, *CL* clearance, *TVCL* typical value for CL for an individual not admitted to an ICU and with CKD-EPI$_{di}$ of 74 ml/min, F_{IC} scaling factor for patients admitted to an ICU, *CKD-EPI$_{di}$* de-indexed CKD-EPI (=CKD-EPI * body surface area/1.73), *RSE* relative standard error based on covariance step in NONMEM, *TBW* total body weight, *V1* volume of distribution of central compartment, *TVV1* typical value for V1 for an individual with TBW of 70 kg, *V2* volume of distribution of the peripheral compartment, *Q* inter-compartmental clearance between V1 and V2.

For the external validation dataset, both GOF and pvcVPC plots of the final pharmacokinetic model (Figures S5 and S6 in supplementary file), were without bias (MPE -0.39 mg/L, 95% CI -8.98 – 1.70 mg/L) but with some imprecision (rRMSE 76.6%). This imprecision seems to be predominantly driven by the high concentrations, since rRMSE reduced to 46.3% when calculated for observations <5 mg/L.

Dose simulations

Table 3 shows a CKD-EPI based dose regimen based on the final model which was designed for obese individuals (TBW > 100 kg) with varying renal (dys)function to obtain similar exposure as compared to lean individuals with a normal renal function receiving the

standard dose of 6 mg/kg. [6] This CKD-EPI dosing regimen uses both body weight (i.e. mg/kg dosing) and indexed CKD-EPI (mL/min/1.73 m^2), with the latter being chosen because this measure is readily available in clinical practice. The proposed dose varies from 6 mg/kg for obese individuals with CKD-EPI > 120 mL/min to 1.8 mg/kg for obese individuals with CKD-EPI < 30 mL/min, with dosing intervals varying between 24 and 48 h, respectively (Table 3). Figure 2 shows that using this CKD-EPI based dosing strategy in obese individuals with varying degrees of renal impairment, similar exposures with similar variability over the first 24-hours after infusion are obtained compared to lean individuals without renal impairment receiving 6 mg/kg TBW who had a median $AUC_{0\text{-}24}$ 85.6 mg*h/L. The figure also shows that TBW- and ABW-based dose regimens yield increasing exposure (> the 125% upper limit of the median $AUC_{0\text{-}24}$ in lean individuals) with decreasing CKD-EPI. Figure S7 in the supplementary file show $AUC_{0\text{-}24}$ versus body weight for the different dose strategies. Time to reach the target trough concentration (< 1 mg/L) for different renal function when using the CKD-EPI based dose regimen are shown in Figure S8 in the supplementary file.

Table 3. CKD-EPI based dosing for gentamicin in obese individuals with varying renal function (expressed as CKD-EPI), relative to standard dose of 6 mg/kg TBW for lean individuals with a normal renal function (>60 mL/min/1.73 m^2).

	Obese individuals >100 kg (non-ICU patients)[a]					**Lean individuals <100 kg (reference)**
CKD-EPI (mL/min/1.73 m^2)	>120	90 – 120	60 – 90	30 – 60	<30	>60
Gentamicin dose, mg/kg (based on TBW in kg)	6 (100 %)	4.8 (80 %)	3.6 (60 %)	2.4 (40 %)	1.8 (30 %)	6 (100 %)
Dose interval (h)[b]	24	24	24	24 – 36	36 – 48	24

[a] Consider 25% dose reduction in ICU patients for all CKD-EPI groups

[b] Based on time to reach the target trough concentration (<1 mg/L) (as shown in Figure S8 in the supplementary file). We recommend to individualize dosing using therapeutic drug monitoring after first gentamicin administration

CKD-EPI Chronic Kidney Disease Epidemiology, *TBW t*otal body weight.

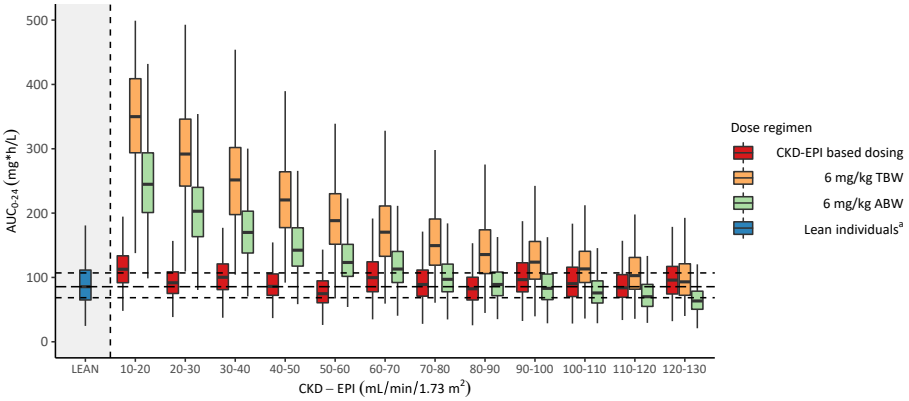


Figure 2. AUC_{0-24} values for different dose regimens versus CKD-EPI based on simulations using the final pharmacokinetic model (n = 10.000 per dose regimen). CKD-EPI based dosing follows the strategy as shown in Table 3. The boxplots show median and interquartile range of the AUC_{0-24} values for each CKD-EPI subgroup. Long-dashed line and dashed lines represent median AUC_{0-24} from the lean group (85.6 mg*h/L) with the corresponding 80 – 125% range, respectively. [a]The lean group consists of lean individuals (TBW <100 kg), without renal impairment (CKD-EPI >60 mL/min) who received a gentamicin dose of 6 mg/kg TBW [6].

DISCUSSION

In this report we show that gentamicin clearance in obese individuals with and without renal impairment can be adequately predicted by renal function (CKD-EPI), total body weight and ICU-admission. The first two covariates can be combined by de-indexing CKD-EPI, where CKD-EPI (in mL/min/1.73 m²) is corrected for BSA to result in a de-indexed CKD-EPI in mL/min. Although some other studies have found renal function estimates to be (to some extent) predictive for gentamicin clearance in obese individuals [22,23], the dataset and methodology in the current study is unique with respect to the ability to precisely characterize the influence of both renal function and body weight simultaneously. This could be done by using a unique dataset of both rich, prospective data collected in a wide range of body weights between 53 and 220 kg with normal renal function, together with a large clinical dataset of obese individuals with a wide range in renal function (CKD-EPI 5.1 – 141.7 mL/min/1.73 m²). The combination of the datasets in our study allowed for the first time the full characterization of the influence of varying degrees of renal dysfunction within varying classes of obesity. The influence of body weight alone on gentamicin CL in the obese population has been described before in several studies [18,24–26], including a recent prospective study by our group in healthy non-obese and morbidly obese individuals without renal impairment of which the data was also used in the current study [9].

With regard to the identified increase in gentamicin CL with obesity, we anticipate that this increase could be explained by either an increase in glomerular filtration or an increase in renal tubular transport. The first explanation remains controversial since for example cefazoline, a drug that is depend on glomerular filtration, showed no increased clearance in obesity [27]. Also for ciprofloxacin, which is mainly cleared renally, no substantial increase in clearance was reported [28]. In contrast, for other renally excreted drugs like tobramycin and vancomycin, increased clearance values were observed with increasing body weights, albeit to varying extend and using varying covariate functions [29,30]. Considering the second explanation, the Organic Cation Transporter 2 (OCT2) has been shown to be increased in obese overfed mice and obese humans, which was associated with increased renal gentamicin tubular uptake [31]. As such, we anticipate that the increase in gentamicin clearance with obesity may be related to the increase in OCT2 transporters in the kidneys of obese individuals. While this hypothesis supports the proposed use of mg/kg in our dosing strategy (Table 3), dose reductions are required in case of reduced CKD-EPI renal function.

In addition to renal function and body weight, ICU-stay showed to be an independent predictor for gentamicin clearance, regardless of renal function, with a reduction in CL of 13% – 34% in case the patient was admitted to the ICU. Although most studies in critically ill patients found creatinine clearance to be predictive for gentamicin clearance [32,33], some studies found critical illness as an additional covariate for gentamicin clearance [34,35]. A possible explanation for our finding might lie in the fact that serum creatinine is actually a late marker for renal impairment [36], necessitating ICU admission as separate covariate in the model. Fortunately, novel biomarkers for acute renal function have emerged that might be better suited for estimating acute kidney failure in an earlier stage [36]. Future research should focus on the performance of these biomarkers in predicting gentamicin clearance. Until then, we suggest to consider a dose reduction of 25% relative to our CKD-EPI based dose nomogram (Table 3) when the patient is admitted to the ICU and there is a clinical suspicion of developing renal failure that may not yet be reflected in serum creatinine.

Strong aspects of our study are the large dataset with both rich, prospectively collected data in obese and non-obese healthy volunteers with normal renal function and clinically collected TDM data in real-world obese patients. As depicted in Figure S1, sampling times were well distributed relative to the start of the gentamicin infusion (from 0 up to 48 hours), maximizing our ability to characterize the full pharmacokinetic profile [37]. Additionally, our data consisted of a wide range of covariates such as renal function and body weight, boosting the power to simultaneously characterize these covariates on gentamicin pharmacokinetics. Secondly, we substantiated the validity of our model and CKD-EPI-based dosing recommendation by validating the predictive performance of our PK-model in an external independent clinical dataset.

In this study we present an easy-to-use CKD-EPI-based dose strategy for gentamicin that is applicable across the whole clinical population of obese patients with body weights up to 220 kg, both with and without renal impairment. Like the pharmacokinetic model, our dose recommendation incorporates both renal function (CKD-EPI) and body weight (mg/kg based dosing), with a reduction in mg/kg dose depending on the CKD-EPI, and a 25% dose reduction to consider upon admittance to the ICU. Additionally, considering the time to reach a trough concentrations below 1 mg/L (shown in Figure S8), extension of the dosing interval beyond 24 hours seems necessary when CKD-EPI drops below 50 mL/min/1.73 m^2. Our proposed dose strategy targets similar exposure as lean individuals with normal renal function receiving 6 mg/kg TBW, which is the recommended dose by EUCAST [6]. $AUC_{0\text{-}24}$/MIC target thresholds for aminoglycoside efficacy have been proposed over the years, although these are mainly based on preclinical (animal) infection models [4]. As such, there is still a lack of data on the performance of these targets in clinical practice. We therefore argue that, until more knowledge is available, we should try to optimize gentamicin treatment in obese individuals with and without renal failure by targeting similar exposures as obtained in lean individuals receiving the currently recommended dose [1,4]. Some hospitals may have other guidelines for dosing gentamicin in lean individuals, for example 5 mg/kg TBW or 7 mg/kg TBW. Our proposed dose strategy for obese individuals can however be easily adapted to target these exposures. For the reader's convenience, we have provided such adapted dose recommendations in Table S3 in the Supplementary file.

Some limitations may apply to our study. First, patients on renal replacement therapy were excluded in our study, so our results cannot be extrapolated to this population. Second, there is still considerable variability in obtained $AUC_{0\text{-}24}$ when using our proposed dose nomogram. However, the magnitude of this variability is similar to what we observed in lean individuals with normal renal function receiving 6 mg/kg TBW. Like it is customary for the normal population, we strongly recommend to individualize the gentamicin dose using therapeutic drug monitoring in obese individuals as well.

In conclusion, based on a pharmacokinetic analysis of individuals with a large range in body weight and renal function, we propose a novel CKD-EPI based dose strategy (Table 3) to be used in the whole clinical obese population. A dose reduction of 25% might be necessary in ICU-patients. Using this dose strategy, a similar exposure as compared to lean subjects without renal impairment receiving 6 mg/kg TBW can be obtained.

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Transparency declaration

R.J.M.B. declares that he has no conflicts of interest with regards to this work. Outside of this work, he has served as consultant to and has received unrestricted research grants from Astellas Pharma Inc., F2G, Amplyx, Gilead Sciences, Merck Sharpe and Dohme Corp., and Pfizer Inc. All payments were invoiced by the Radboud University Medical Centre. All other authors declare no conflicts of interest.

Author contributions

C.S., E.H.P.A.D., R.J.M.B. and C.A.J.K. designed the study, C.S., E.H.P.A.D., A.M.S. and M.L.B. collected the data, C.S., C.A.J.K. analyzed the data, C.S., C.A.J.K drafted the initial manuscript, all authors thoroughly revised the manuscript and all authors approved the final version of the manuscript.

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SUPPLEMENTARY FILE

Table S1. Equations used for body weight descriptors.

Body weight descriptor	Formula	Reference
TBW (total body weight)	Total body weight (kg)	
BMI (body mass index, kg/m^2)	TBW (kg)/((Length (m)^2)	
BSA (body surface area, m^2)	√(TBW (kg) * Length (cm)/3600)	[38]
IBW (ideal body weight, kg)	50 (or 45.5 if female) + 2.3 * (Length (cm) * 0.3937-60)	[39]
ABW (adjusted body weight, kg)	IBW (kg) + (0.4 * TBW-IBW) If TBW<IBW, TBW is used as ABW	[18]
LBW (lean body weight, kg)	9270 * TBW / (6680+216 * BMI) if male 9270 * TBW / (8780+244 * BMI) if female	[12]

Table S2. Equations used for renal function estimates.

Renal function estimate	Formula	Reference
MDRD (Modification of Diet in Renal Disease, ml/min/1.73m^2)	186.3 * (creatinine (mcmol/l)/88.4)$^{-1.154}$ * AGE (years)$^{0.203}$ * 0.742 (if female) * 1.210 (if black)	[40]
De-indexed MDRD (mL/min)	MDRD * BSA/1.73	
CKD-EPI (Chronic Kidney Disease Epidemiology, mL/min/1.73 m^2)	141 * min(creatinine (mg/dl)/k,1)^a * max(Scr/k,1)$^{-1.209}$ * 0.993^{age} * 1.018 (if female) * 1.159 (if black) k = 0.7 (females) or 0.9 (males) a = -0.329 (females) or -0.411 (males) min = minimum of creatinine/k or 1 max = maximum of creatinine/k or 1	[41]
De-indexed CKD-EPI (mL/min)	CKD-EPI * BSA/1.73	
CG-TBW (mL/min)	(140 – age (years)) * TBW (kg) / (0.82 * creatinine (mcmol/l)) * F F = 0.85 (females) or 1 (males)	[42]
CG-LBW (mL/min)	(140 – age (years)) * LBW (kg) / (0.82 * creatinine (mcmol/l))	[22]
GFR (mL/min)	(1000 * creatinine$_{urine}$ (mmol/l) / creatinine$_{serum}$ (mcmol/l)) * (volume$_{urine}$ (mL) / collection time (hours))	

Table S3. CKD-EPI based dosing for gentamicin in obese individuals with varying renal functions (expressed as CKD-EPI), *relative to standard dose of 5 mg/kg or 7 mg/kg TBW* for lean individuals with a normal renal function (> 60 mL/min/1.73 m²).

	Obese individuals > 100 kg (non-ICU patients)[a]					Lean individuals < 100 kg (reference)
CKD-EPI (mL/min/1.73 m²)	>120	90 – 120	60 – 90	30 – 60	< 30	> 60
Gentamicin dose, mg/kg (based on TBW in kg)	5 (100 %)	4 (80 %)	3 (60 %)	2 (40 %)	1.5 (30 %)	5 (100 %)
Gentamicin dose, mg/kg (based on TBW in kg)	7 (100 %)	5.6 (80 %)	4.2 (60 %)	2.8 (40 %)	2.1 (30 %)	7 (100 %)

[a] Consider 25% dose reduction in ICU patients for all CKD-EPI groups

CKD-EPI Chronic Kidney Disease Epidemiology, *TBW t*otal body weight.

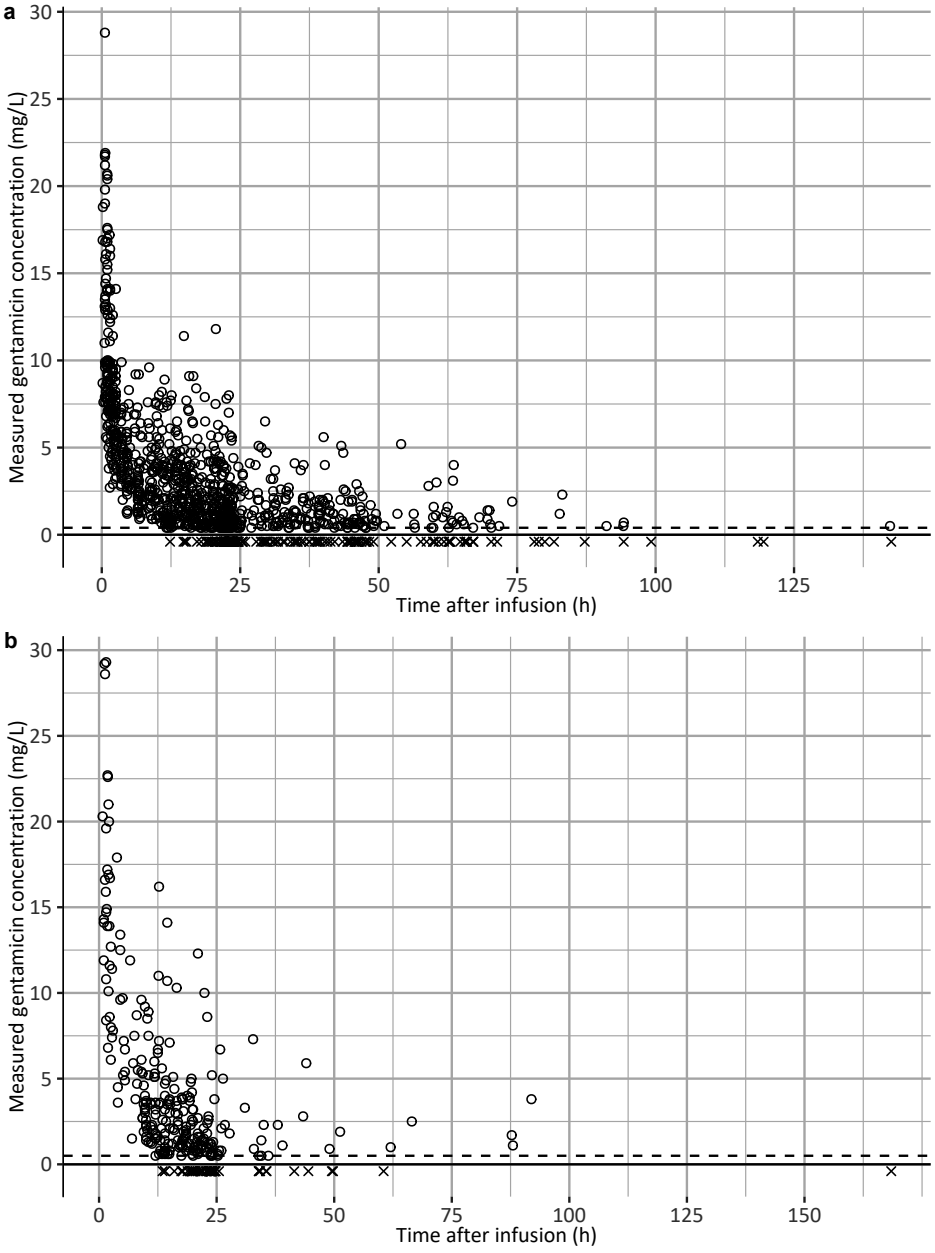


Figure S1. Observed gentamicin concentrations (open circles) versus time after start of the last gentamicin dose for (a) the training dataset (n = 542 individuals, 1187 samples) and (b) the external validation dataset (n = 208 individuals, 321 samples). Values below lower limit of quantification (LLOQ, dashed horizontal line) are shown as crosses below the x-axis (16.3 % of observations in (a), 19.0 % of observations in (b)).

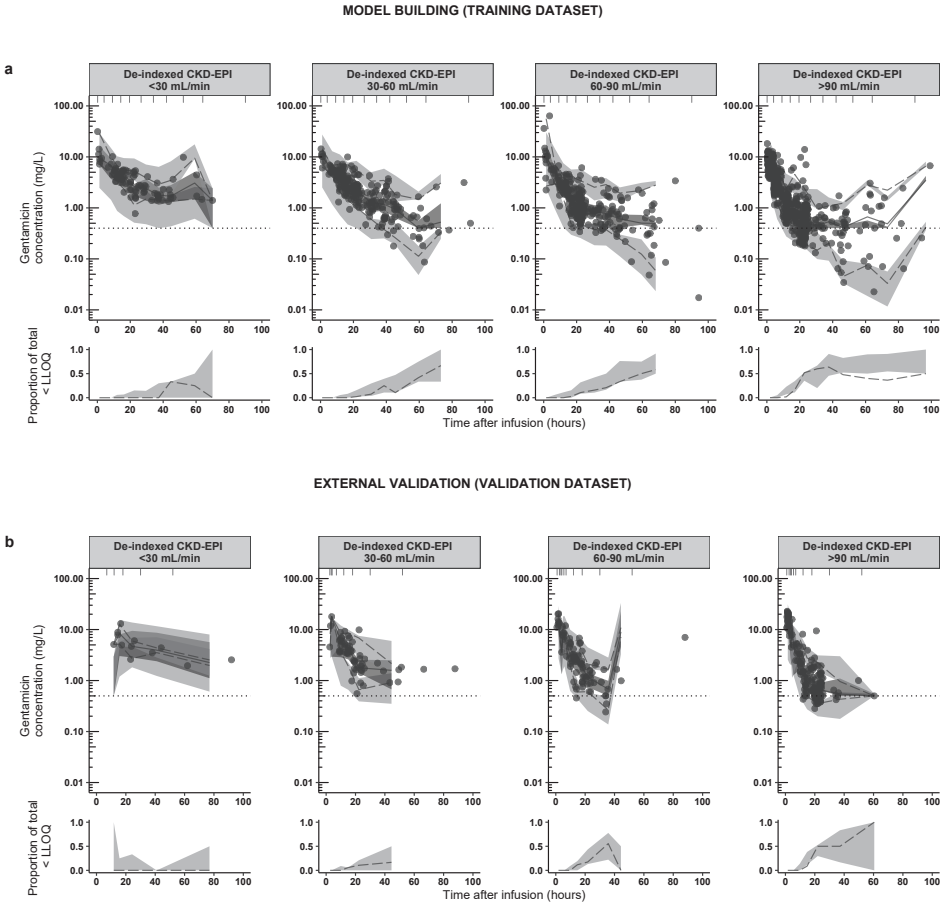


Figure S2. Prediction and variability corrected visual predictive checks (pvcVPC) of the final model , split for de-indexed CKD-EPI subgroup, based on (a) the training and (b) the external validation dataset. In the upper panels, the median, 2.5th and 97.5th percentiles of observed concentrations are shown as solid, lower and upper dashed lines. Grey shaded areas represent the 95% confidence intervals of the median (dark grey) and 2.5th and 97.5th percentiles (light grey) of predicted concentrations (n = 1000) based on the pharmacokinetic model. The lower limit of quantification (LLOQ) is depicted by the dotted grey line. Intervals of the bins are shown by the vertical ticks on the top of the plot. Lower panels show the observed proportion below the LLOQ (dashed line), where shaded areas represent the 95% confidence intervals based on predicted concentrations (n = 1000). *CKD-EPI* Chronic Kidney Disease Epidemiology, *LLOQ* Lower limit of quantification.

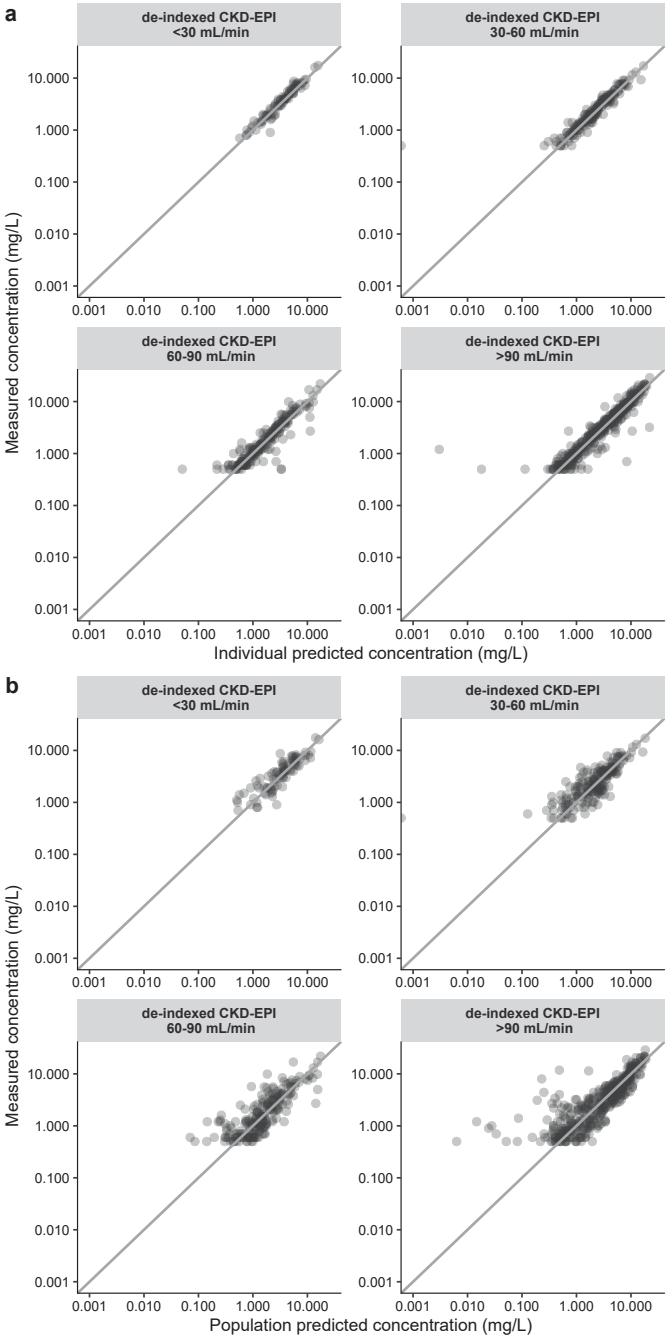


Figure S3. Goodness-of-fit plots of the final model with *the training dataset*. Observed versus individual (a) or population (b) predicted gentamicin concentrations, split for renal function groups (based on de-indexed CKD-EPI). The grey lines represent the line of identity (x = y). *CKD-EPI* Chronic Kidney Disease Epidemiology.

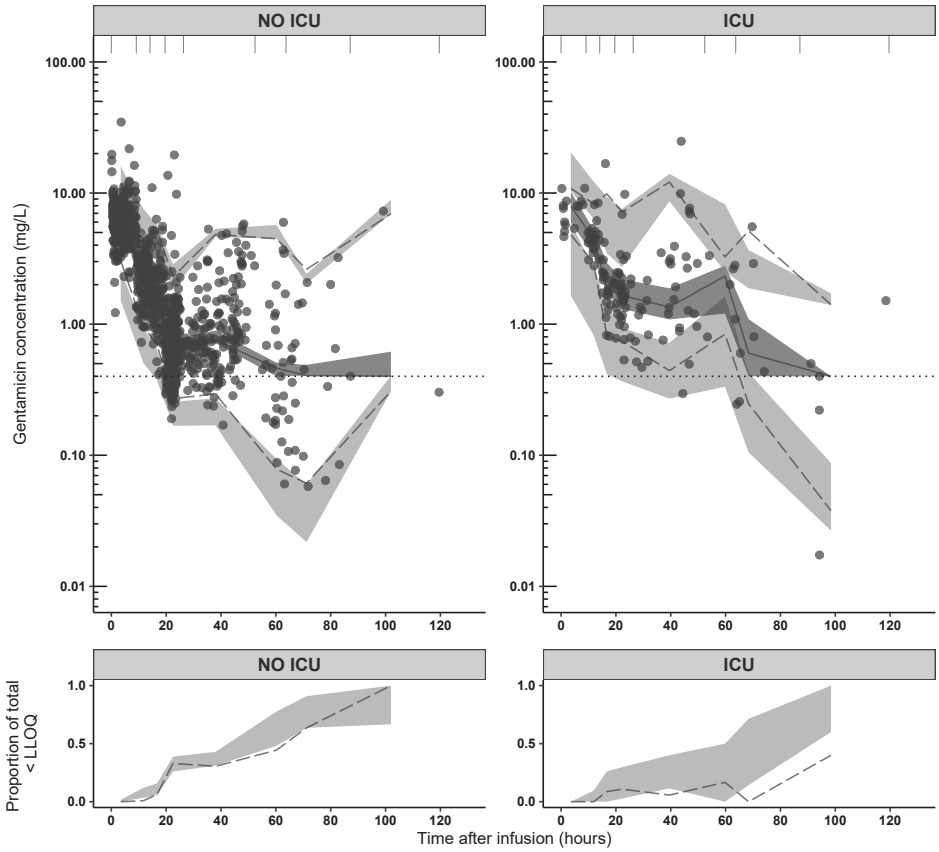


Figure S4. Prediction and variability corrected visual predictive checks (pvcVPC) of the final model, split for ICU-admission status, based on *the training dataset*. In the upper panels, the median, 2.5th and 97.5th percentiles of observed concentrations are shown as solid, lower and upper dashed lines. Grey shaded areas represent the 95% confidence intervals of the median (dark grey) and 2.5th and 97.5th percentiles (light grey) of predicted concentrations (n = 1000) based on the pharmacokinetic model. The lower limit of quantification (LLOQ) is depicted by the dotted grey line. Intervals of the bins are shown by the vertical ticks on the top of the plot. Lower panels show the observed proportion below the LLOQ (dashed line), where shaded areas represent the 95% confidence intervals based on predicted concentrations (n = 1000). *ICU* Intensive Care Unit, *LLOQ* Lower limit of quantification.

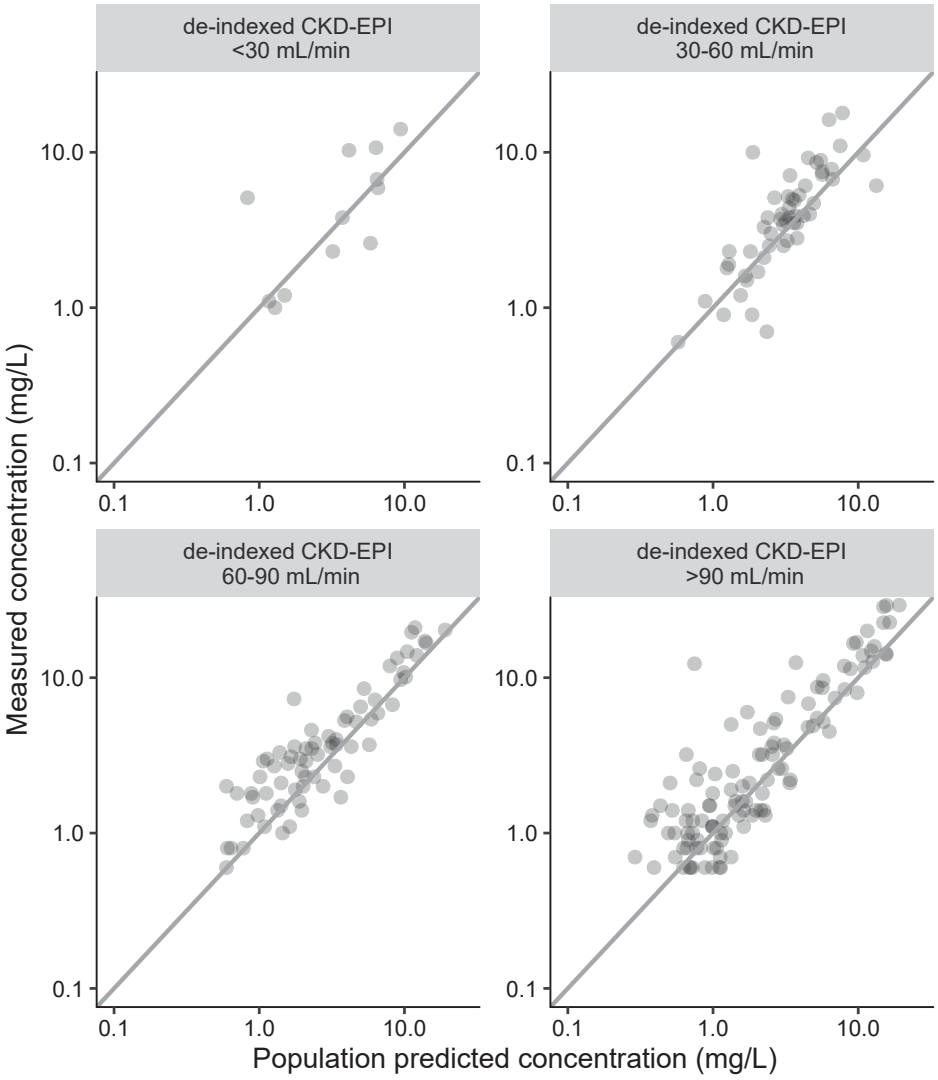


Figure S5. Goodness-of-fit plots of the final model with *the external validation dataset* using MAXEVAL = 0. Observed versus population predicted gentamicin concentrations, split for renal function groups (based on de-indexed CKD-EPI. The grey lines represent the line of identity (x = y).

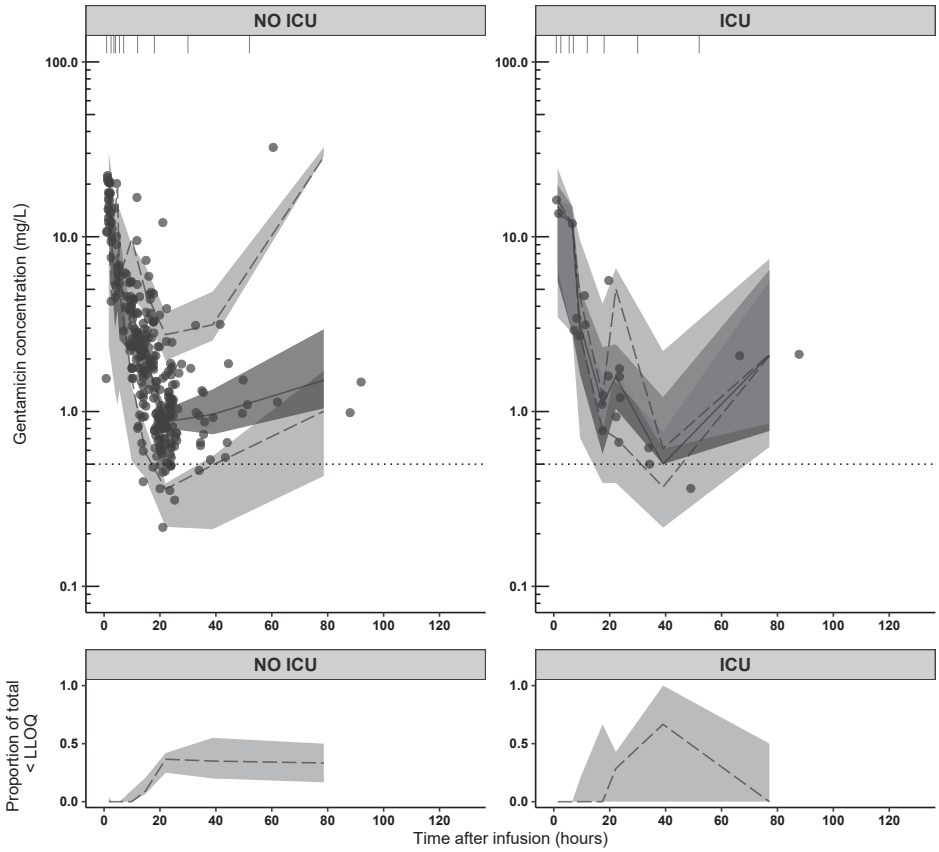


Figure S6. Prediction and variability corrected visual predictive checks (pvcVPC) of the final model, split for ICU admission status, based on *the external validation dataset*. In the upper panels, the median, 2.5th and 97.5th percentiles of observed concentrations are shown as solid, lower and upper dashed lines. Grey shaded areas represent the 95% confidence intervals of the median (dark grey) and 2.5th and 97.5th percentiles (light grey) of predicted concentrations (n = 1000) based on the pharmacokinetic model. The lower limit of quantification (LLOQ) is depicted by the dotted grey line. Intervals of the bins are shown by the vertical ticks on the top of the plot. Lower panels show the observed proportion below the LLOQ (dashed line), where shaded areas represent the 95% confidence intervals based on predicted concentrations (n = 1000). *ICU* Intensive Care Unit *LLOQ* Lower limit of quantification.

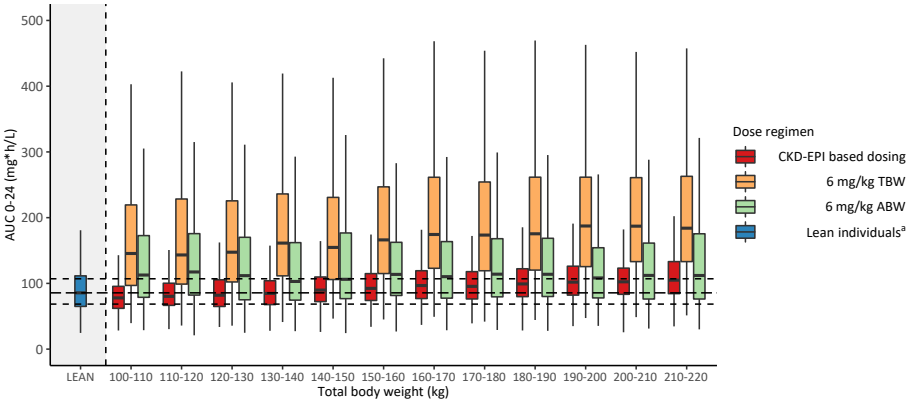


Figure S7. $AUC_{0\text{-}24h}$ values for different dose regimens versus total body weight based on simulations using the final pharmacokinetic model (n = 10.000 per dose regimen). CKD-EPI based dosing follows the strategy as shown in Table 3 in the main article. The boxplots show median and interquartile range of the $AUC_{0\text{-}24}$ values for each total body weight subgroup. Long-dashed line and dashed lines represent median $AUC_{0\text{-}24}$ from the lean group (85.6 mg*h/L) with the corresponding 80 – 125% range, respectively. [a]The lean group consists of lean individuals (TBW <100 kg), without renal impairment (CKD-EPI >60 mL/min) who received a gentamicin dose of 6 mg/kg TBW. *ABW* adjusted body weight, $AUC_{0\text{-}24}$ area under the curve from 0-24 hours, *CKD-EPI* Chronic Kidney Disease Epidemiology, *TBW* total body weight.

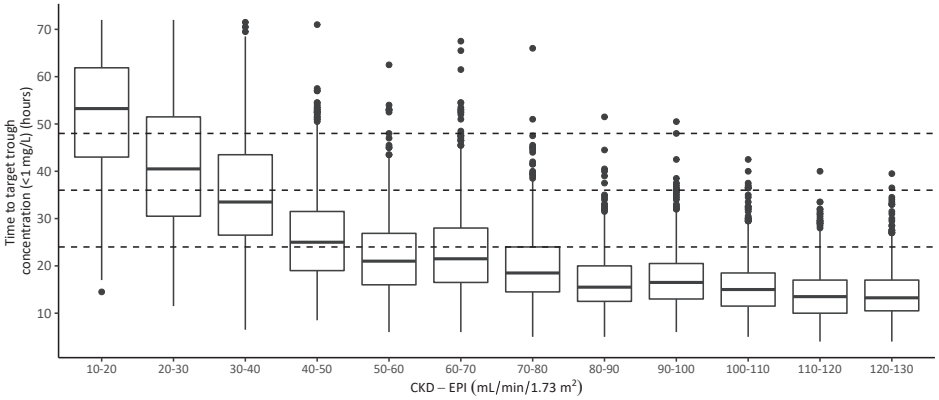


Figure S8. Time after dose to reach target trough concentration (<1 mg/L) for each CKD-EPI subgroup after a single gentamicin dose using the CKD-EPI guided dose strategy for obese individuals (shown in Table 3 in the manuscript). Predicted time to reach target concentration is based on simulations using the final pharmacokinetic model (n = 10.000). The boxplots show median and interquartile range for each CKD-EPI subgroup. Dashed lines represent 24, 36 and 48 hours after dose. *CKD-EPI* Chronic Kidney Disease Epidemiology.

NONMEM CONTROL STREAM FOR THE FINAL MODEL

```
$PROBLEM GENTA
$INPUT ID        TIME    AMT     RATE    DV      LNDV    MDV     EVID    TAD
HT      WT       WTGRP   LBW     BMI     IBW     ABW     AGE     BSA     IC
IC_pres SEX      RACE    LLOQ    ULOQ    A_ULOQCREAT     CREAT_FIRST     GFR
MDRD    CGLBW    CGLBW_FIRST     CGTBW   CKD     CKD_di  CKD_di_FIRST    MDRD_
di      MDRD_di_FIRST   NF_CGLBW       NF_CKD_di       STD
$DATA antonius_comb.prn IGNORE=# IGNORE=(A_ULOQ.EQ.1)
$SUBROUTINE ADVAN3 TRANS4
$PK
TVCL    = THETA(1)*((CKD_di/74.0)**THETA(7))*(THETA(8)**IC); TVCL
TVV1    = THETA(2)*((WT/70)**THETA(9)); TVV1
TVQ     = THETA(3) ; TVQ
TVV2    = THETA(4) ; TVV2
;
CL = TVCL*EXP(ETA(1))
V1 = TVV1*EXP(ETA(2))
Q = TVQ*EXP(ETA(3))
V2 = TVV2*EXP(ETA(4))
;
S1 = V1;
;
ET1=ETA(1)
ET2=ETA(2)
ET3=ETA(3)
ET4=ETA(4)

$THETA
(0, 5) ; TVCL
(0, 10) ; TVV1
(0, 12) ; TVQ
(0, 133) ; TVV2
(0, 0.308) ; SD PROPORTIONAL ERR
(0, 0.255) ; SD ADD
(1) FIX ; CL_CKD_di EXP
(0, 0.774) ; CL_ICU factor
(1) FIX ; V1_WT EXP
```

```
$OMEGA BLOCK(2)
0.0874 ; CL ETA 1
-0.025 0.0726 ; V1 ETA 2
$OMEGA
0 FIX ; Q ETA 3
0 FIX ; V2 ETA 4

$ERROR
TYPE=1
IF(DV.LT.LLOQ) TYPE = 2

PROP=THETA(5)*F ; proportional part
ADD=THETA(6) ; additive part
SD=SQRT(PROP*PROP + ADD*ADD) ;

IPRED = F
DUM = (LLOQ - IPRED) / SD
CUMD = PHI(DUM)
IF (TYPE .EQ. 1.OR.NPDE_MODE.EQ.1) THEN
F_FLAG = 0
Y = IPRED + SD * ERR(1)
ENDIF
IF (TYPE .EQ. 2.AND.NPDE_MODE.EQ.0) THEN
F_FLAG = 1
Y = CUMD
MDVRES=1
ENDIF
;
IF(TYPE.EQ.2) DV_LOQ=LLOQ
;
IRES = DV - IPRED
IWRES = IRES/SD

$SIGMA
1 FIX ; ERR 1
$ESTIMATION METHOD=1 INTER MAXEVAL=9999 NOABORT NUMERICAL SLOW
POSTHOC LAPLACIAN SIGDIGITS=2;
$COVARIANCE UNCONDITIONAL MATRIX=R SLOW PRINT=E;
```

$TABLE ID TIME IPRED IWRES CWRES AMT TVCL CL TVV1 V1 TVQ Q TVV2 V2 ET1 ET2 ET3 ET4 MDV TAD HT WT WTGRP LBW BMI IBW ABW AGE BSA IC SEX LLOQ ULOQ A_ULOQ CREAT MDRD CGLBW CGTBW CKD CKD_di MDRD_di CREAT_FIRST CGLBW_FIRST CKD_di_FIRST MDRD_di_FIRST NF_CGLBW NF_CKD_di STD NOPRINT ONEHEADER



7



Dosing recommendations for vancomycin in obese children and adolescents with varying renal function based on a population pharmacokinetic study in 1892 children aged 1 – 18 years

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Submitted for publication

ABSTRACT

Objective Vancomycin is an effective but potentially nephrotoxic antibiotic commonly used for severe gram-positive infections for which guidelines for dose adjustments for obese children and adolescents with or without renal impairment are urgently needed. This study describes the pharmacokinetics of vancomycin in this clinical population, ultimately to design practical dosing guidelines.

Design A retrospective population pharmacokinetic study.

Setting Twenty-one hospitals of the Utah, USA based HMO Intermountain Healthcare organization.

Patients All patients aged 1 – 18 years who received more than 1 dose of vancomycin and had ≥1 vancomycin concentration measured between January 2006 and December 2012.

Measurements Data on vancomycin dosages, vancomycin concentrations, and covariates such as age, gender, body weight, creatinine clearance (CL_{cr}, bedside Schwartz equation), ward, race, or neutropenic status were collected. Population pharmacokinetic analysis and simulations were performed using NONMEM7.4.

Main results In total, 1892 patients (5524 samples) were included, with body weight range 6 – 188 kg (1344 normal weight, 247 overweight, and 301 obese patients) and CL_{cr} down to 8.6 mL/min/1.73m^2. In a two-compartment model, clearance (CL) was found to significantly increase with total body weight (TBW) and CL_{cr}. The central and peripheral volume of distribution and intercompartmental clearance increased with TBW. The model performed well for all age, weight, and renal function ranges, outperforming more sophisticated models separating weight for age and weight excess or incorporating maturation using a body weight-dependent exponent. Based on the model, a dosing guideline is proposed that integrates body weight and CL_{cr} and will lead to effective and safe exposures across all ages, body weight, and renal functions in the paediatric population.

Conclusions We have characterized the full pharmacokinetic profile of vancomycin in obese children and adolescents aged 1 – 18 years and propose a practical dosing guideline that integrates both body weight and renal function.

INTRODUCTION

Over the past decades, the prevalence of childhood obesity has increased at an alarming rate. Where childhood obesity practically did not exist approximately 50 years ago, 41 million children under five years of age were considered overweight or obese in 2014 [1]. In the United States of America, approximately 20% of children aged 5 – 18 year is considered obese [2]. Paediatric obesity is typically defined using growth charts with age and sex-specific values for the body mass index (BMI). The Centers for Disease Control and Prevention (CDC) define overweight and obesity as a BMI in the 85th-95th percentile or above the 95th percentile of these charts, respectively [3]. As a result, clinicians frequently must prescribe medication to children who are overweight.

It has been shown for adults that obesity can impact drug pharmacokinetics by altering different physiological processes, such as cardiac output, renal and hepatic perfusion and function of drug metabolizing or transporting enzymes [4,5]. These principles presumably also apply to obese children, although well-designed studies that explore this are scarce [5,6]. Children are generally underrepresented during drug development trials, and, if children are included, often there is no active inclusion of obese children [7]. Consequently, drug labels do not provide information on drug dosing in obese children, and specific guidelines for drug dosing in paediatric obesity are currently scant [7]. Clinical trials in obese children can be methodologically challenging since age- and obesity-related influences are both reflected in a child's body weight, i.e. body weight can increase as a result of growth and development (weight for age), and of overweight or obesity (excess weight) [8]. Pharmacokinetic trials in paediatric obesity should ideally include an in-depth analysis that allows for the study of the distinct influence of maturation versus overweight on drug pharmacokinetics [9], as has been demonstrated for busulfan, midazolam and metformin [10–12].

Vancomycin is a glycopeptide antibiotic that is widely used in serious gram-positive infections including those with beta-lactam resistant *Staphylococcus aureus* and is known for its potential nephrotoxic side effects. It has been well established that vancomycin efficacy and nephrotoxicity closely relate to the 24 h area under the curve (AUC_{24}) in relation to the minimal inhibitory concentration (MIC) [13]. An AUC_{24}/MIC threshold of 400, corresponding to an AUC_{24} of ≥400 mg*h/L assuming a MIC of 1 mg/L, has been well defined as an efficacy target, which is predominantly based on *S. aureus* infections in adults but can also be applied to children [13]. In adults, an increased risk of nephrotoxicity has been observed with exposures above 677 up to 1300 mg*h/L [14,15]. As such, a leading consensus guideline from infectious disease specialists, hospital pharmacists, and paediatricians from the US advocate an AUC_{24} target window between 400 – 700 mg*h/L to be used in children to maximize efficacy while minimizing the risk of nephrotoxicity [13].

Dosing of vancomycin in normal weight children has been investigated thoroughly [13]. However, despite its extensive use, there is to date limited data on how to tailor the dose in obese children and adolescents [13]. Some small retrospective studies have shown that with the same mg/kg dosing, higher trough concentrations are seen in obese children [16–18], although other studies contradict these results [19,20]. None of these studies have reported on the relationship between trough concentrations and AUC_{24}, which is relevant since trough concentrations are routinely measured while it is known that the relation between trough concentrations and AUC_{24} depend on age and the dosing interval [21,22]. The limited number of pharmacokinetic studies conducted have proposed different covariates for vancomycin clearance in obese children and adolescents. Among others, body size descriptors like total body weight (TBW), body surface area (BSA), or fat-free mass (FFM), parameters representing the renal function such as serum creatinine or creatinine clearance (CL_{cr}) or age have been suggested [23–26].

Hence, for obese children and adolescents, current evidence suggests that the usual paediatric vancomycin dosages should be adjusted. However, the optimal dosing strategy to ensure an AUC_{24} 400 – 700 mg*h/L in obese children and adolescents yet remains to be established, particularly when these obese children suffer from renal dysfunction. This study characterizes the population pharmacokinetics of vancomycin in a large, multi-centre clinical population of normal weight, overweight and obese children and adolescents, with varying renal function, to design practical dose recommendations for this population.

MATERIALS AND METHODS

Patients and setting

This retrospective, pharmacokinetic study was conducted using data from twenty-one hospitals of the Utah, USA based HMO Intermountain Healthcare organization. We selected all patients aged 1 – 18 years who had at least two vancomycin administrations, at least one vancomycin concentration measured, and at least one weight measurement registered between start and end of treatment with vancomycin. According to local clinical practice, vancomycin dosage and concentration measurements were left to the discretion of the treating physician. Generally, vancomycin was dosed as 15 to 20 mg/kg, administered two, three or four times per day as a 60-min infusion. Dosing adjustments were made based on therapeutic drug monitoring (TDM) blood samples which were collected as part of routine medical care. Samples could be drawn within 30 min before the dose (trough concentration), 30 min after the end of the intravenous infusion (peak concentration) or at other time points. Patients that received renal replacement therapy or extracorporeal membrane oxygenation during hospital admission were excluded from the analysis. The study was reviewed and approved by the Intermountain Healthcare and University of Utah Institutional Review Boards, and a waiver of informed consent was granted.

Data collection

Data were extracted from the electronic patient record system from 1st January 2006 to 31st December 2012. Demographics, lab values, and clinical PK data were extracted from the Intermountain Healthcare system enterprise data warehouse at the University of Utah. Data were excluded from the analysis when date and times of drug administration or drug concentrations were unavailable, where in case of missing dose amounts in less than 20% per individual, these were imputed using the last known administered amount.

Vancomycin serum drug concentrations were quantified using immunoassay via the Abbott Architect System. Assay validation was performed for clinical purposes. The linear range for the assay was 1.1 to 100 mg/L, and the limit of quantitation was 1.1 µg/mL. The intraday and interday relative standard deviations ranged from 4.7% to 7.1%.

Other data included age, total body weight (TBW), length, gender, race, ICU-stay, serum creatinine, absolute neutrophil count, absolute lymphocyte count and C-reactive protein (CRP). Overweight and obesity were defined as >85th percentile or >95th percentile of the BMI (corrected for age and sex) growth charts of the WHO for age 1 – 2 years, and CDC for 2 – 18 years [3,27,28]. To be able to distinguish between the influence of growth-related changes in weight and obesity-related changes in weight, for each patient body weight related to growth ($WT_{for\ age\ and\ length}$) and excess body weight (WT_{excess}), was calculated according to equation 1 and 2 (adapted from Van Rongen et al. [10]):

$$WT_{age\ and\ length} = BMI_{for\ age\ and\ gender} \times length^2 \quad (1)$$

$$WT_{excess} = TBW - WT_{age\ and\ length} \quad (2)$$

Where TBW is total body weight in kg, length in cm and $BMI_{for\ age\ and\ gender}$ is the p50 BMI value based on the gender specific WHO or CDC BMI-for-age growth charts for 1 – 2 years and 2 – 18 years, respectively [27,28].

If a patient's height was unknown, height was imputed using the median value of the CDC height-for-age chart [27]. Body Surface Area (BSA) was calculated using the Mosteller equation [29]. FFM was estimated using the equations of Al-Sallami and Peters [30,31]. Serum creatinine, quantified using IDMS Traceable Vitros CREA Slides and the Vitros 5.1 FS Chemistry System analyzer (Ortho Clinical Diagnostics, Inc, Rochester, New York), was included when measured within 168 h before or after a vancomycin dose. Within an individual, missing creatinine values were imputed using a next-observation-carried-backward strategy where typical values were imputed using the equation from Ceriotti et al. in case no creatinine values were available for an individual [32]. CL_{Cr} was estimated using the bedside Schwartz equation and was studied both

expressed in mL/min/1.73 m^2 [33] and deindexed by multiplication with BSA/1.73 (CL_{cr_di}). We also calculated the ratio between the observed and typical creatinine value for age (creatinine-ratio). Neutropenia was defined as an absolute neutrophil count <1.5 * 10^9 cells/L blood.

Population pharmacokinetic analysis

Log-transformed vancomycin serum concentrations were analysed using non-linear mixed-effects modelling (NONMEM v7.4, Icon Development Solutions, Ellicott City, MD, USA [34]) with Perl-speaks-NONMEM (v4.9.0) and the Pirana (v2.9.9) interface [35,36]. R (v3.6.1) and Rstudio (v1.2.1335) were used for data manipulation and visualization. Vancomycin measurements reported as being below the limit of quantification (0.7% of the observations) or drawn within 1 hour after the start of the infusion (n = 218 samples, 3.7% of the observations) were excluded. Patients were analysed as separate individuals when age increased with ≥10% or when there was ≥14 days between vancomycin administrations. Population pharmacokinetic modelling was conducted using first-order conditional estimation with inter-individual variability assumed to be log-normally distributed. One- two- and three-compartment models with additive, proportional, or a combined error model were evaluated. Nested models were compared using the objective function value (OFV, i.e. -2log likelihood [-2LL]). For structural and statistical models, a drop ≥3.84, corresponding to a p-value of <0.05 for one degree of freedom, was considered statistically significant. Models were evaluated by inspection of goodness-of-fit plots (observed versus individual or population predicted vancomycin concentrations, conditional weighted residuals versus time after dose or population predicted vancomycin concentrations), which were split for age, weight and renal function. Lastly, the precision of parameter estimates, shrinkage, and the conditional number (ratio between the highest and lowest eigenvalue) were taken into consideration.

For the covariate analysis, potential covariates were identified based on inter-individual variability versus covariate plots. Continuous covariates were entered into the model using equation (3) for exponential relations and (4) for linear relations:

$$P_i = P_p \times \left(\frac{COV}{COV_{standard}}\right)^X \quad (3)$$

$$P_i = P_p \times \left(1 + Y \times \left(COV - COV_{median}\right)\right) \quad (4)$$

where P_i and P_p are the individual and population parameter estimates, COV is the covariate value, COV_{median} is the median value for the covariate. X represents the exponent for a power function, and Y is the slope parameter for the linear covariate relationship. Linear covariate relations could also be entered into the model by using equation 3 with X fixed to 1. As it has been shown that with body weight as a covariate the scaling factor X may decrease with age for clearance in children [37], for X also a body weight-dependent exponent (BDE) according to equation (5) was tested [38,39]:

$$X = F \times TBW_i^Z \quad (5)$$

where TBW_i is the individual's total body weight, F is the intercept of the scaling exponent, and Z is the exponent that allows the scaling exponent to change with body weight.

A WT_{excess} covariate model was tested using equation (6), as described earlier [10,11]:

$$P_i = P_p \times \left(\frac{WT_{age\ and\ length}}{TBW_{median}}\right)^U + (V \times WT_{excess}) \quad (6)$$

where P_i and P_p are the individual and population parameter estimates, $WT_{age\ and\ length}$ is the body weight related to growth (equation 1), WT_{excess} the excess body weight (equation 2), TBW_{median} is the median total body weight, U is the scaling exponent for $WT_{age\ and\ length}$ (either fixed to 0.75 or estimated), V represents the linear influence of WT_{excess} on the parameter value. Categorical covariates were entered into the model by calculating a separate pharmacokinetic parameter for each category of the covariate.

Inclusion of a covariate was justified upon assessing the OFV drop (≥10.8 points, corresponding with p <0.001) between models with or without this covariate. Also, goodness-of-fit plots were reviewed as described earlier with specific emphasis on the plots split for age (1 – 2, 2 – 12 and 12 – 18 years), estimated Cl_{cr} (<30, 30 – 60, 60 – 90 and >90 mL/min/1.73 m^2) and weight group (normal weight, overweight and obese). Lastly, it was assessed whether the inter-individual variability decreased, and if trends in the inter-individual variability versus covariate plot disappeared.

The resulting final model was internally validated by assessment of normalized prediction distribution errors (NPDE) (n = 10.000 datasets) and prediction and variability corrected visual predictive check (pvcVPC) (n = 500 datasets). These diagnostics were split for age group (1 – 2, 2 – 12 and 12 – 18 years), estimated renal function (<30, 30 – 60, 60 – 90 and >90 mL/min/1.73 m^2) and weight group (normal weight, overweight and obese) [40]. Parameter precision of the structural and final model was analysed by the sampling importance resampling (SIR) procedure [41].

Dose simulations

To evaluate existing dosing guidelines and, if necessary, design a new guideline concentration-time profiles were simulated for several typical individuals from the dataset with different ages, body weight and renal functions using the ranges found across the dataset. Dosing guidelines from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, the Pediatric Infectious Diseases Society and the Society of Infectious Diseases Pharmacists (abbreviated to IDSA) [13], the Dutch Paediatric Formulary [42] and the

British National Formulary for Children (BNFc) [43] were evaluated (see supplementary file). Based on the final model, a dosing guideline aiming for an AUC_{24} of 400 – 700 mg*h/L at day 3 after the start of treatment (AUC_{day3}) as primary target was developed. Secondary target was an AUC_{24} in the first 24 h (AUC_{day1}) within 400 – 700 mg*h/L. Lastly, trough (C_{min}) concentrations corresponding to the primary target were explored.

RESULTS

Data was obtained for 1924 individuals, after which patients on renal replacement therapy or extracorporeal membrane oxygenation (n = 26) or without a recorded body weight (n = 6) were excluded. This resulted in 1892 patients in which 5524 vancomycin concentrations were available for analysis (Figure 1). Of these patients, 247 (13%) and 301 (16%) individuals fulfilled the criteria for overweight and obesity, respectively, resulting in a broad range of body weights from 6 – 188 kg. Figure 1 shows the wide scatter in sampling time after dose for the three groups. Most characteristics, including age and renal function, were similarly distributed across the three weight groups (Table 1). There was a broad range in CL_{cr} (bedside Schwartz equation) with values as low as 8.6 mL/min/1.73 m^2. In total, 12 patients had a CL_{cr} under 30 mL/min/1.73 m^2, of which 5 patients were overweight or obese. All relevant baseline characteristics are shown in Table 1.

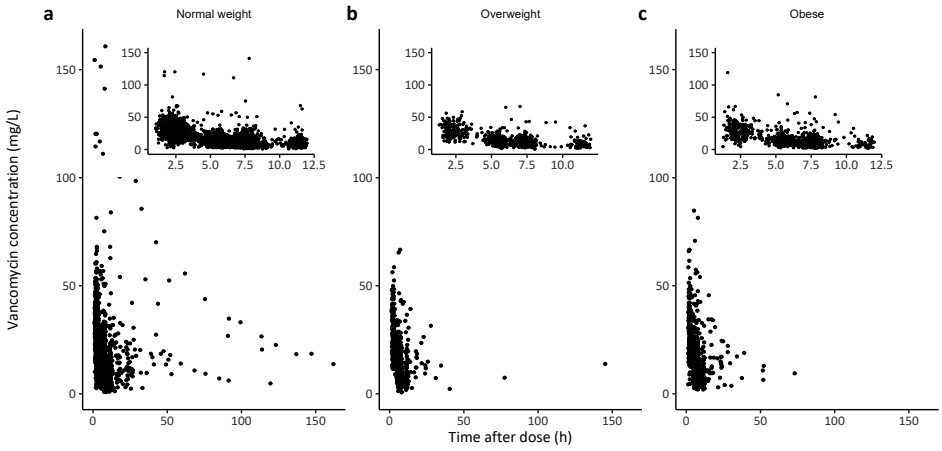


Figure 1. Observed vancomycin concentrations in mg/L versus time after dose in hours for (a) non-obese, (b) overweight, and (c) obese individuals. Inserts show the same data for the time frame 0 – 12 hours after the last dose.

Population pharmacokinetic analysis

A two-compartment model with inter-individual variability on clearance (CL) and peripheral volume of distribution (V2) with a proportional residual error model best described the data. The pharmacokinetic parameters of the structural model without covariates are shown in Table 2.

In the covariate analysis, we found an important influence of both renal function expressed using bedside Schwartz formula (CL_{cr}) and total body weight (TBW) on CL. Vancomycin CL was best described by linear implementation of CL_{cr} which was maximized at 120 mL/min/1.73 m^2 and a power equation for TBW (ΔOFV -2356.1 compared to the structural model without covariates [p <0.001]). The specific influence of TBW and CL_{cr} on vancomycin CL is visualized in Figure 2. This combined covariate model outperformed models with the separate implementation of TBW or CL_{CR}, i.e. TBW on CL with a power function (ΔOFV -1125.7 [p <0.001] compared with the structural model without covariates), TBW on CL with a body weight-dependent exponent (ΔOFV -1180.9 [p <0.001] compared with the structural model without covariates) and CL_{cr_di} on CL using a power function (ΔOFV -2230.3 [p <0.001] compared with the structural model without covariates). A covariate model that uses $WT_{age\ and\ length}$ and WT_{excess} (equation 6) instead of TBW resulted in a similar OFV and goodness-of-fit as the model with only TBW as covariate (ΔOFV -1129.2 versus ΔOFV -1125.7 compared with the structural model without covariates, respectively [p >0.01]). For the implementation of CL_{cr}, a model with an estimated exponent compared to a linear model led to similar results regarding the goodness-of-fit and OFV (estimated exponent 0.94, ΔOFV -6.1 compared to the model with a linear function with one additional degrees of freedom [p >0.01]). These results indicate that regarding the influence of body weight on vancomycin clearance, the influence of weight from growth is similar to the influence of excess weight. Inclusion of neutropenia as a binary covariate on CL did not improve the model (ΔOFV +0.8 compared to the model with TBW and CL_{cr} on CL [p >0.05]). No other covariates for CL could be identified.

Both V1 and V2 were significantly influenced by TBW in a linear function (ΔOFV -830.4 [p <0.001] compared to the model without covariates on V1 or V2). There was no significant difference between a linear or a power function with an estimated exponent for TBW (estimated exponent 1.05, ΔOFV -2.3 points compared to the model with TBW on V1 and V2 linearly, p >0.05). The model with TBW linearly on V1 and V2 provided a slightly better fit compared to a WT_{excess} model for V1 and V2 using equation (6), which resulted in an OFV reduction of -813.5 points (p >0.01). The addition of TBW exponentially on Q gave a further improvement in OFV (ΔOFV -113.4 [p <0.001]). Lastly, the covariance between CL and V2 was included in the model using an OMEGABLOCK, decreasing OFV with 36 points.

Table 1. Baseline characteristics.

Characteristic	Normal weight (n = 1344)
Age (years)	6.9 [2.9 – 13.2] (1.0 – 18.0)
Age group (N, (% of the total of age group))	1 – 2 year: 214 (66)
	2 – 12 year: 727 (72)
	12 – 18 year: 403 (71)
Gender (% male)	57.3
Race (N, (% of the total of the group)	Caucasian: 1198 (72)
	Asian: 11 (85)
	Hispanic: 17 (65)
	African American: 27 (62)
	Other: 91 (62)
TBW (kg)	20.6 [13.0 – 38.8] (5.8 – 82.6)
Height (cm)	119 [92 – 150] (62 – 203)
BMI (kg/m^2)	16.1 [14.6 – 17.7] (8.6 – 25.6)
BSA (m^2)	0.83 [0.58 – 1.28] (0.32 – 2.10)
Serum creatinine (mg/dL)	0.40 [0.30 – 0.54] (0.06 – 8.20)
Bedside Schwartz creatinine clearance (ml/min/1.73 m^2)	121.2 [101.2 – 144.6] (8.6 – 963.5)
Bedside Schwartz group[a] (N, (% of the total of the group))	>90: 1100 (73)
	60 – 90: 200 (63)
	30 – 60: 37 (64)
	<30: 7 (58)
Patients admitted to ICU (%)	466 (35)
Patients with neutropenia (N, (% of total))	223 (17)
No. of samples (N, (% of total))	3968 (72)
No. of samples per individual	4 [2 – 7] (1 – 37)
Sampling time after dose (h)	5.8 [4.3 – 7.5] (1.0 – 162.0)

Values are shown as median [interquartile range] (range) unless specified otherwise

[a] Schwartz group is shown in mL/min/1.73 m^2

BMI Body Mass Index, *BSA* Body Surface Area.

Overweight (n = 247)	Obese (n = 301)
7.2 [3.0 – 12.6] (1 – 17.6)	6.9 [2.5 – 13.2] (1.0 – 18.0)
1 – 2 year: 41 (13)	1 – 2 year: 68 (21)
2 – 12 year: 137 (14)	2 – 12 year: 135 (14)
12 – 18 year: 69 (12)	12 – 18 year: 98 (17)
53.4	54.1
Caucasian: 217 (13)	Caucasian: 248 (15)
Asian: 2 (15)	Asian: 0 (0)
Hispanic: 1 (4)	Hispanic: 8 (31)
African American: 8 (19)	African American: 8 (19)
Other: 19 (13)	Other: 37 (25)
25.0 [13.8 – 51.4] (7.3 – 99.3)	30.0 [14.0 – 78.1] (7.5 – 188.0)
115 [87 – 149] (63 – 193)	116 [85 – 159] (54 – 196)
18.9 [17.9 – 23.2] (16.9 – 23.2)	23.2 [19.7 – 29.8] (18.1 – 60.1)
0.89 [0.58 – 1.45] (0.36 – 2.31)	1.00 [0.57 – 1.86] (0.35 – 3.04)
0.40 [0.30 – 0.57] (0.10 – 3.53)	0.44 [0.30 – 0.61] (0.12 – 3.16)
114.7 [91.0 – 142.3] (14.8 – 291.1)	111.7 [91.3 – 134.5] (21.3 – 323.9)
>90: 186 (12)	>90: 220 (15)
60 – 90: 48 (15)	60 – 90: 68 (22)
30 – 60: 9 (16)	30 – 60: 12 (21)
<30: 4 (33)	<30: 1 (8)
91 (37)	113 (38)
53 (22)	40 (13.3)
698 (13)	858 (16)
4 [2 – 6] (1 – 34)	4 [2 – 7] (1 – 34)
5.9 [4.5 – 7.6] (1.3 – 145.3)	6.4 [4.8 – 7.7] (1.3 – 73.0)

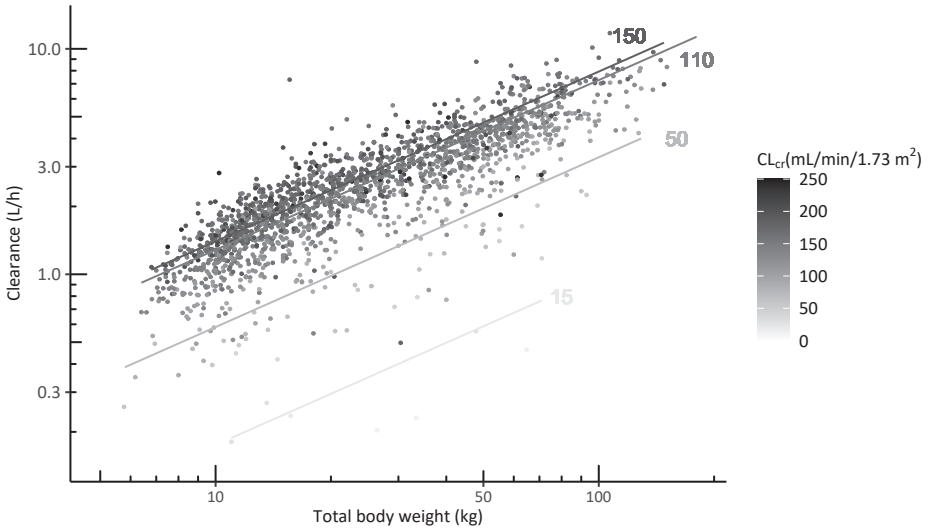


Figure 2. Vancomycin clearance (in L/h) versus total body weight (in kg) for varying creatinine clearance values (CL_{cr}). Each dot represents one individual, with darker colour representing a higher CL_{cr}. The lines show how clearance changes with body weight over the available weight range according to the final model for four typical values of CL_{cr} (i.e., 15, 50, 110 and 150 mL/min/1.73 m²), with corresponding CL_{cr} value shown in the figure for each line (mL/min/1.73 m²). *CL_{cr}* creatinine clearance based on the bedside Schwartz equation (in mL/min/1.73 m²).

As a result of introducing these covariates, inter-individual variability on CL reduced from 52.8% in the structural model without covariates to 28.7% in the final model, at a slight increase in inter-individual variability on V2 from 89.4% to 109.5% (shrinkage 57%). As the goodness-of-fit and OFV substantially deteriorated when inter-individual variability for V2 was removed from the model (ΔOFV +457.2 [p <0.001]), we decided to retain it in the final PK model. Figure 3 shows that each covariate gave a distinct improvement in goodness-of-fit plot across the different subpopulations and that all subpopulations are well described. For the group with the lowest renal function (<30 mL/min/1.73 m²), some over-prediction is seen, which may result from the small number of individuals (n = 12). The validity of our model across all subgroups was confirmed by NPDE (Figure S1, supplementary file) and pvcVPC (Figure 4 and S2-3 in the supplementary file) across different subpopulations. The final pharmacokinetic model parameters are shown in Table 2.

Table 2. Population pharmacokinetic model parameters of the structural base model (without covariates) and the final model (with covariates) for vancomycin in normal weight, overweight and obese children and adolescents aged 1 – 18 years old with and without renal impairment.

Parameter	Structural model (RSE %)	Final model (RSE %) [95% CI]
Fixed effects		
CL (L/h) $TVCL \times \left(\frac{TBW}{22.1}\right)^{\theta_1} \times \left(\frac{SCHW^{a}}{100}\right)$	2.17 (2)	-
TVCL (L/h)	-	2.12 (1) [2.07 – 2.17]
θ_1	-	0.745 (2) [0.720 – 0.768]
V1 (L) $TVV1 \times \left(\frac{TBW}{22.1}\right)$	5.27 (8)	-
TVV1 (L)	-	8.90 (3) [8.50 – 9.33]
Q (L/h) $TVQ \times \left(\frac{TBW}{22.1}\right)^{\theta_2}$	2.24 (4)	-
TVQ (L)	-	1.55 (5) [1.44 – 1.65]
θ_2	-	0.599 (9) 0.517 – 0.685]
V2 (L) $TVV2 \times \left(\frac{TBW}{22.1}\right)$	11.9 (8)	-
TVV2 (L)	-	12.3 (6) [11.2 – 13.6]
Inter-individual variability (IIV, %) [b,c]		
CL	52.8 (3)	28.7 (5) [27.1 – 30.7]
Covariance IIV_{CL-V2}	-	-0.085 [-0.11 - -0.062]
V2	89.4 (7)	110 (7) [95.9 – 130]
Residual variability		
Proportional error[d,e]	0.107 (7)	0.0789 (6) [0.0746 – 0.0836]
OFV	-1886.4	-5222.5

[a] Schwartz value is maximized to 120 mL/min/1.73 m²

[b] Shrinkage of inter-individual variability in the final model is 24% for CL, 57 % for V2

[c] Coefficient of variation, calculated by $\sqrt{(e^{\omega^2} - 1)}$

[d] Proportional error is shown as σ

[e] Epsilon shrinkage for the final model is 16%

CI confidence interval obtained from sampling importance resampling (SIR) procedure, *CL* clearance, *OFV* objective function value, *Q* inter-compartmental clearance between V1 and V2, *RSE* relative standard error based on the covariance step in NONMEM, SCHW creatinine clearance according to bedside Schwartz equation, *TBW* total body weight, *TVCL* typical value of CL for an individual weighing 22.1 kg and with creatinine clearance of 100 ml/min/1.73 m², *TVQ* typical value of Q for an individual weighing 22.1 kg, *TVV1* typical value of V1 for an individual weighing 22.1 kg, *TVV2* typical value of V2 for an individual weighing 22.1 kg, *V1* volume of distribution of central compartment, *V2* volume of distribution of the peripheral compartment.

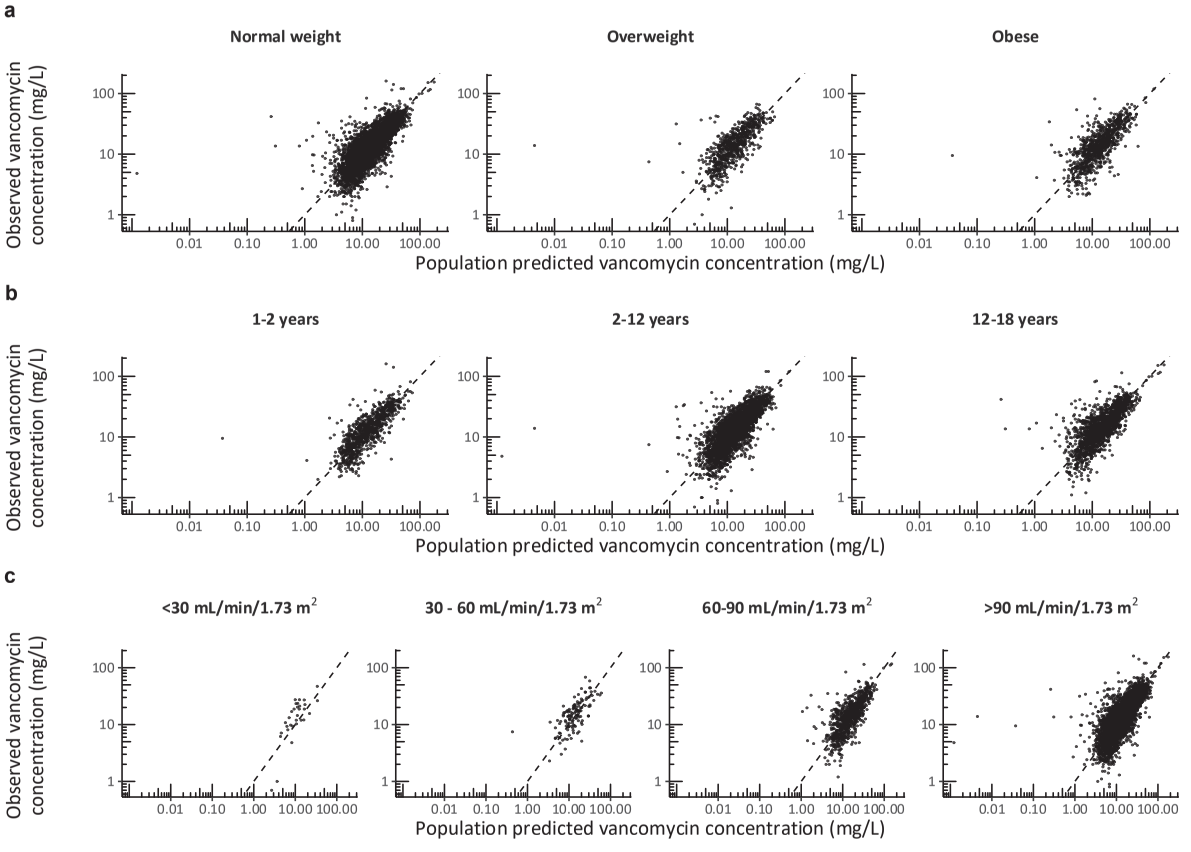


Figure 3. Observed versus population predicted vancomycin concentrations for the final model, split for (a) weight group, (b) age group or (c) renal function group (creatinine clearance based on the bedside Schwartz equation).

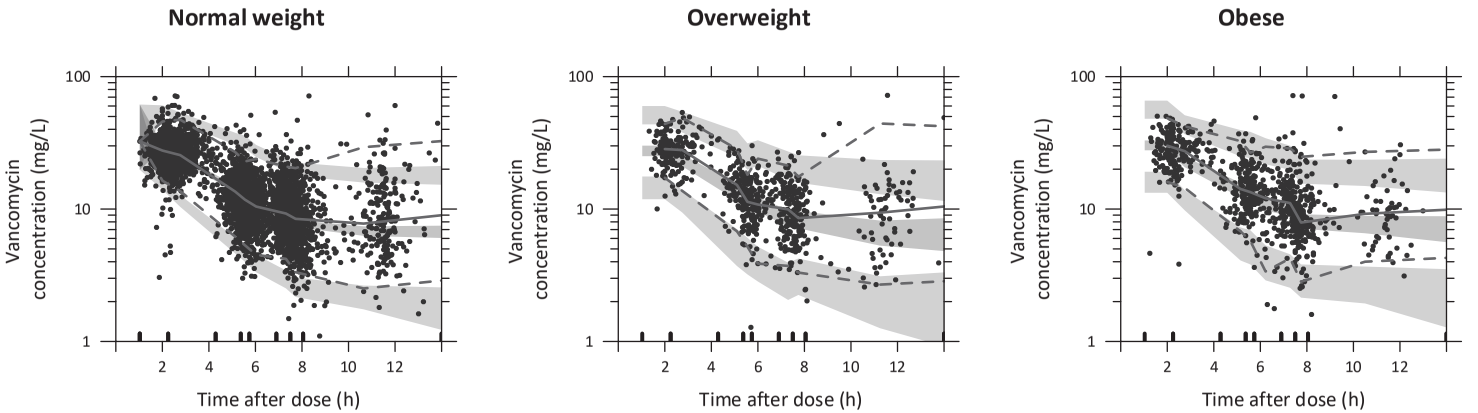


Figure 4. Prediction and variability corrected visual predictive check (pvcVPC), split for weight. Prediction corrected observations are shown as dots, with the median, 2.5th and 97.5th percentiles shown as solid, lower, and upper dashed lines. Grey shaded areas represent the 95% confidence intervals of the median (dark grey) and 2.5th and 97.5th percentiles (light grey) of predicted concentrations (n = 500) based on the pharmacokinetic model. Intervals of the bins are shown by the vertical ticks on the bottom of the plot.

Dose simulations and proposed dosing guideline

Based on the influence of both renal function and body weight on vancomycin clearance, we developed dosing recommendations for the paediatric population (Table 3). As shown in Table 3, the first dose is 15 mg/kg for all groups followed by doses adjusted to body weight and renal function. The obtained concentration-time profiles using this dosing guideline for six representative individuals from the dataset (normal weight and morbidly obese individuals ranging from 1 – 17 years and 11 – 118 kg) are shown in Figure 5. For each individual, four curves with different renal functions (Schwartz 10 – 120 mL/min/1.73 m^2) are shown. For reference, the profiles for the same individuals using the currently leading paediatric dosing guidelines are shown in Figure S4 in the supplementary file. When the proposed dose nomogram is used, the obtained AUC_{day3} (defined as the AUC from 48 to 72 hours after the first dose) was within the target of 400 – 700 mg*h/L for all individuals, regardless of body weight, weight group (obese or normal weight), renal function or age. Additionally, already in the first 24 h target AUC's were reached in all individuals, except for the individuals with renal function >120 mL/min/1.73 m^2 (Figure 5). Similar results are obtained when the dosing guideline is adapted to a continuous infusion dosing regimen (Figure S5 in the supplementary file). Here, 15 mg/kg is given as a loading dose, followed after 3 hours by the proposed daily dose given as a 24 h infusion. For the reader's convenience, we have provided this continuous infusion dosing guideline in the supplementary file (Table S1). The results obtained using the dosing guideline as shown in Table 3 and Figure 5 contrast with what was obtained using the currently leading dosing guidelines (IDSA, Dutch Paediatric Formulary, BNFc), as shown in Figure S4, where the current guidelines result in high, potentially toxic exposures (AUC_{day3} >700 mg*h/L) especially in children with renal impairment or who are considered obese. This particularly applies to BNFc and IDSA guidelines, which do not recommend dose adjustments for patients with reduced renal function. Figure 5 shows that for the typical individuals trough concentrations corresponding to an AUC_{day3} 400 – 700 mg*h/L vary between 7.2 and 23 mg/L, when dosed according to the proposed dosing guideline in Table 3.

Table 3. Dosing guideline for intermittent dosing of vancomycin in children and adolescents aged 1 – 18-years based on total body weight and renal function according to bedside Schwartz.

Schwartz creatinine clearance (mL/min/1.73 m^2)	Total body weight (kg)			Relative daily dose (%)
	<30	30 – 70	>70	
>90	15 mg/kg every 6 h	15 mg/kg every 8 h	18 mg/kg every 12 h	100%
50 – 90	11 mg/kg every 6 h[a]	11 mg/kg every 8 h[a]	12 mg/kg every 12 h[a]	70%
30 – 50	5 mg/kg every 6 h[a]	5 mg/kg every 8 h[a]	6 mg/kg every 12 h[a]	35%
10 – 30	5 mg/kg every 12 h[a]	3 mg/kg every 12 h[a]	3 mg/kg every 12 h[a]	15%

[a] First dose is 15 mg/kg.

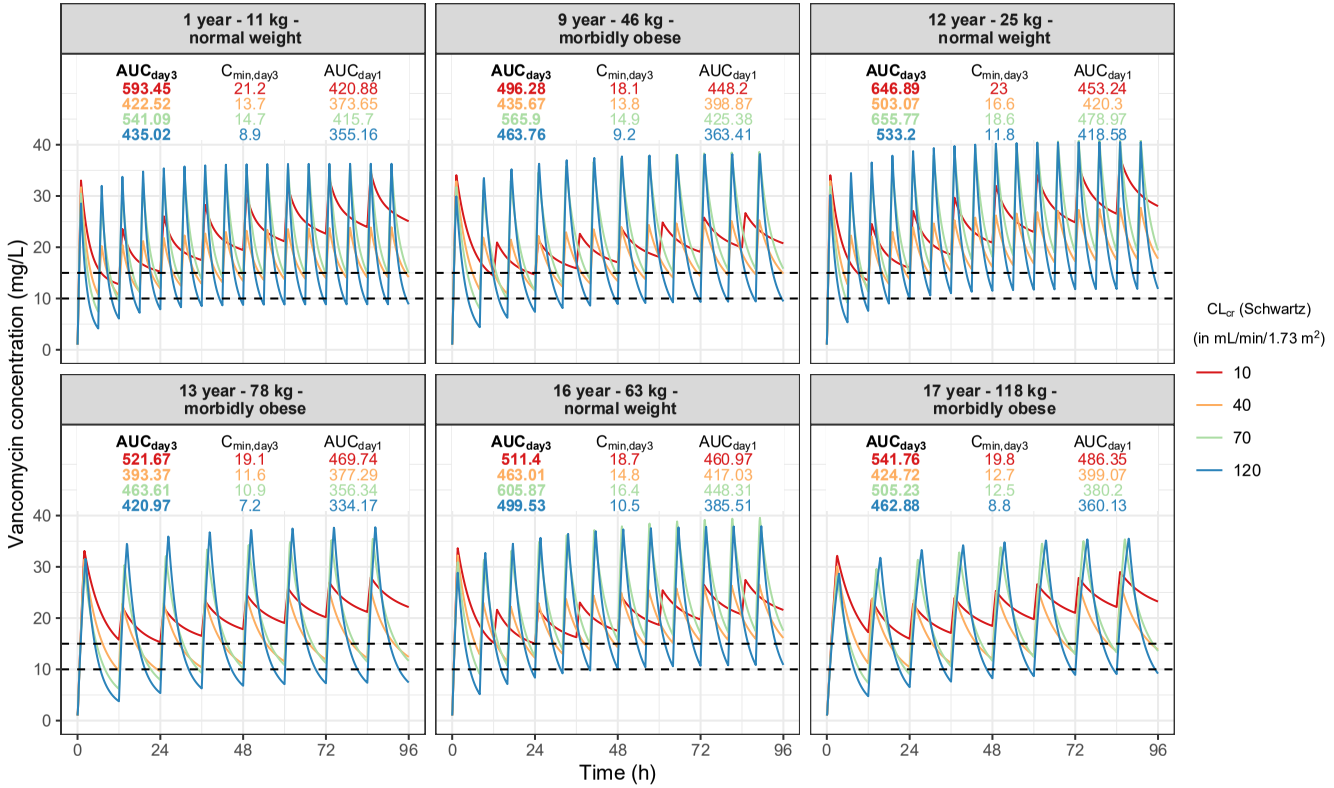


Figure 5. Vancomycin concentrations (mg/L) versus time (hours) in different typical individuals with body weight ranging 10 – 120 kg and renal function ranging 10 – 120 mL/min/1.73 m² where vancomycin is dosed according to the proposed dosing guideline (Table 3). For each individual, AUC (in bold), $C_{min,}$ at day 3, as well as AUC at day 1 are shown in the graph (where colour corresponds to the individual's renal function). Dashed lines represent the target concentrations for the trough concentrations (10 – 15 mg/L). *AUC* area under the curve, C_{min} minimum (trough) concentration.

DISCUSSION

In this study, we provide a practical paediatric dosing guideline based on a thorough characterization of the vancomycin pharmacokinetics in a large paediatric and adolescent population aged 1 – 18 years that consists of normal weight, overweight and obese individuals with a wide range of renal functions. We have demonstrated that vancomycin clearance can be well predicted using a combination of renal function calculated by the bedside Schwartz formula and total body weight. To our best knowledge, the paediatric pharmacokinetics of vancomycin has not been described before in such a large and rich dataset, with a broad range and overlay of multiple relevant covariates such as age, body weight and renal function and where the vancomycin samples showed a good distribution in time after dose, especially over the first 12 h. This straightforward dosing guideline is in line with the IDSA vancomycin dose recommendation for non-obese children (15 mg/kg four times daily) [13] and our recently proposed dose recommendations for vancomycin in obese adults (35 mg/kg per day) [44]. However, it adds dose adaptations for paediatric obesity and renal impairment, the latter in both normal weight and overweight/obese children. We demonstrate that by following our proposed dosing guideline (Table 3), effective exposures with minimal risk of toxicity (AUC_{day3} between 400 and 700 mg*h/L) can be expected throughout the population. Besides, by starting with a first (loading) dose of 15 mg/kg in all groups, target exposures can be reached in the first 24 h after the start of treatment for most individuals, both in intermittent or continuous infusion regimens. Finally, we show that trough concentrations may vary vastly, with values ranging from 7.2 – 23 mg/L in our typical individuals, even though the exposure is within the target for these individuals (Figure 5). The variability in trough concentrations related to target exposure as a result of dosing frequency, age or weight has been described before for several populations, including obese adults and normal-weight children [21,22,44]. Therefore, clinicians should not base dose adjustments on trough concentrations alone, but preferably use Bayesian forecasting to relate TDM samples to predict exposure, as is also recommended in the recently revised vancomycin therapeutic drug monitoring guideline [13]. For Bayesian forecasting, the current PK model can be used as a basis.

There is currently a limited number of vancomycin pharmacokinetic studies that have been performed in obese children or adolescents [18,23–26,45]. In contrast to our study, the majority of these publications lack specific dose recommendations, in particular regarding the combination of renal impairment and obesity. Several studies found that when vancomycin was dosed on a similar mg/kg basis in obese and non-obese children, higher trough concentrations were obtained in obese children [18,23,45]. This finding is in agreement with our observations, showing that the IDSA and BNFc guidelines lead to increasing exposure and trough concentrations with increasing body weight to the point where the dose is being capped. Most pharmacokinetic studies found that clearance increases with body weight, but varying

covariate relationships have been described. An analysis by Lanke et al. in 463 adolescents aged 12 – 18 years found that vancomycin clearance increased with TBW and creatinine clearance based on the bedside Schwartz equation, similar to our results [24]. Another study in 196 mostly adolescent overweight and obese children found that besides serum creatinine, fat-free mass best predicted vancomycin clearance [25]. In their dataset, total body weight could not be identified as a predictor of clearance. It is unclear what explains these results, but it cannot be excluded that these findings are explained by the absence of adolescents with normal weight unlike the data of our study. Lastly, Le et al. have also found that in 87 pairs of obese and non-obese children, aged 2 – 18 years, vancomycin clearance can best be predicted by a combination of total body weight (using an allometric function with exponent 0.75), serum creatinine and age [26], which is roughly in line with our results. However, the authors state that the differences between obese and non-obese individuals are small and do not necessitate any dose adjustments. Our study clearly show that dose adjustments are however necessary to prevent subtherapeutic or toxic exposures.

Some limitations of our study should be addressed. Children under one year of age were excluded in this study. Therefore, readers should not use our results in children below one year of age for which we refer to other dosing guidelines [21]. In addition, although we included patients with renal function ranging down to 8.6 mL/min/1.73 m^2, there were relatively few patients with an estimated renal function <30 mL/min/1.73 m^2 (n = 12). The diagnostics of our final model show some underprediction of vancomycin concentrations in this group (Figure 3C), while the dose recommendations show that due to an increased elimination half-life, steady-state concentration has not been reached on day 3 in this patient group. Consequently, our dose recommendations must be used with extra caution for this subgroup. Also, vancomycin was given exclusively as intermittent infusions in the population included in our dataset. With this study design we can adequately estimate clearance, which mainly drives the maintenance dose for both intermittent and continuous regimens. However, some caution should be applied when extrapolating our results to continuous infusion regimens. Lastly, there is considerable variability in the PK model. This stresses the need to apply TDM still to guide dose adjustments further, as is currently widespread practice for vancomycin in the paediatric population [13].

In the covariate analysis, we have investigated several approaches for the inclusion of weight as a covariate for vancomycin clearance. First, we found that for predicting clearance, there was no benefit of a sophisticated model that separately characterizes the influence of weight for age-and-length and weight excess (equations 1, 2 and 6) over a simple covariate model using only total body weight. This implies that for vancomycin clearance in children, there seems to be no difference in the influence of weight resulting from growth and development and excess weight resulting from obesity. Our results are in line with studies with similar

populations for metformin and midazolam, where for metformin clearance and midazolam volume of distribution a $WT_{for\ age\ and\ length}/WT_{excess}$ model performed similar as compared to a model with TBW as a covariate [10,11]. For busulfan clearance, a large study in children and adolescents including many with underweight and overweight showed that estimating an additional factor that accounts for under- or overweight (using the Z-score) did not give a better description of the data than a model with only TBW [12]. Second, we could not identify a maturation model for clearance with a body weight-dependent exponent in the power function to capture the decrease in exponent with age (equation 5). This is not unexpected, since it is well-known that the maturation of renal excretion processes such as glomerular filtration rate (GFR) is nearly complete around one year of postnatal age [46]. As such, in our population of children over one-year-old, such a maturation function was not of added value. This is substantiated by another pharmacokinetic analysis of vancomycin, which was done in non-obese children without renal dysfunction where almost 80% of the included patients were younger than one year [39]. This study found a body weight-dependent exponent to be superior over a model with a power function for TBW. Third, we estimated an exponent of 0.745 for the effect of TBW on vancomycin clearance. This value is close to 0.75 which is often used for weight-based allometric scaling of paediatric drug clearance from adult values. Although the principles of allometric scaling have been well established in predicting drug clearance in normal-weight children over five years of age, this is not the case for obese children or children aged below five years [47]. For this reason, we decided to keep the estimated value of 0.745 in the final model, keeping in mind that we cannot rule out coincidence as the cause for finding a similar value as the allometric exponent of 0.75 in this particular population.

CONCLUSIONS

We have successfully characterized the population pharmacokinetics of vancomycin in children and adolescents aged one year and above, with varying degrees of obesity and renal functions. Vancomycin clearance can be well predicted using a combination of CL_{cr} (using the bedside Schwartz equation) and total body weight. Using this model, we have designed a dosing guideline that provides quantitative detail on the IDSA recommendation of 15 mg/kg four times daily by specifying the dose reductions required for renal impairment in both obese and non-obese individuals. With this dosing guideline, effective and safe exposures at day 3 (AUC_{day3} of 400 – 700 mg*h/L), but also in the first 24 h of treatment are expected throughout the paediatric population aged 1 – 18 years.

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SUPPLEMENTARY FILE

Paediatric dosing guidelines used for simulations:

Infectious Diseases Society of America, the American Society of Health-System Pharmacists, the Pediatric Infectious Diseases Society and the Society of Infectious Diseases Pharmacists (IDSA) [13]:
15 mg/kg every 6 hours (max 3600 mg / day). Obese: loading dose 20 mg/kg.

Dutch Paediatric Formulary [42]:
15 mg/kg every 6 hours + GFR 50 – 80: every 24h, GFR 10 – 50 every 48 hours. Maximum 4 gram/day.

British National Formulary for Children (BNFc) [43]:
< 12y: 10 – 15 mg/kg every 6h (no maximum dose).
12 years and older: 15 mg/kg every 8 hours (maximum 2 g).

Table S1. Dosing guideline for continuous infusion of vancomycin in children and adolescents aged 1 – 18-years based on total body weight and renal function according to bedside Schwartz.

Schwartz creatinine clearance (mL/min/1.73 m²)	Total body weight (kg)			Relative daily dose (%)
	<30	30 -70	>70	
>90	60 mg/kg over 24 h[a]	45 mg/kg over 24 h[a]	36 mg/kg over 24 h[a]	100%
50 – 90	44 mg/kg over 24 h[a]	33 mg/kg over 24 h[a]	24 mg/kg over 24 h[a]	70%
30 – 50	20 mg/kg over 24 h[a]	15 mg/kg over 24 h[a]	12 mg/kg over 24 h[a]	35%
10 – 30	10 mg/kg over 24 h[a]	6 mg/kg over 24 h[a]	6 mg/kg over 24 h[a]	15%

[a] Loading dose is 15 mg/kg, followed after 3 hours with proposed maintenance dose.

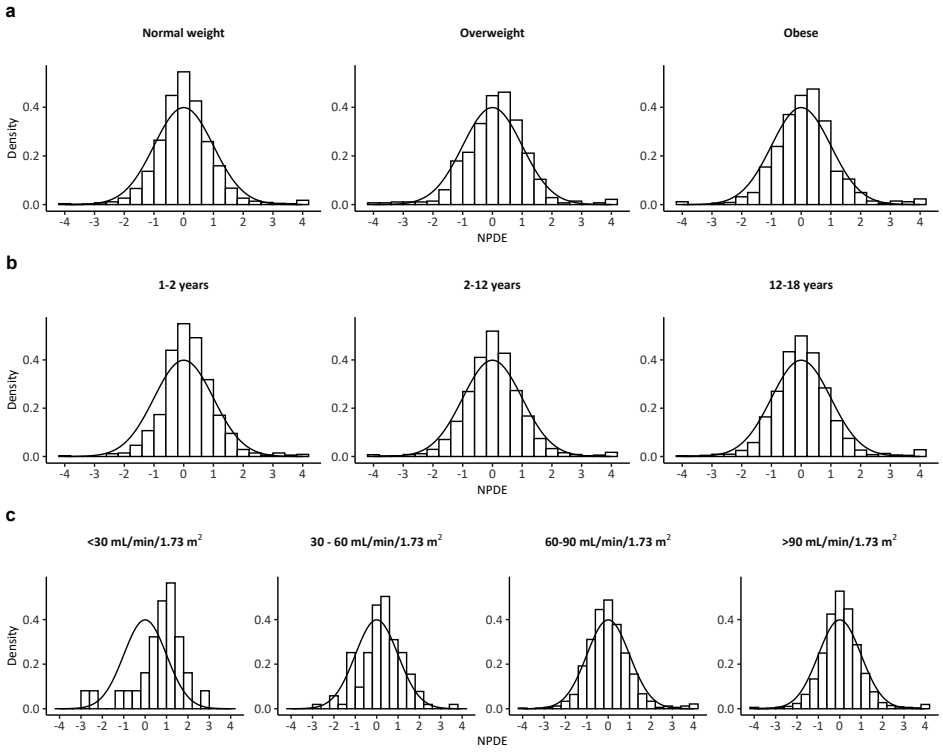


Figure S1. Distribution of the normalized prediction distribution errors (NPDE) for the final model, split for (a) weight group, (b) age group or (c) renal function group (based on the bedside Schwartz equation). The solid line depicts a normal distribution.

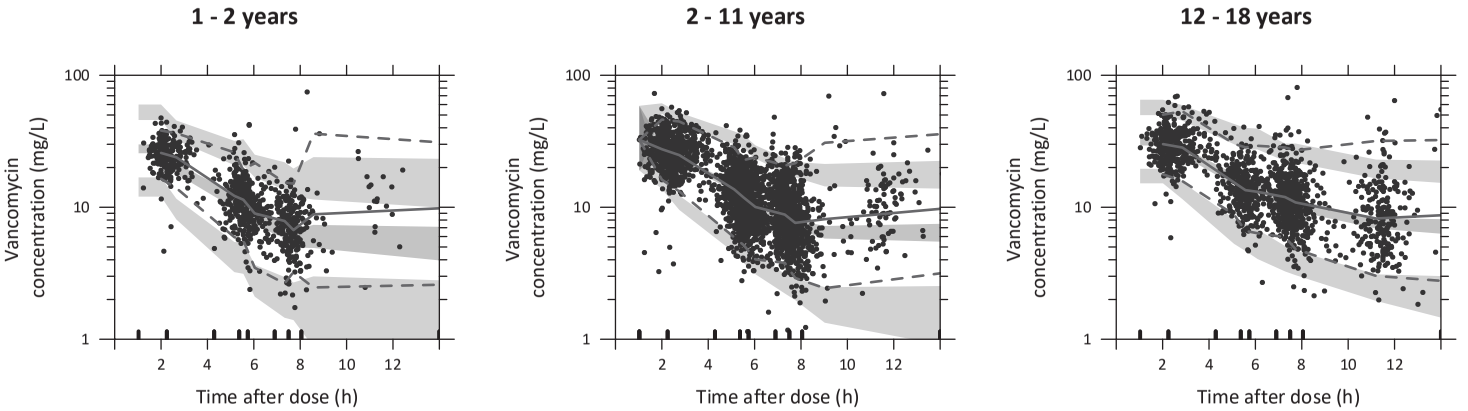


Figure S2. Prediction and variability corrected visual predictive check (pvcVPC), split for the age. Prediction corrected observations are shown as dots, with the median, 2.5th and 97.5th percentiles shown as solid, lower, and upper dashed lines. Grey shaded areas represent the 95% confidence intervals of the median (dark grey) and 2.5th and 97.5th percentiles (light grey) of predicted concentrations (n = 500) based on the pharmacokinetic model. Intervals of the bins are shown by the vertical ticks on the bottom of the plot.

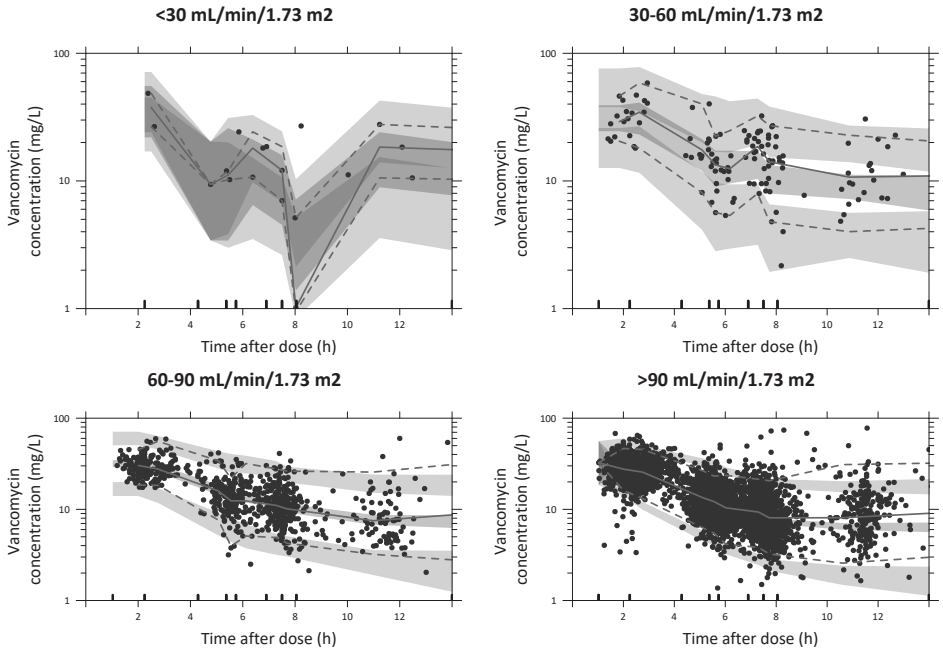


Figure S3. Prediction and variability corrected visual predictive check (pvcVPC), split for renal function group based on bedside Schwartz. Prediction corrected observations are shown as dots, with the median, 2.5th and 97.5th percentiles shown as solid, lower, and upper dashed lines. Grey shaded areas represent the 95% confidence intervals of the median (dark grey) and 2.5th and 97.5th percentiles (light grey) of predicted concentrations (n = 500) based on the pharmacokinetic model. Intervals of the bins are shown by the vertical ticks on the bottom of the plot.

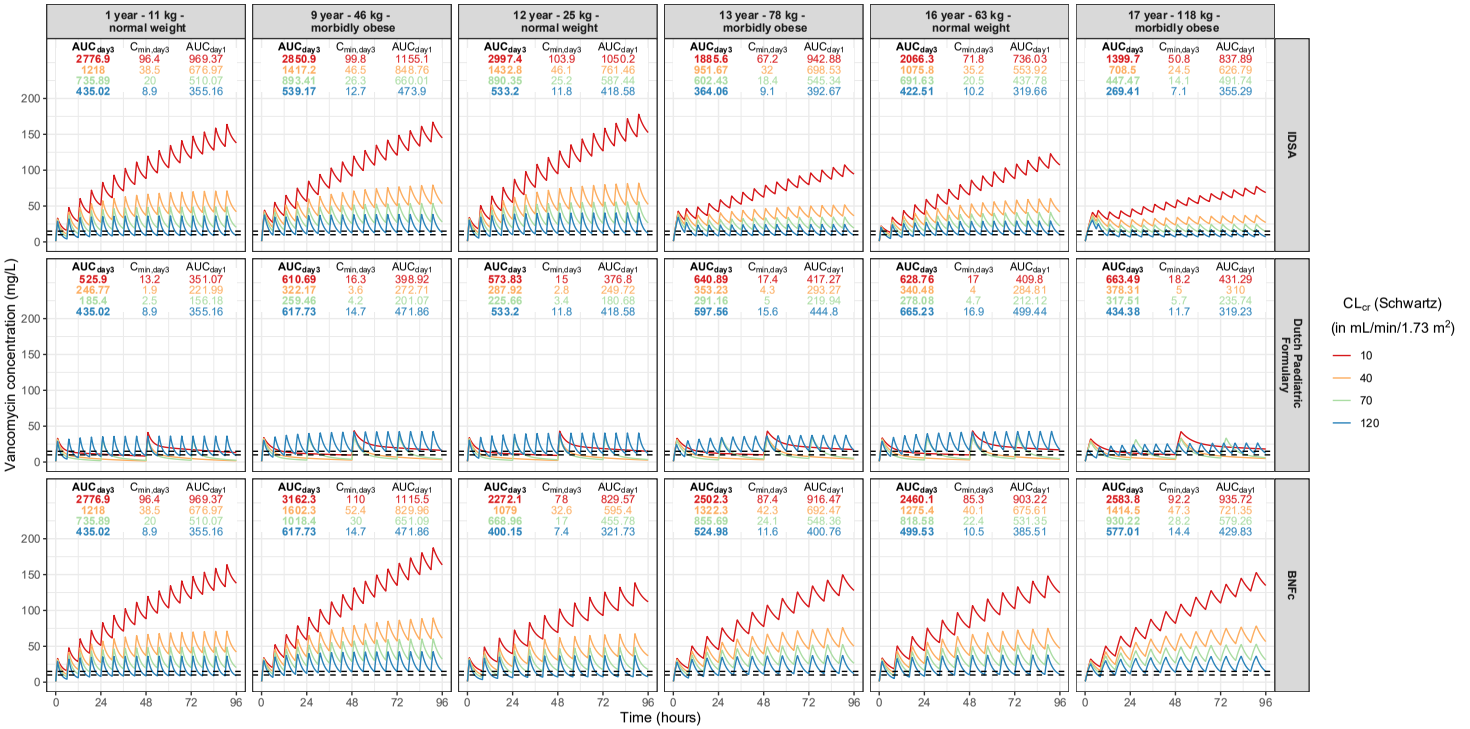


Figure S4. Vancomycin concentrations (mg/L) versus time (hours) in several typical individuals with bodyweight ranging 10 – 120 kg and renal function ranging 10 – 120 ml/min/1.73 m² where vancomycin is dosed according to three existing dosing guidelines: Infectious Diseases Society of America (IDSA, upper panel), Dutch Paediatric Formulary (middle panel) and British National Formulary for Children (BNFc, lower panel). For each individual, AUC (in bold), $C_{min,}$ at day 3, as well as AUC at day 1 is shown in the graph (where colour correspondents to the individual's renal function). Dashed lines represent the target concentrations for the trough concentrations (10 – 15 mg/L). *AUC* area under the curve, C_{min} minimum (trough) concentration.

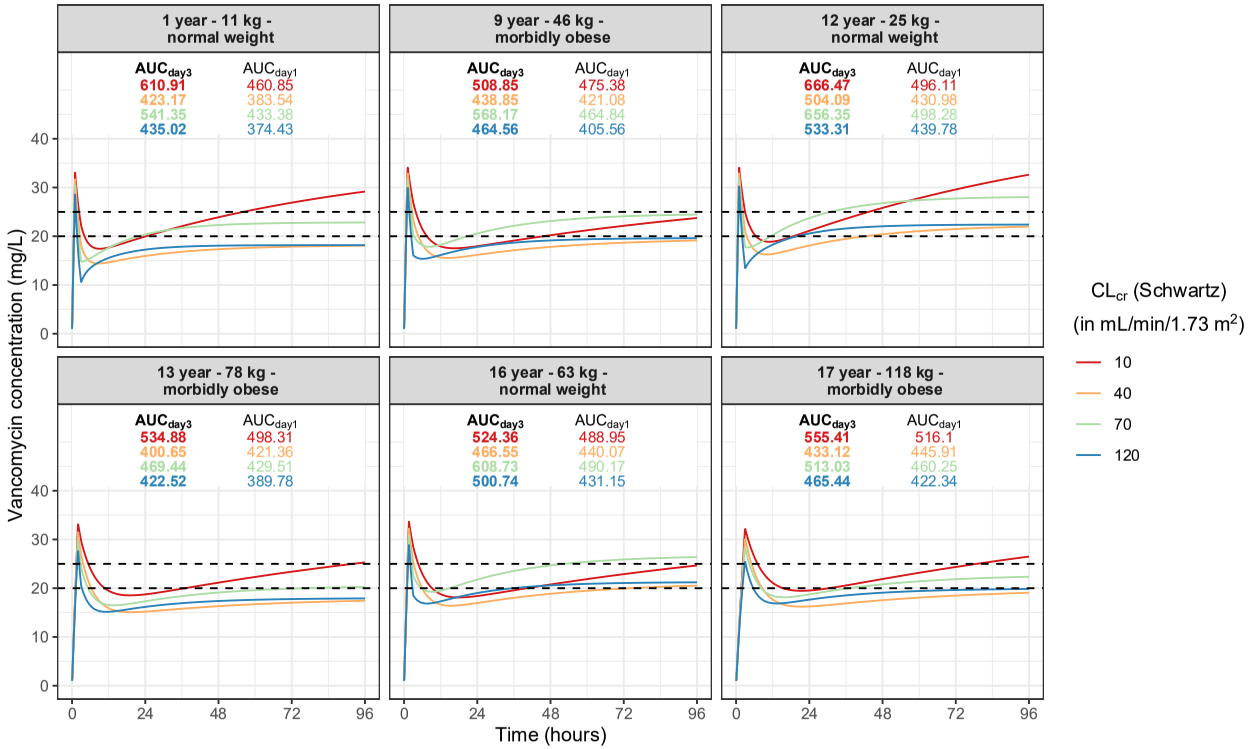


Figure S5. Vancomycin concentrations (mg/L) versus time (hours) in different typical individuals with body weight ranging 10 – 120 kg and renal function ranging 10 – 120 ml/min/1.73 m² where vancomycin is dosed as continuous infusion according to the proposed dose nomogram (Table 3). Here, the first dose of 15 mg/kg was given as a loading dose, after 3 hours followed by the proposed daily maintenance dose given as a 24 h infusion. For each individual, AUC at day 3 (in bold), as well as AUC at day 1 is shown in the graph (where colour corresponds to the individual's renal function). Dashed lines represent the target concentrations for continuous infusion (20 – 25 mg/L). *AUC* area under the curve.

NONMEM CONTROL STREAM FOR THE FINAL MODEL

```
$PROBLEM VANCO 1-18
$INPUT ID TIME AMT RATE DV=DROP LNDV=DV MDV
LLOQ BLQ OCC EVID HT WT LBW_AS LBW_P BSA WTAGE
WTEXS BMI GRP AGED AGEG SEX RACE RRT ICU HOSP
TIMo TAD CREAT CREAT_TV CREAT_FIRST CREAT_BL SCHW
SCHW_FIRST SCHW_di SCHW_di_FIRST SCHW_BL S C H W _ B L _
di SCHW_SL SCHW_di_SL CREAT_IMP NEUT NPEN RIFLE
NEPHROTOX NPENE CRP LYMPH SCHW_GRP

$DATA nonmem_1_18J_NOCB_SCHW_GRP.prn IGNORE=# IGNORE=(RRT.EQ.1)
IGNORE=(BLQ.EQ.1) IGNORE=(WT.LT.0)
$SUBROUTINE ADVAN3 TRANS4
$PK
SCHW_MAX=SCHW
IF(SCHW.GT.120) SCHW_MAX=120
CREAT_RATIO=CREAT/CREAT_TV
;
IF (WT.GT.0) THEN
TVCL_WT = THETA(1) * ((WT/22.1)**THETA(6)); TVCL_WT
TVV1 = THETA(2)*((WT/22.1)**THETA(7))
TVQ = THETA(3)*((WT/22.1)**THETA(8))
TVV2 = THETA(4)*((WT/22.1)**THETA(7))
ELSE
TVCL_WT = THETA(1)
TVV1 = THETA(2)
TVQ = THETA(3)
TVV2 = THETA(4)
ENDIF
;
TVCL = TVCL_WT*((SCHW_MAX/100)**THETA(5))
;
CL = TVCL*EXP(ETA(1))
V2 = TVV2*EXP(ETA(2))
;
V1 = TVV1*EXP(ETA(3))
Q = TVQ*EXP(ETA(4))
```

```
;
S1 = V1 ;
;
ET1=ETA(1)
ET2=ETA(2)
ET3=ETA(3)
ET4=ETA(4)

$THETA
(0, 2.12) ; TVCL_WT
(0, 8.87) ; TVV
(0, 1.54) ; Q
(0, 12) ; V2
(1) FIX ; CL_SCHW EXP
(0.753) ; CL_WT_EXP
(1) FIX ; EXP V1_V2_WT
(0,0.75) ; Q_WT_EXP

$OMEGA BLOCK(2)
0.0822 ; CL ETA 1
-0.0313 ; COVAR ET1-ET2,
0.67 ; V2 ETA 2

$OMEGA
0 FIX ;V1 ETA 3
0 FIX ;Q ETA 4

$ERROR

IPRED=0
IF(F.GT.0) IPRED = LOG(F)

IRES = DV - IPRED
W = F
IF(W.EQ.0) W = 1
IWRES = IRES/W

Y = IPRED+ERR(1) ;
```

```
$SIGMA
0.0788 ; PROP ERR IN LOGDOMAIN

$ESTIMATION METHOD=1 INTER MAXEVAL=9999 POSTHOC ;
$COVARIANCE PRINT=E ;
$TABLE ESAMPLE=10000 ID TIME IPRED IWRES CWRES AMT TVCL CL TVV1 V1 TVQ
Q TVV2 V2 ET1 ET2 ET3 ET4 NPDE MDV BLQ LLOQ CREAT_RATIO HT WT LBW_AS
LBW_P BSA WTAGE WTEXS BMI GRP AGED AGEG SEX RACE RRT ICU HOSP TIM0 TAD
CREAT CREAT_FIRST CREAT_BL SCHW SCHW_GRP SCHW_FIRST SCHW_di SCHW_di_
FIRST SCHW_BL SCHW_BL_di SCHW_SL SCHW_di_SL CREAT_IMP NEUT NPEN RIFLE
NEPHROTOX NPENE CRP LYMPH NOPRINT ONEHEADER
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Part IV



Main findings, considerations and perspectives





8



Shaping the landscape for renally cleared antibiotics in obesity: main findings, considerations and perspectives

MAIN FINDINGS

Although it is well known that (patho)physiological changes in obese patients can influence the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs implying adjusted doses, there is still a need for specific dose guidelines for many classes of drugs [1]. This is exemplified by aminoglycosides (such as gentamicin or tobramycin) and vancomycin, which are renally cleared antibiotics that are commonly used for severe bloodstream infections. Despite being rather old drugs, discovered during the 'Golden Age' of antibiotic discovery in the 1950's and 1960's, there is still much debate on how these drugs should be dosed in real-world (morbidly) obese patients, and specifically how clearance or volume of distribution are influenced by a combination of excessive overweight, renal impairment and/or critical illness in this population. Specifically in children, maturation of renal clearance processes are an additional factor influencing the pharmacokinetics. Gaining more quantitative knowledge on these influences is of utmost importance since the efficacy of these drugs closely relates to blood concentrations and therefore should be dosed sufficiently high [2,3]. On the other hand, aminoglycosides and vancomycin are known to be nephrotoxic when blood concentrations surpass a certain toxic threshold [4,5]. Knowledge on the pharmacokinetics in these vulnerable populations is of eminent importance to safeguard adequate therapy. However, given the lack of high-quality evidence on the changes in pharmacokinetics of these drugs in the (morbidly) obese population, both in adults and children, we still remain in the dark as to how the gentamicin, tobramycin or vancomycin dose should be adapted in (morbidly) obese individuals with or without renal dysfunction and critical illness. This exposes this population to an increased risk of either underdosing, and therefore less effective treatment of severe infections, or overdosing, leading to more toxicity. In this thesis we aimed to characterize the pharmacokinetics of gentamicin, tobramycin and vancomycin in morbidly obese patients and to provide practical dose recommendations that lead to an effective and safe antibiotic treatment for obese children, adolescents and adults.

As an introduction, in **Chapter 2**, we presented a comprehensive overview of the (patho) physiological changes that occur with obesity, and how these changes may influence the pharmacokinetics and pharmacodynamics of drugs. Additionally, body size descriptors that are commonly used to guide drug dosing were discussed. Although this topic has been increasingly studied over the recent years, we identified several gaps in our current knowledge, particularly regarding the influence of obesity on drug absorption and clearance, both major pharmacokinetic parameters driving exposure. An example of such a knowledge gap is the influence of obesity on hepatically cleared drugs. Although it is known that inflammatory processes associated with obesity may hamper CYP3A4 activity, clearance of the CYP3A4-metabolized drug midazolam was shown not to be decreased in obese individuals. This result may be explained by the different influence of obesity on the parameters that determine a

drug's clearance (liver blood flow and intrinsic clearance), with increases in one parameter (liver flow) being compensated by decreases in the other (intrinsic clearance). A second example is the obesity-related change in renal clearance. While glomerular filtration rate (GFR) in general appears to increase with obesity, this does not necessarily mean that all renally excreted drugs have a higher clearance in obesity, which we exemplified in Chapter 2 with data from cefazoline and fluconazole. Moreover, over time, renal function might actually decrease, since obesity is also an important risk factor for developing chronic kidney disease. Additionally, many renally excreted drugs also undergo active tubular secretion which might be separately influenced by obesity. We identified an urgent need for more studies that further unveil the exact influence of obesity on renal clearance. Lastly, we discussed in Chapter 2 the common assumption that drug distribution can be well predicted using a drug's lipophilic properties with lipophilic drugs diffusing into adipose tissue more easily. We have presented several examples from the literature that show that not all drugs behave accordingly, as drug properties other than lipophilicity play a role in drug distribution.

In the next chapters, we studied the pharmacokinetics of several renally cleared antibiotics, i.e. gentamicin, tobramycin and vancomycin, in non-obese and (morbidly) obese adult but otherwise healthy individuals. In **Chapter 3**, we characterized the pharmacokinetics of gentamicin across body weights using a prospective rich sampling study design where we included morbidly obese patients undergoing bariatric surgery (n = 20) with body weights up to 221 kg and non-obese healthy volunteers (n = 8). We found that total body weight (TBW) predicted gentamicin clearance (using a power equation with exponent 0.73) and volume of distribution of the central compartment (using a power equation with exponent 1.25). To obtain similar exposure across body weights in this population with a normal renal function, we presented a dose nomogram based on a 'dose weight', calculated as $70 \times (TBW/70)^{0.73}$.

In **Chapter 4,** we studied the pharmacokinetics of tobramycin in both morbidly obese individuals undergoing bariatric surgery (n = 20) and non-obese healthy volunteers (n = 8). We found that with body weights up to 194 kg, volume of distribution increases linearly with body weight. In contrast to gentamicin, we found that tobramycin clearance could be best predicted by a serum creatinine-based renal function estimate, namely de-indexed Modification of Diet in Renal Disease (MDRD), expressed in ml/min. Although by de-indexation body weight is indirectly introduced in this covariate through body surface area, this result points out that TBW is less predictive for tobramycin clearance than for gentamicin clearance in the obese population with normal renal function. For gentamicin, we found no significant relation between renal function and clearance. This might be explained by subtle differences in renal clearance routes. We proposed a hypothesis that gentamicin clearance, compared to tobramycin, might be more relying on OCT2-mediated active renal transport. OCT2 appears to be induced by body weight in obesity, based on data from both a preclinical obese mouse model [6] and human

clinical studies with metformin, a known OCT2 substrate [7]. Also, tobramycin was reported to accumulate less in the kidney and therefore is potentially less nephrotoxic, indicating less dependency upon OCT2-mediated renal uptake [8]. Since this hypothesis has not been properly studied so far, further research is warranted to clarify these differences between tobramycin and gentamicin. At the end of chapter 5, we have presented a dose nomogram based on de-indexed MDRD that is expected to result in similar, less variable exposure in (morbidly) obese individuals with normal renal function compared to lean individuals receiving the standard dose of 5 mg/kg TBW.

In **Chapter 5** we studied the glycopeptide antibiotic vancomycin. In a prospective pharmacokinetic study in morbidly obese patients undergoing bariatric surgery (n = 20) and non-obese healthy volunteers (n = 8), with body weights from 60 – 235 kg, we found that vancomycin clearance increased with body weight following the equation CL = 5.72 x $(TBW/70)^{0.535}$. In a three-compartment model, volume of distribution of the second compartment (V2) increased with linearly with body weight, whereas age also had a small influence on the central compartment (V1) and V2. This model was externally validated using earlier published data from six obese and four non-obese individuals [9]. Using Monte Carlo simulations we showed that we could maximize the portion of individuals within the target exposure (24-h area under the curve (AUC_{24h}) of 400 – 700 mg*h/L) by dosing 35 mg/kg/day (maximized at 5500 mg/day). The FDA drug label fixed dose of 1000 mg twice daily [10] leads to unacceptable underexposure while another often recommended dosage of 45 mg/kg/day [3] leads to an unacceptable risk of toxicity. In addition, to aid in therapeutic drug monitoring (TDM) in obese patients, our study showed that for obese patients, a target AUC_{24h} of 400 – 700 mg*h/L corresponds to steady state trough concentrations between 5.7 – 14.6 mg/L. This is much lower than what is recommended as a target trough concentration in leading guidelines (15 – 20 mg/L) [3]. Therefore, clinicians should be aware that in obese individuals, below target trough concentrations do not necessarily correspond with subtherapeutic exposure and as such we advise to estimate the individual's AUC using TDM with Bayesian forecasting software.

In the previous chapters, the influence of weight was characterised while keeping other covariates such as renal function within normal limits. Thereto, these studies were done with individuals who were obese, but otherwise relatively healthy. Yet, obesity is not the sole factor introducing variability in clearance and volume of distribution. For the studied drugs it is known that both renal function and critical illness are important determinants for clearance in non-obese adults. For this reason, in **Chapter 6** we further characterized the pharmacokinetics of gentamicin by combining the prospectively collected data in obese and non-obese individuals with a large retrospectively collected dataset derived from (critically ill) obese individuals with and without impaired renal function (n = 542). Here we found

that a combination of TBW and renal function (estimated using the serum creatinine based Chronic Kidney Disease Epidemiology equation [CKD-EPI]) could well describe the changes in gentamicin clearance in the real-world population. These two covariates were combined in the de-indexed CKD-EPI, which equals CKD-EPI (expressed as ml/min/1.73 m^2) multiplied by body surface area (BSA)/1.73. Additionally, we found that patients admitted to the ICU had an almost 25% lower clearance, independent of renal function. With some other studies also reporting critical illness as a separate predictor for gentamicin clearance [11,12], this finding might be a result of serum creatinine lagging behind as marker for renal impairment. Using the final model, which was externally validated in a second dataset with similar patient characteristics (n = 208), we designed an easy-to-use dose nomogram for obese individuals that incorporated both body weight and renal function. In this nomogram, a mg/kg dose should be reduced with decreasing CKD-EPI values, and the dosing interval extended beyond 24h when CKD-EPI drops below 50 ml/min/1.73 m^2. Earlier, in Chapter 4, we proposed a dose nomogram for tobramycin on basis of a study in obese adults with a normal renal function, that uses de-indexed MDRD. Figure 1 illustrates that this nomogram results in similar doses compared to the dose nomogram we propose for gentamicin in Chapter 6 that uses CDK-EPI and body weight, with the exception of a subgroup of patients with CKD-EPI <50 ml/min/1.73 m^2. This particular group of patients with renal impairment was not included in the tobramycin study. As such, it appears feasible to use an overarching model and dosing guideline incorporating both weight and renal function like the one presented in Chapter 6 to predict exposure of tobramycin and gentamicin as exemplified in Figure 1. Such a combined approach remains to be validated for tobramycin but seems a practical uniform tactic.

In the second real-world study, **Chapter 7** describes the results of a pharmacokinetic study on vancomycin in a large obese and non-obese paediatric population consisting of 1892 children and adolescents aged 1 – 18 years. We extracted data on vancomycin administrations, serum concentrations and covariates from 21 hospitals in the Utah area in the USA. The dataset consisted of both a wide age range, as well as a large distribution of overweight (body weight up to 188 kg, with 13% and 16% of patients being overweight and obese, respectively) and renal function (lowest estimated creatinine clearance 8.6 ml/min/1.73 m^2). Moreover, the range in sampling time after dose varied largely which provides optimal information for population pharmacokinetic modelling. In this population, vancomycin clearance could be predicted using a relatively simple covariate model with body weight and renal function, depicted by the bedside Schwartz formula (SCHW): $CL = 2.12 \times (TBW/22.1)^{0.745} \times (SCHW/100)$. This model outperformed more sophisticated models such as one that separately characterizes the influence of weight for age and weight excess or one that employs a body size dependent exponent for the influence of body weight that accounts for maturation. Such a body size dependent exponent model was originally developed to be able to distinguish between the influence of increasing weight resulting from growth and maturation versus the influence of

weight from obesity. Ultimately, we proposed a straightforward dose regimen that bridges the existing IDSA recommendations for non-obese children (15 mg/kg four times daily without specific recommendations for obesity or renal function) and the in Chapter 5 proposed dosing strategy for obese adults, with adaptions for renal impairment and overweight. Using this dosing strategy, we demonstrated that on target exposure on day 3 (AUC_{24h} between 400 and 700 mg*h/L) can be expected throughout the entire population for any given weight and renal function. One limitation in the study was the relatively low number of included individuals with a renal function <30 ml/min/1.73 m^2 (n = 12). As such, extra caution should be put in place when our dose recommendations are used in this paediatric subpopulation. Similar to what we found in the adult population, we noticed that there is large variability in obtained vancomycin trough concentrations, with trough concentrations varying between 6.9 – 21.5 mg/L in several typical individuals, despite being within the exposure (AUC_{24h}) target. This again underlines estimation of the patient's vancomycin AUC using a limited sampling strategy in conjunction with Bayesian forecasting software as a preferred method above targeting trough concentrations.

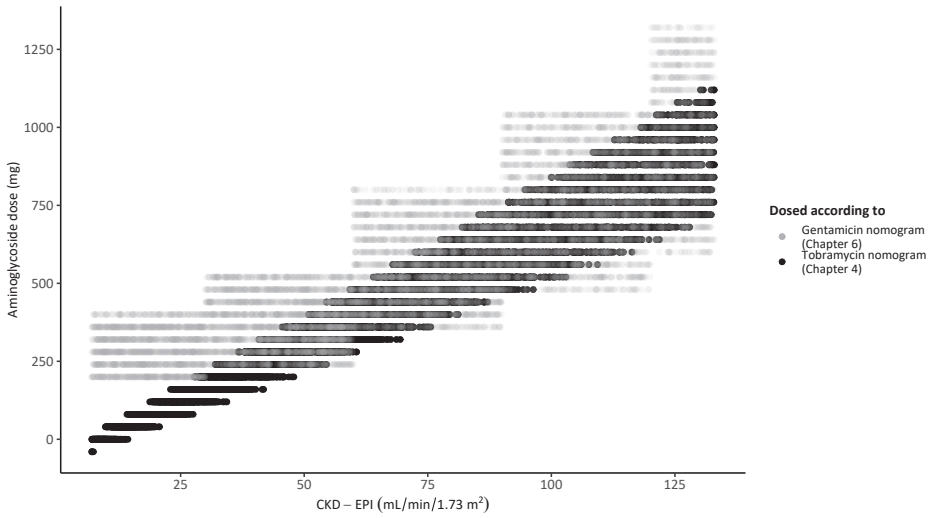


Figure 1. Comparison of the aminoglycoside dose (rounded to nearest multiple of 40 mg) versus CKD-EPI (in ml/min/1.73 m^2) according to the dose nomogram proposed for gentamicin based on the study in a real world population in Chapter 6 (with doses based on CKD-EPI and body weight) and according to the dose nomogram proposed for tobramycin in obese individuals in Chapter 4 (with dose based on de-indexed MDRD). Each dot represents one individual. The population consists of 10.000 subjects with body weights from 100 – 220 kg, with randomly assigned CKD-EPI values varying from 7 – 133 ml/min/1.73 m^2. For the tobramycin nomogram, we assumed that each individual's MDRD was the same as the CKD-EPI, after which this was de-indexed by multiplying by BSA/1.73. For calculating each BSA, height was imputed as 180 cm (for males) or 167 cm (for females) and gender allocated randomly. *CKD-EPI* Chronic Kidney Disease Epidemiology equation.

CONSIDERATIONS AND PERSPECTIVES

In this section we will discuss the results that were obtained in this thesis from a broader perspective. First, we will reflect on the methodological approach that we chose for our studies. Second, we will evaluate what the results can teach us on how pharmacokinetics change in the obese population, with a focus on the prediction of volume of distribution and clearance in obese individuals. Lastly, we will discuss how the clinical use of the obtained knowledge can be maximized.

METHODOLOGICAL APPROACH

To get to dose recommendations for obese patients in the 'real-world' or daily clinical practice, we first characterized the influence of obesity using a prospective, rich sampling pharmacokinetic study design in non-obese and (morbidly) obese, but otherwise healthy individuals without severe organ dysfunction. The (morbidly) obese individuals were included during their admission for a bariatric operation (Chapters 3,4 and 5). Next, we conducted an extension study in real-world patients combining the prospective data with retrospectively collected data from clinical patients with and without renal dysfunction or critical illness (gentamicin, Chapter 6). In the past, pharmacokinetic studies were conducted either in a prospective, rich sampling design in obese healthy volunteers [13], or by means of a retrospective, sparse (therapeutic drug monitoring) design with peak and trough concentrations only [14]. Our approach combines both designs, which has several benefits. First, the prospective design in obese healthy individuals provides us with the opportunity to include patients with a wide range of body weights, with weights varying between 53 and 235 kg in the studies presented in this thesis. Besides being obese, participants were otherwise healthy and as such, by keeping all other variables like renal function or critical illness constant except weight, this allowed us to specifically characterize the influence of body weight on drug pharmacokinetics. Second, because of the planned surgery, the obese study participants are all admitted to the hospital for at least two days, receive a venous catheter and are monitored closely during the admission. As such, we can limit the study related burden for participants. The impact of surgery on PK is considered negligible as surgery is performed laparoscopically in a short procedure (around 45 minutes) with minimal blood loss (usually <50 mL). Third, over the years we have established a consortium of closely collaborating departments involved in these studies (surgery, anesthesiology and clinical pharmacy). This strongly increases the feasibility of conducting such studies. The biggest benefit of our approach however comes from combining the prospective, rich data from healthy obese volunteers with TDM data collected in the real-world clinical setting. This is a valuable model development strategy, since it provides us with the opportunity to simultaneously study a wide variety of covariates: In prospectively

collected data in obese healthy individuals there is a large variability in body weight as a result of the study design, while in the retrospectively collected TDM data, there is usually a large variability in covariates such as renal function and critical illness. Both datasets separately would most likely not have sufficient information to develop a robust pharmacokinetic model and dose recommendations. Similar efforts to extent the developed models for tobramycin and vancomycin in real-world clinical obese populations are currently under way.

PREDICTABILITY OF VOLUME OF DISTRIBUTION IN OBESE INDIVIDUALS

For all drugs studied within this thesis (gentamicin, tobramycin and vancomycin) we have separately identified total body weight as the most predictive covariate for volume of distribution. As discussed in Chapter 2, it is often assumed that a drug's lipophilicity or hydrophilicity determines how and whether the volume of distribution changes. All three studied drugs are considered hydrophilic (Log P values of -3.1 (gentamicin), -5.8 (tobramycin) and -3.1 (vancomycin) [15]), so one might expect that obesity may not influence the volume of distribution. Our results show that volume of distribution for these drugs increases linearly with TBW, following the equation $CL = CL_{70kg} \times (TBW/70)$, where CL_{70kg} is the typical clearance for an individual weighing 70 kg. In Chapter 3, where we studied the pharmacokinetics of gentamicin in obese and non-obese healthy individuals, we identified a model where the factor TBW/70 was scaled with an exponent of 1.25. However, in the extension study to real-world patients (Chapter 6), a model with an exponent fixed to 1 led to the best fit. This points towards a similar drug penetration into adipose tissue as in normal, lean tissue. Although other explanations for this linear increase of volume of distribution such as alterations in protein or tissue binding cannot be excluded, these are less likely given the low protein binding of the studied drugs [16,17]. Our findings are in line with what has been reported for several other drugs and has been described by Jain et al. in a review paper on this topic [18]. For example, the highly lipophilic anaesthetic propofol, shows no change in volume of distribution in obese individuals, while the volume of distribution of similarly lipophilic drugs such as midazolam or diazepam strongly increase with increasing body weight [19–21]. In conclusion, our results show that alterations in volume of distribution in obesity cannot be predicted by lipophilicity alone.

BODY SIZE DESCRIPTORS FOR PREDICTING DRUG CLEARANCE IN THE OBESE POPULATION

Over the years, many researchers have tried to identify an optimal body size descriptor as an alternative for total body weight to guide drug dosing in obesity. One reason to investigate alternative body size descriptors is that drug excretion may be correlated with lean tissue as adipose tissue may be considered 'inactive', and therefore might not increase linearly with total body weight [22]. Several body size descriptors have been described for specific drugs or drug categories, for example pharmacokinetic mass (PM) for fentanyl [23] and adjusted body weight (ABW) for aminoglycosides [24]. Ideal body weight (IBW) is often recommended for drugs that show no change in pharmacokinetics in obese individuals compared to non-obese individuals, as has been found for certain muscle relaxants [25]. BSA is predominantly used in chemotherapy, for non-obese as well as obese patients [26]. Since the introduction of this spectrum of body size descriptors, several efforts have been undertaken in determining a *universal* body size descriptor that predicts pharmacokinetics in obesity regardless of the drug at hand. The most important candidate in this light is Lean Body Weight (LBW), as described by Janmahasatian et al. in 2005 [22,27,28]. This body size descriptor predicts the Fat Free Mass (FFM) using a complex formula including TBW, height and gender [27]. Technically, FFM consists of all body tissue without fat, where LBW in its original meaning comprises all lean tissue (organs, blood, water), including a small portion of fatty tissue in the organs [29]. Since this portion is very small (less than 5% [29]), it is generally accepted that LBW and FFM are used interchangeably in drug pharmacokinetics.

Several papers have advocated the use of LBW as body size descriptor for predicting drug clearance in obese individuals [22,28]. The basis for using LBW was given by a study in 2008, where in 17 individuals (9 obese and 8 lean) with normal renal function, GFR normalized for LBW was found to be similar between obese and non-obese individuals, although a trend towards a lower normalized clearance was visible in the obese group [30]. The theoretical concept here is that the mass of organs involved in drug clearance (kidney's and liver) is better represented by LBW than TBW. Indeed, LBW was found to be a better predictor compared to TBW for clearance of acetaminophen, a hepatically cleared drug in 28 obese and non-obese patients [31]. In contrast, in this thesis we show that there are no large differences between LBW or TBW for predicting vancomycin clearance (Chapter 5), or in the case of gentamicin, TBW even outperformed LBW in predicted clearance in obese patients with a normal renal function (Chapter 4). This shows that LBW cannot be used as a *universal* body size descriptor for drug clearance. In addition, our results pointed out some features of LBW that are crucial when LBW is used as a covariate in a pharmacometrics analysis or as a basis for drug dosing. In this section, we will address these aspects of LBW in more detail.

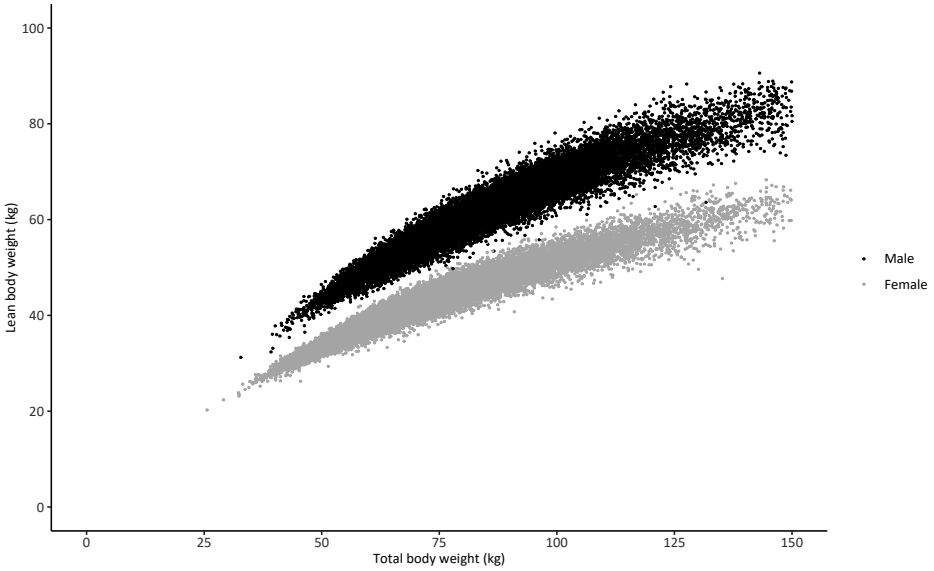


Figure 2. Lean body weight (kg) versus total body weight (kg) derived from data from the NHANES dataset [32] coloured by gender (males as black dots, females as grey dots, n = 48.348).

One of the variables in the LBW-equation as proposed by Janmahasatian et al. is gender [27]. To illustrate the large impact of gender on LBW, we show the LBW in Figure 2 for 48.348 individuals derived from the National Health and Nutrition Examination Survey (NHANES) database, which is a large database consisting of representative data from adults from the USA gathered between 1999 to 2016 [32]. As can be seen in the figure, LBW is approximately 25% lower in females compared with males. This has some major implications for drug dosing: when dosed on LBW, females receive lower doses as compared to males with the same body weight, which is especially of relevance for obese individuals. For example, it was demonstrated in Chapter 3 that for obese individuals >100 kg, a gentamicin dose of 8 mg/kg LBW results in similar exposure compared to the proposed dose nomogram with TBW as basis (3.5 – 5 mg/kg TBW) for the whole population (Chapter 3, Figure 4). However, when these results are split by gender, large differences can be observed, with females receiving 8 mg/kg LBW having considerably lower exposure compared to males receiving 8 mg/kg LBW (Figure 3).

From the observations illustrated in Figure 3, it can be concluded that the use of LBW for dosing may have important implications for the exposure in males versus females. Therefore, close inspection of gender differences is important when investigating LBW as a covariate. Typically, when screening for a possible influence of covariates, the first step is to inspect the individual (post-hoc) clearances versus covariate plots. In order to further illustrate the relevance of gender in covariate model building with LBW, plots for drug clearance versus

TBW and LBW are shown in Figure 4 for the studies from Chapters 3 and 5 (gentamicin and vancomycin, respectively) and for the earlier mentioned study with acetaminophen (data derived from the study by Van Rongen et al. [31]). In this figure, it is visible that for gentamicin, TBW outperforms LBW in predicting clearance, whereas for acetaminophen LBW shows a better fit than TBW. More specifically, for gentamicin, when using LBW (Figure 4a) obese females and males of the same LBW have substantially different clearance values, whereas for TBW (Figure 4b), male and female individuals of the same TBW have similar clearances. In other words, when using LBW (Figure 4a), two parallel lines can be identified, one of females and one for males, implying that when using LBW, gender is another covariate. In contrast, the acetaminophen data illustrate that for individuals with the same TBW (Figure 4f), gender is an additional factor influencing acetaminophen clearance. This is resolved when using LBW and as such, it is for acetaminophen justified to use LBW as a covariate. These differences between TBW and LBW are less clear for vancomycin (Figure 4c and 4d), where both covariates result in a similar goodness-of-fit and objective function value. Upon close inspection, it is visible that around a LBW of 50 – 75 kg, introduction of LBW might result in a gender difference, as obese females still show a lower clearance compared to non-obese males (with the same TBW), albeit not as clearly as seen for gentamicin. There are insufficient data points to state this with certainty. For now, this might be a reason to not include LBW in the vancomycin model, although there were no large differences between LBW and TBW with regard to OFV and goodness-of-fit. This demonstrates the added value of critically assessing covariate plots, such as those presented in Figure 4 and inter-individual variability-versus-gender plots made before and after introduction of LBW as a covariate. These findings also show that the importance of including both genders with a sufficient range in bodyweights in a pharmacokinetic study when investigating LBW as a possible covariate.

To conclude, there is insufficient evidence to use LBW as a *universal* body size descriptor to predict drug clearance in obese individuals. Additionally, the importance of gender when investigating LBW as a covariate in pharmacokinetics in general deserves more attention. It is important to realize that when a drug is dosed using LBW, females receive a lower dose compared to males with the same body weight, increasing the risk of underexposure in females, or overexposure in males. We have shown that, depending on the drug, this may occur (gentamicin) or not (acetaminophen), where we demonstrate the importance of assessing covariate plots such as shown in Figure 4.

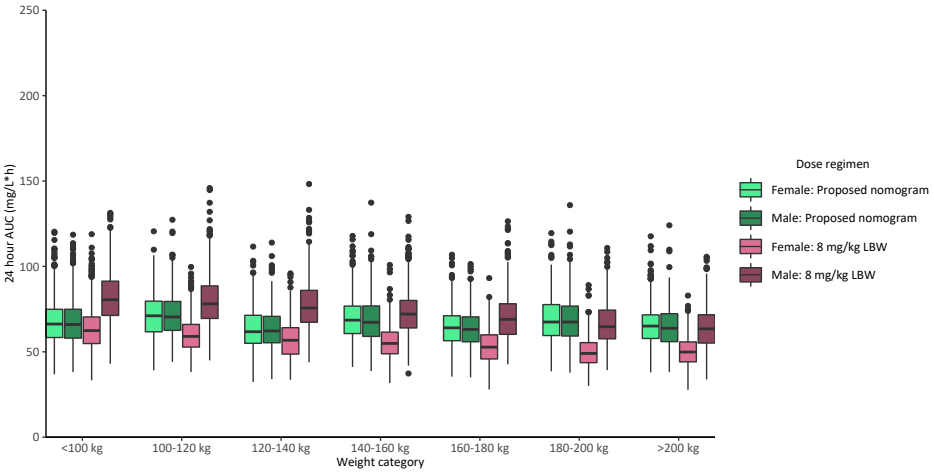


Figure 3. Boxplots (median and 95% confidence interval) representing gentamicin AUC_{24} for different weight categories upon the proposed nomogram (based on a 'dose weight' calculated as $70 \times (TBW/70)^{0.73}$, Chapter 3) (green) or 8 mg/kg LBW (red) on the basis of the pharmacokinetic model as presented in Chapter 3, split for gender (females and males light and dark, respectively). Results are based on Monte-Carlo simulations (n = 10.000 subjects per dose regimen with weight ranging 50 – 215 kg), similar to Figure 4 in Chapter 3. *LBW* lean body weight, *TBW* total body weight.

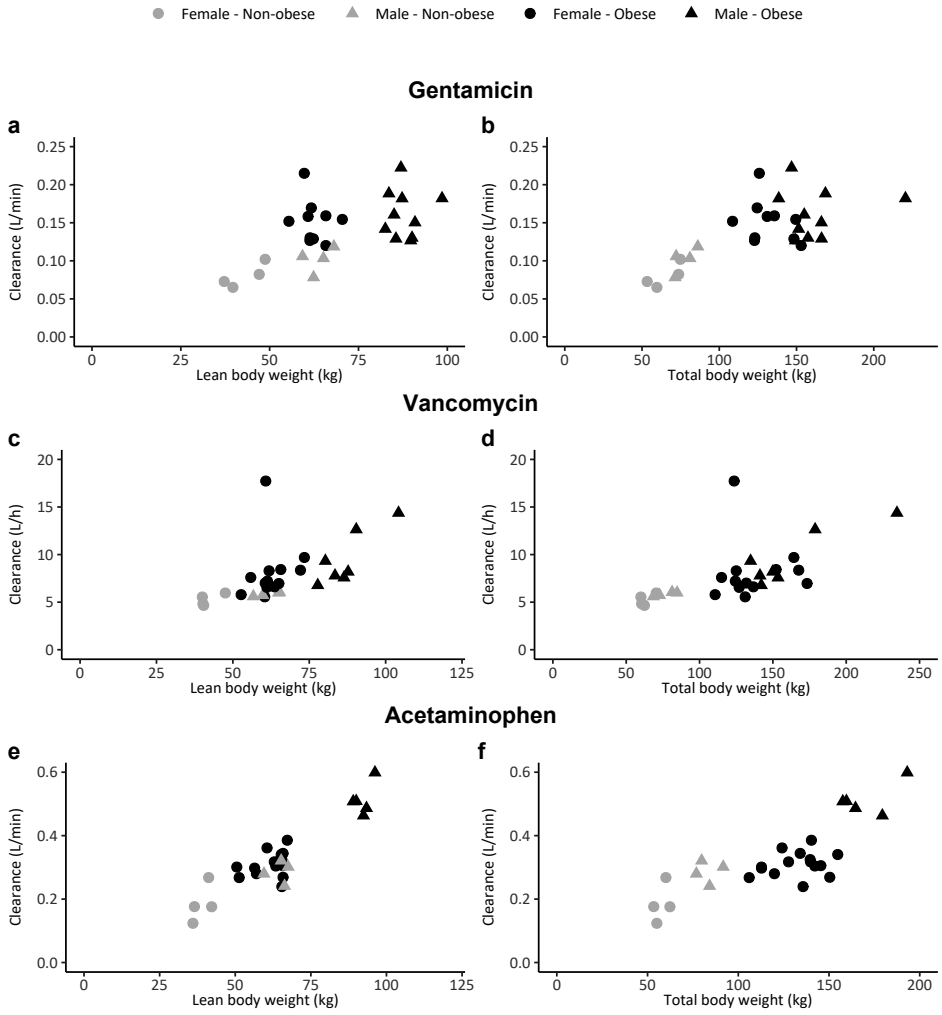


Figure 4. Clearance of gentamicin (Chapter 3), vancomycin (Chapter 5) or acetaminophen (data obtained by Van Rongen et al. [31], with permission) versus lean body weight (a, c, e) or total body weight (b, d, f) for non-obese (grey figures) and morbidly obese individuals (black figures). Females and males are shown in circles and triangles, respectively.

PREDICTING DRUG CLEARANCE OF RENALLY CLEARED DRUGS IN OBESE ADULTS

In clinical practice, assessment of renal function is usually done by estimating glomerular filtration rate (GFR) using serum creatinine-based estimations such as the MDRD [33], CKD-EPI [34] or, in children, the Schwartz equation [35]. These equations produce an estimate of GFR indexed for a standard BSA of 1.73 m^2 to allow for comparison between individuals. In contrast to lean individuals, where this 'indexed' and de-indexed (or absolute) measurements of GFR are not very different [36], indexation in the obese population leads to a significant underestimation of the 'true' value (measured using an isotopic method) [36]. The Cockcroft-Gault (CG) formula, which strictly speaking estimates creatinine clearance instead of GFR, is commonly used in the USA to guide drug dosing. This equation uses total body weight and is expressed as absolute clearance in ml/min, in contrast to CKD-EPI and MDRD. However, also CG was originally developed in a lean population, and was reported to overestimate GFR in obese individuals [37,38]. Over the years, there has been much debate what might be the most accurate method for estimation of renal function in the obese population. Some have advocated de-indexing MDRD or CKD-EPI equations [39–41], while others propose to use CG with a different body size descriptor such as LBW [37,42]. The latter seems the most rational, since serum creatinine is primarily related to muscle mass which, in obesity, might be best described by LBW [30].

Another approach to estimate GFR in obese individuals is by assessing clearance of renally excreted drugs, which is an approach that has been applied before in children and critically ill adults [43–45]. However, many renally excreted drugs are not only cleared trough glomerular filtration, but also undergo active tubular secretion. It is likely that tubular processes are also to a certain extent involved for gentamicin, tobramycin and vancomycin. Therefore, the best method for estimating GFR in the obese may or may not be by estimating clearance of these drugs. Vice-versa, it is not necessarily the 'best' predictor for estimating GFR that can best predict drug clearance in obesity. For this reason, we chose an empirical approach in this thesis for estimating the drug clearance, which is to evaluate several methods, such as using MDRD or CKD-EPI with de-indexation, CG with LBW or by using the measured 24-hour creatinine clearance.

We found for tobramycin (Chapter 5) and gentamicin (Chapter 6) that de-indexed MDRD or CKD outperformed their non-indexed counterparts or the CG equation with LBW. Although CG with LBW might be a good predictor for GFR in obese individuals [37,42], this shows that it is the best predictor for clearance in the renally cleared drugs studied here. One explanation could be that drug clearance might be larger than GFR due to active (renal) processes that are influenced by body weight and resembles the BSA-correction in

de-indexation of MDRD or CKD. This is the most pronounced for gentamicin, based on the fact that for this drug, we found body weight to be best predictive in obese individuals without renal impairment (Chapter 3), which is possibly due to a body weight dependent influence of the renal drug transporter OCT2. Interestingly, a better performance of MDRD or CKD-EPI over CG with LBW in predicting aminoglycoside clearance in an obese population was reported before [14]. In conclusion, the most suitable estimate for renal function to guide drug dosing of renally excreted drugs in obese individuals seems dependent on the drug's particular renal clearance route (passive and/or active). Although we have undertaken the first steps in this thesis in clarifying how the renal clearance route exactly translates to changes in drug clearance with obesity this needs to be further clarified in future studies.

MODEL INFORMED PRECISION DOSING: IMPLEMENTATION OF PHARMACOKINETIC MODELS IN CLINICAL PRACTICE

In this thesis, we characterized the pharmacokinetics of gentamicin, tobramycin and vancomycin in non-obese and morbidly obese healthy volunteers and, for gentamicin and vancomycin, have extended these results to clinical populations of obese adult patients (gentamicin) or obese children and adolescents (vancomycin), with and without renal impairment. With the developed pharmacokinetic models, we have established dose recommendations that can be implemented in daily practice. The next step is the use of this information to support precision dosing in daily clinical practice, a concept known as model-informed precision dosing (MIPD). Recently, an interesting overview of the lessons learned from over 50 years of MIPD was published by many key opinion leaders [46]. In this paper, several challenges regarding adoption of MIPD in healthcare were identified, of which some can be considered relevant for the models developed in this thesis. Here, we will discuss how integration of the results of this thesis in MIPD can be facilitated, what steps were done and where we should focus on in the future.

Within a MIPD framework, the developed pharmacokinetic models can be directly used in daily clinical practice. In this setting, information from real-time monitoring, for example via TDM, is used in conjunction with a population pharmacokinetic model to estimate or forecast individual PK parameters (mostly using Bayesian statistical methods) and aid in optimizing the dose for the individual patient [46]. To facilitate the use of our models in this way, we have collaborated with the developers of the software package MwPharm++ (Mediware a.s, Prague, Czech Republic), to readily include the developed population pharmacokinetic models

in their software. This software package is widely used for MIPD, especially in The Netherlands. However, by publication of the raw model structure in international, peer-reviewed journals, we have ensured that virtually any MIPD software package can implement the developed population PK models.

Another aspects that aids the adoption of the models is an external validation of our results. This means that the predictive performance of the models are tested in a population sample different than the one used for model development and is considered imperative in light of rigor and reproducible science [46]. In this thesis, we have used different sources of data for an external validation. For vancomycin, we have included an external validation using previously published raw data from a different obese population (Chapter 5) [9]. For gentamicin, the performance of the developed model was validated using independent data from a similar population provided by a second hospital (Chapter 6). These validations further strengthen confidence in the obtained results and dose recommendations. For the tobramycin (Chapter 4) and vancomycin (Chapter 5) models, external validations are currently in preparation. An important remark here is that while an external validation is important, dose recommendations or models based on well-designed PK studies that show a substantial, clinically relevant covariate effect but lack an external validation, should still be implemented in clinical practice.

A crucial step in the implementation of study results is the integration of the dose recommendations in leading guidelines. To facilitate this, we have closely collaborated with associations that are responsible for developing guidelines since the first stages of study design. These include the Royal Dutch Society for Pharmacy (KNMP), the Dutch Working Party on Antibiotic Policy (SWAB) and the Dutch Society of Hospital Pharmacists (NVZA). After publication of the results in international peer reviewed journals, the dose recommendations for gentamicin, tobramycin and vancomycin for the adult obese patients have been implemented in the *Informatorium Medicamentorum*, a major knowledge database under redaction of the KNMP which forms the primary source for drug dosing information and medication monitoring for Dutch (hospital) pharmacists and general practitioners. Additional implementation of our recommendations in other leading national and international guidelines will remain a priority in the nearby future.

CONCLUSIONS

The prevalence of obesity in adults and children has dramatically increased over the last decades. It is known that obesity can significantly alter pharmacokinetics of many drugs and as clinicians will increasingly be treating obese patients with antibiotic therapy, we have tried to close some knowledge gaps that exist regarding the pharmacokinetics of three frequently used antibiotics in the obese population. For these drugs, namely gentamicin, tobramycin and vancomycin, we have developed population pharmacokinetic models and proposed straightforward dose recommendations to be used in the obese population. For gentamicin and vancomycin, we have extended these dose recommendations towards the clinical, real-world population of obese adult (gentamicin) and paediatric and adolescent (vancomycin) patients with and without renal impairment.

With the work presented in this thesis we show that the pharmacokinetics of these antibiotics are significantly impacted by obesity. For gentamicin, which we studied in both non-obese, healthy and hospitalized obese individuals with and without renal impairment, we found that clearance increased with body weight and renal function (combined using de-indexed CKD-EPI), and was lower in patients admitted to the ICU. Tobramycin clearance correlated strongest with de-indexed MDRD in (morbidly) obese healthy volunteers with normal renal function. Compared to gentamicin, body weight seems to be of a lesser impact on tobramycin clearance, since we could not identify total body weight as a covariate for clearance in the tobramycin study. The pharmacokinetics of vancomycin were characterized in two special populations, namely morbidly obese and non-obese adults (with normal renal function), and second in lean, overweight and obese hospitalized children and adolescents aged 1 – 18 year with and without renal impairment. For both populations we found that clearance can be predicted using a combination of body weight and renal function. For all studied drugs, volume of distribution consequently increased linearly with total body weight.

Based on these studies we have designed several straightforward dose recommendations to be used in the obese adult, paediatric and adolescent populations. In addition, the studies from this thesis have provided us with some insights regarding pharmacokinetics in obesity. First, our results showed that volume of distribution of the three drugs increases linearly with TBW, which points towards a similar contribution of adipose tissue and lean tissue to drug distribution. Considering that all studied drugs are hydrophilic, our results showed that alterations in volume of distribution in obesity cannot be predicted by lipophilicity alone. Secondly, we discussed the importance of gender when using lean body weight (LBW) as a covariate in pharmacokinetic analyses or as a basis for drug dosing. Thirdly, we have shown that the methods that appear suitable in estimating glomerular filtration in obesity, such as the Cockcroft-Gault equation with LBW, are not necessary the best predictors for clearance of renally cleared drugs.

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9



Dutch summary

Vormgeven van het landschap voor renaal uitgescheiden antibiotica in obesitas – onderzoek in volwassenen, adolescenten en kinderen

Sinds 1975 neemt de wereldwijde prevalentie van obesitas alarmerend toe [1]. Obesitas, een aandoening die door de Wereldgezondheidsorganisatie (WHO) wordt gedefinieerd als 'een excessieve ophoping van vetweefsel die de gezondheid kan beïnvloeden', wordt veelal gemeten door middel van de Body Mass Index [BMI]. Er is sprake van obesitas bij personen met een BMI ≥30 kg/m^2, terwijl morbide obesitas, als indicatie voor een bariatrische operatie, door de Nederlandse Vereniging van Heelkunde wordt gedefinieerd als een BMI ≥40 kg/m^2, dan wel ≥35 kg/m^2 in combinatie met ernstige, obesitas-gerelateerde aandoeningen [2,3]. In regio's als de Verenigde Staten, het Midden-Oosten of Noord-Afrika voldoet op dit moment meer dan 30% van de volwassen bevolking aan de criteria voor obesitas [1]. Wereldwijd hebben 1 op de 20 kinderen excessief overgewicht, terwijl dit 50 jaar geleden praktisch nog niet voor kwam [4]. In sommige regio's liggen deze cijfers echter nog hoger, zoals bijvoorbeeld in de Verenigde Staten waar op dit moment 1 op de 5 kinderen obesitas heeft [4].

Obesitas gaat gepaard met (patho)fysiologische veranderingen die de farmacokinetiek (PK) en farmacodynamiek (PD) van veel geneesmiddelen kan beïnvloeden. Dit betekent dat veel geneesmiddelen op een andere manier moeten worden gedoseerd bij deze patiëntengroep [5]. Een belangrijk voorbeeld van zulke geneesmiddelen zijn aminoglycosiden (zoals gentamicine of tobramycine) en vancomycine, renaal (via de nier) uitgescheiden geneesmiddelen die veel worden toegepast bij ernstige infecties, bijvoorbeeld van de bloedbaan of kunstmateriaal zoals een heupprothese. Hoewel dit oude geneesmiddelen zijn, op de markt gekomen tijdens de 'Gouden Eeuw' van het antibiotica-onderzoek in de jaren 50 en 60 van de 20^e eeuw, is er tot op de dag van vandaag veel discussie hoe deze geneesmiddelen gedoseerd moeten worden in de (morbide) obese patiënt. Kennis hierover is van groot belang omdat het bekend is dat de effectiviteit van deze geneesmiddelen nauw gerelateerd is aan de concentraties die in het bloed worden bereikt [6,7]. Daarnaast weten we dat aminoglycosiden en vancomycine nierschade kunnen geven wanneer de concentraties in het bloed een zekere drempelwaarde overschrijden [8,9]. Kennis van hoe specifieke farmacokinetische parameters zoals klaring en distributievolume worden beïnvloed door een combinatie van (excessief) overgewicht, nierfunctiestoornissen en kritische ziekte, een combinatie die we veelvuldig tegenkomen in deze populatie, is dus van groot belang. In het geval van kinderen speelt daarnaast nog de natuurlijke ontwikkeling van deze processen (maturatie) een belangrijke rol. Desondanks ontbreekt kwalitatief goed onderzoek naar dergelijke veranderingen van de farmacokinetiek in de (morbide) obese populatie, zowel in volwassenen als in kinderen. Dit vergroot het risico op onderdosering, en dus een minder effectieve behandeling van ernstige infecties, of juist overdosering, en zo een mogelijk schadelijke behandeling, voor (morbide) obese patiënten met en zonder nierfunctiestoornissen.

Dit proefschrift heeft als doel om de farmacokinetiek van gentamicine, tobramycine en vancomycine in morbide obese patiënten in combinatie met mogelijk andere relevantie patiëntkarakteristieken zoals nierfunctiestoornissen of (kritische) ziekte zoals we die in de echte wereld tegenkomen. Voor vancomycine beogen we daarnaast de invloed van overgewicht, nierfunctie en maturatie te onderzoeken in een klinische populatie van kinderen en adolescenten met en zonder overgewicht of nierfunctiestoornissen. De methodologie die we voor deze studies gebruiken is populatie farmacokinetiek, wat beschouwd wordt als een van de belangrijkste methodes om het gedrag van geneesmiddelen in het lichaam te kwantificeren en rationele doseerrichtlijnen te ontwikkelen [10]. Deze analysemethode maakt gebruik van wiskundige modellen (*non-linear mixed effects models*) om de relatie tussen een dosis van een geneesmiddel en de concentraties in bijvoorbeeld het bloed te beschrijven. Hierbij kunnen de invloeden van verschillende patiëntkenmerken zoals gewicht, leeftijd, geslacht of de nierfunctie op de parameters van deze modellen worden onderzocht. Met de opgedane kennis hopen we meer inzicht verkrijgen in de veranderingen van renaal geklaarde geneesmiddelen in obesitas en doseerrichtlijnen ontwikkelen voor (morbide) obese kinderen, adolescenten en volwassenen voor de bestudeerde geneesmiddelen.

Ter introductie, hebben we in **Hoofdstuk 2** van dit proefschrift een uitgebreid literatuuroverzicht gepresenteerd van de (patho)fysiologische veranderingen die samengaan met obesitas en hoe deze veranderingen de farmacokinetiek en farmacodynamiek van geneesmiddelen kan beïnvloeden. Hoewel er steeds meer onderzoek wordt gepubliceerd, zijn er nog steeds veel onduidelijkheden op dit gebied, met name met betrekking tot veranderingen in de opname en uitscheiding (klaring) van geneesmiddelen. Een voorbeeld hiervan is de groep van via de lever afgebroken geneesmiddelen, met als veelgebruikt voorbeeld het geneesmiddel midazolam. Midazolam wordt voornamelijk in de lever door het enzym CYP3A4 afgebroken. Hoewel bekend is dat de CYP3A4-activiteit verminderd is in obese personen, werd in studies geen verandering in de midazolam klaring waargenomen in morbide obese patiënten. Hoewel nog niet zeker is hoe dit verklaard kan worden, is een hypothese dat in obesitas een verminderde intrinsieke hepatische klaring kan worden gecompenseerd door een toegenomen doorbloeding van de lever. Ook met betrekking tot veranderingen in klaring van renaal uitgescheiden geneesmiddelen bestaan nog veel onduidelijkheden. Hoewel over het algemeen lijkt dat de glomerulaire filtratie snelheid (GFR) toeneemt in obesitas, geldt niet zonder meer dat klaring van renaal uitgescheiden geneesmiddelen toeneemt, zoals we in Hoofdstuk 2 laten zien met voorbeelden van cefazoline en fluconazol. Ook weten we nog weinig van de specifieke invloed van obesitas op actief geneesmiddeltransport in de nieren. Tot slot bespraken we in Hoofdstuk 2 het algemene idee dat het distributievolume van geneesmiddelen in obesitas kan worden voorspeld met de mate van vetoplosbaarheid van een geneesmiddel, waarbij aangenomen wordt dat een hogere vetoplosbaarheid resulteert

in betere penetratie in vetweefsel. We lieten enkele voorbeelden zien van geneesmiddelen die zich niet volgens dit principe gedragen, waarbij duidelijk is dat veranderingen in geneesmiddeldistributie bij obesitas complexer is dan veelal wordt aangenomen.

In de daaropvolgende volgende hoofdstukken hebben we de farmacokinetiek van enkele renaal geklaarde antibiotica, namelijk gentamicine, tobramycine en vancomycine in non-obese en (morbide) obese maar verder relatief gezonde volwassenen onderzocht. In **Hoofdstuk 3** brachten we de farmacokinetiek van gentamicine bij verschillende lichaamsgewichten in kaart door middel van een prospectieve, rijk gesampelde studie waarbij we morbide obese patiënten die een bariatrische operatie ondergingen (n = 20), met lichaamsgewichten tot 221 kg, en non-obese gezonde vrijwilligers (n = 8) includeerden. Hier vonden we dat het totaal lichaamsgewicht de gentamicine klaring (volgens een machtsvergelijking met exponent 0.73) en distributievolume (volgens een machtsvergelijking met exponent 1.25) goed kon voorspellen. Om tot een vergelijkbare blootstelling te komen voor elk lichaamsgewicht in de populatie met een normale nierfunctie, presenteerden we in dit hoofdstuk een doseernomogram gebaseerd op een 'doseergewicht', gedefinieerd als $70 \times (\text{totaal lichaamsgewicht}/70)^{0.73}$.

In **Hoofdstuk 4** bestudeerden we de farmacokinetiek van tobramycine in morbide obese individuen die een bariatrische operatie ondergingen (n = 20), alsook in non-obese gezonde vrijwilligers (n = 8). Voor een lichaamsgewicht tot 194 kg, concludeerden we dat het distributievolume voor tobramycine lineair toeneemt met lichaamsgewicht. In tegenstelling tot gentamicine, vonden we dat de tobramycine klaring het beste kon worden voorspeld door een serum creatinine-gebaseerde schatting van de nierfunctie, namelijk gede-indexeerde *Modification of Diet in Renal Disease* (MDRD), uitgedrukt in ml/min. Hoewel door deze de-indexatie met behulp van lichaamsoppervlak indirect lichaamsgewicht wordt geïntroduceerd als covariaat, wijzen deze resultaten erop dat, voor de obese populatie met een normale nierfunctie, lichaamsgewicht minder voorspellend is voor tobramycine klaring dan bij gentamicine het geval is. Een mogelijke verklaring hiervoor zou kunnen zijn dat de klaring van gentamicine sterker wordt gedreven door actief renaal transport door het OCT2 transporteiwit. Van dit transporteiwit is uit dieronderzoek in obese muizen bekend dat de activiteit wordt geïnduceerd door lichaamsgewicht [11]. Ook blijkt in mensen met obesitas de klaring van metformine, een OCT2 substraat, toegenomen [12]. Tot slot wijst de bevinding dat tobramycine minder in de nieren lijkt te worden opgenomen en zodoende mogelijk minder nefrotoxisch is op een verminderde afhankelijkheid van tobramycine op OCT2 [13]. Deze mogelijke verschillen tussen tobramycine en gentamicine zijn echter vooralsnog onvoldoende onderzocht. In het slot van Hoofdstuk 4 presenteerden we een doseernomogram voor tobramycine, gebaseerd op gede-indexeerd MDRD, waarmee een vergelijkbare en minder variabele blootstelling in (morbide) obese patiënten met een normale nierfunctie wordt verwacht, in vergelijking met patiënten met een normaal lichaamsgewicht die de standaarddosering van 5 mg/kg krijgen.

In **Hoofdstuk 5** presenteerden we de resultaten van een prospectieve, farmacokinetische studie in een groep van morbide obese patiënten die een bariatrische operatie ondergingen (n = 20) en non-obese gezonde vrijwilligers (n = 8) met lichaamsgewichten tussen 60 en 235 kg. We stelden hier vast dat de klaring van vancomycine toeneemt met lichaamsgewicht volgens de vergelijking Klaring (in liter per uur) = 5.72 x (totaal lichaamsgewicht/70)$^{0.535}$. In een 3-compartimenteel model nam het distributievolume van het tweede compartiment (V2) lineair toe met lichaamsgewicht. Dit model werd extern gevalideerd met behulp van data uit een eerder gepubliceerde studie in 6 obese en 4 non-obese individuen. Op basis van Monte Carlo simulaties lieten we zien dat het deel van patiënten die binnen de doelblootstelling (een 24-uurs *area under the curve* (AUC_{24h}) van 400 – 700 mg*h/L) uitkomen kan worden gemaximaliseerd door 35 mg/kg/dag (met maximale dagdosering 5500 mg) te geven. Verschillende andere veelgebruikte doseringen leiden tot een onacceptabel lage blootstelling en dus ineffectieve behandeling, of juist een onacceptabel hoge blootstelling en een hoger op toxiciteit. Tot slot lieten we ter ondersteuning van *therapeutic drug monitoring* (TDM) zien dat in obese patiënten een AUC_{24h} tussen 400 – 700 mg*h/L overeenkomt met een dal spiegel tussen 5.7 – 14.6 mg/L. Dit is veel lager dan de doelconcentraties die worden genoemd in de vigerende richtlijnen (15 – 20 mg/L) [7]. Voor obese patiënten geldt dus dat een relatief lage vancomycine dal spiegel dus in veel gevallen niet betekent dat deze patiënt ook een te lage blootstelling heeft.

In de voorgaande hoofdstukken werd de invloed van gewicht onderzocht in studies met obese patiënten die verder relatief gezond waren, waarmee andere variabelen zoals nierfunctie binnen normaalwaarden werden gehouden. Het is echter bekend dat obesitas niet de enige factor is die voor variabiliteit in farmacokinetiek zorgt. Om deze reden hebben we **in Hoofdstuk 6** de farmacokinetiek van gentamicine verder gekarakteriseerd door de eerder prospectief verzamelde data van obese en non-obese proefpersonen te combineren met een grote retrospectieve dataset afkomstig uit een tweetal ziekenhuizen, met data van (kritisch zieke) obese patiënten met en zonder nierfunctiestoornissen (n = 542) die werden behandeld met gentamicine en waarbij één of meer gentamicine bloedspiegels zijn gemeten. In deze analyse zagen we dat een combinatie van totaal lichaamsgewicht en nierfunctie (op basis van het serum creatinine volgens de *Chronic Kidney Disease Epidemiology* vergelijking [CKD-EPI]), welke gecombineerd konden worden door een de-indexatie van CKD-EPI, uitgedrukt als de CKD-EPI (in ml/min/1.73 m^2) vermenigvuldigd met [lichaamsoppervlak/1.73]. Daarbij werd een 25% lagere klaring waargenomen in patiënten die waren opgenomen op de intensive care, ongeacht de nierfunctie. Met dit model, dat tevens extern gevalideerd was in een tweede dataset met vergelijkbare patiëntkarakteristieken (n = 208), ontwierpen we een gemakkelijk te gebruiken gentamicine doseernomogram als verfijning van de in Hoofdstuk 3 voorgestelde doseerstrategie welke alleen geschikt was voor (morbide) obese patiënten zonder nierfunctiestoornissen. In het

nieuwe nomogram wordt rekening gehouden met zowel de invloed van lichaamsgewicht als die van nierfunctie, doordat een op lichaamsgewicht gebaseerde dosering (in mg/kg) wordt gereduceerd bij een dalende nierfunctie (gemeten als CKD-EPI).

In de tweede *real-world* studie gepresenteerd in **Hoofdstuk 7** beschrijven we de resultaten van een farmacokinetische studie naar vancomycine in een groot cohort van 1892 obese en non-obese kinderen en adolescenten. Hiertoe extraheerden we data over vancomycine toedieningen, bloedspiegel bepalingen en verschillende covariaten uit de systemen van 21 ziekenhuizen in de regio in en rondom Utah in de VS. De dataset bestond uit klinische patiënten met een grote spreiding in leeftijd (1 – 18 jaar), lichaamsgewicht (6 – 188 kg), mate van overgewicht (13% overgewicht, 16% obesitas) en nierfunctie (laagste creatinineklaring 8.6 ml/min/1.73 m^2). In deze populatie konden we de vancomycineklaring het beste voorspellen met een relatief simpel model op basis van lichaamsgewicht en nierfunctie, geschat met behulp van de bedside Schwartz-formule. Dit model deed het niet slechter dan complexere modellen waarbij de invloed van gewicht op basis van normale groei en overgewicht separaat wordt gekarakteriseerd of waarbij rekening wordt gehouden met maturatie door de grootte van het effect van lichaamsgewicht op klaring te laten afnemen met lichaamsgewicht. Tenslotte presenteerden we op basis van deze resultaten aan het einde van Hoofdstuk 7 een eenvoudige doseerrichtlijn die een brug slaat tussen de bestaande doseeradviezen voor non-obese kinderen en de in Hoofdstuk 5 voorgestelde doseerstrategie voor (morbide) obese volwassenen, waarbij aanpassingen worden gedaan op basis van nierfunctie en (over)gewicht. We lieten zien dat met behulp van deze doseerrichtlijn voor de gehele bestudeerde populatie van kinderen en adolescenten voor elk gewicht en nierfunctie de doelblootstelling kan worden bereikt (i.e. een AUC_{24h} tussen 400 en 700 mg*h/L). Een limitatie van deze studie was wel een relatief lage hoeveelheid patiënten met een nierfunctie onder 30 ml/min/1.73 m^2. Voorzichtigheid is dus geboden bij het volgen van de doseerrichtlijn in deze subpopulatie. Vergelijkbaar met de volwassene populatie vonden we ook in dit pediatrische cohort een grote variabiliteit in vancomycine dal spiegels, welke tussen 6.9 – 21.5 mg/L waren voor enkele representatieve patiënten waarbij de doelblootstelling werd behaald.

In het slot van dit proefschrift, in **Hoofdstuk 8**, bespraken we de belangrijkste bevindingen nogmaals en bekeken deze vanuit een breder perspectief. We gaven een reflectie op de gekozen methodologie, wat de resultaten ons kunnen leren over veranderingen in distributievolume en klaring bij obese individuen en, tot slot, hoe de klinische toepassing van de uitkomsten kan worden gemaximaliseerd.

Om tot doseerrichtlijnen voor obese patiënten te komen zoals we die in de *real-world* of dagelijkse klinische praktijk zien, hebben we allereerst prospectieve, rijk gesampelde studies opgezet waarin we non-obese en (morbide) obese, maar verder relatief gezonde proefpersonen hebben geïncludeerd. Hierbij konden we een grote variatie in lichaamsgewichten onderzoeken, terwijl andere mogelijk invloedrijke factoren zoals nierfunctie binnen normaalwaarden werden gehouden. Voor gentamicine hebben we als vervolgstap een studie uitgevoerd bij klinische patiënten waarbij we de eerder verzamelde prospectieve data combineerden met retrospectief verzamelde data van in het ziekenhuis opgenomen obese patiënten, met en zonder nierfunctiestoornissen, die werden behandeld met gentamicine en waarbij gentamicineconcentraties in het bloed waren gemeten. Deze methodologie heeft belangrijke voordelen ten opzichte van veelgebruikte studiedesigns waarbij óf alleen gebruik wordt gemaakt van prospectieve, rijke data uit obese gezonde vrijwilligers, óf alleen retrospectieve, beperkte data op basis van *therapeutic drug monitoring* wordt geanalyseerd. Het combineren van zulke studieontwerpen, zoals in deze thesis is gedaan voor gentamicine, heeft verschillende voordelen. Zo kan op deze manier, door te stratificeren op gewicht in een prospectieve studie, data worden verzameld bij proefpersonen met een grote spreiding in lichaamsgewicht (van 53 tot 235 kg in onze studie), waardoor we optimaal in staat zijn de specifieke invloeden van gewicht te kunnen karakteriseren. Het grootste voordeel van de combinatie van studieontwerpen ligt misschien wel in de mogelijkheid om op deze manier een grote variatie aan verschillende, invloedrijke covariaten tegelijkertijd te kunnen analyseren. De prospectieve data bestaat uit individuen met een grote variatie aan lichaamsgewicht, terwijl patiënten in een klinische, retrospectieve dataset, vanwege de karakteristieken van een klinische patiëntenpopulatie, over het algemeen een grote variatie heeft in andere covariaten zoals nierfunctie en kritische ziekte. Een analyse van deze datasets separaat bevat waarschijnlijk niet genoeg informatie om tot een robuust farmacokinetische model en doseeradviezen te komen die toepasbaar zijn op de gehele klinische populatie. Vergelijkbare inspanningen worden momenteel ondernomen om ook voor tobramycine en vancomycine de huidige modellen te kunnen uitbreiden naar de gehele klinische patiëntenpopulatie.

Tevens bespraken we in Hoofdstuk 8 enkele meer algemene inzichten op het gebied van de veranderende farmacokinetiek in obese patiënten die de studies in dit proefschrift ons hebben opgeleverd. Zoals ook al werd besproken in Hoofdstuk 2, wordt vaak aangenomen dat de vetoplosbaarheid van een geneesmiddel bepaald hoe het distributievolume veranderd in een patiënt met overgewicht. De in dit proefschrift bestudeerde geneesmiddelen kunnen worden beschouwd als hydrofiele (wateroplosbare) geneesmiddelen, waarvan veelal wordt verondersteld dat het distributievolume niet veranderd in obesitas. Onze studieresultaten laten zien dat voor al deze geneesmiddelen, het distributievolume lineair toeneemt. Hoewel hiervoor verschillende verklaringen aan te dragen zijn, lijken deze bevindingen te wijzen op een relatief goede penetratie van deze geneesmiddelen in vetweefsel, Deze resultaten laten zien dat het distributievolume van een geneesmiddel in obesitas niet kan worden voorspeld op basis van alleen de vetoplosbaarheid.

Onze studieresultaten werpen ook nieuw licht op de voorspelling van geneesmiddelklaring in obesitas. Er wordt in het veld van farmacokinetisch onderzoek door vele onderzoekers gezocht naar een enkele, universele gewichtsmaat (*body size descriptor)* die, ongeacht het type geneesmiddel, gebruikt kan worden als doseerparameter in plaats van het totaal lichaamsgewicht. Een belangrijke kandidaat voor zo'n algemene gewichtsmaat is *lean body weight* (LBW). LBW wordt berekent met een empirische, complexe formule op basis van lichaamsgewicht, lengte en geslacht en is een weerspiegeling van de 'vetvrije massa', wat min of meer hetzelfde is als het gewicht van de organen, bloed en water. De invloed van geslacht op LBW is groot, met een fors lagere LBW voor vrouwen met eenzelfde lichaamsgewicht, wat vaak wordt miskend in farmacokinetische studies en doseerrichtlijnen. In Hoofdstuk 8 demonstreerden we dit door de resultaten van de doseersimulaties met gentamicine uit Hoofdstuk 2 uit te splitsen op geslacht. Hoewel in de originele figuren een dosering van 8 mg/kg LBW *op populatieniveau* vergelijkbare resultaten leken op te leveren in vergelijking met het voorgestelde doseernomogram (op basis van totaal lichaamsgewicht), bleek in de uitgesplitste simulaties dat vrouwen een zeer lage dosering zouden krijgen, terwijl mannen juist een zeer hoge dosering kregen. Ook legden we in Hoofdstuk 8 de relatie tussen geneesmiddelklaring en totaal lichaamsgewicht versus LBW van twee in dit proefschrift uitgevoerde studies (gentamicine, vancomycine) en een eerder uitgevoerde studie van Van Rongen et al.. Deze studie keek naar de farmacokinetiek van paracetamol in patiënten met en zonder obesitas [14] en vond een sterkere correlatie tussen LBW en klaring ten opzichte van totaal lichaamsgewicht. Wij rapporteerden in de studies in dit proefschrift juist een sterkere correlatie voor totaal lichaamsgewicht en klaring (gentamicine) of vergelijkbare resultaten voor totaal lichaamsgewicht en LBW (vancomycine). In Hoofdstuk 8 laten we het belang van geslacht zien bij de keuze voor LBW of totaal lichaamsgewicht als covariaat, met name in situaties waarin LBW en totaal lichaamsgewicht op het oog vergelijkbare resultaten geven, zoals in onze vancomycine studie. Tevens wijst de vergelijking van deze drie studies er ook op dat LBW niet kan worden gebruikt als universele doseerparameter voor obese patiënten.

Een derde inzicht dat in Hoofdstuk 8 aan bod kwam betrof de voorspelling van de klaring van renaal geklaarde geneesmiddelen in obese patiënten met en zonder nierfunctiestoornissen. In de dagelijkse klinische praktijk wordt de nierfunctie vaak als glomerulaire filtratiesnelheid (GFR) geschat met behulp van een op serum-creatinine gebaseerde methode zoals de Cockcroft-Gault (CG) [15], MDRD [16], CKD-EPI [17] of, in kinderen, de Schwartz formule [18]. Behalve de CG-formule, geven deze formules de geschatte GFR in een naar een standaard lichaamsoppervlak van 1.73 m^2 genormaliseerde waarde (uitgedrukt in ml/min/1.73 m^2). Al deze formules zijn oorspronkelijk ontwikkeld in een (grotendeels) non-obese populatie, en het is bekend dat al deze formules niet goed in staat zijn de nierfunctie accuraat te schatten in obese patiënten. Gedurende de jaren zijn

hiertoe verschillende correcties voorgesteld, zoals het simpelweg omrekenen van de MDRD of CKD-EPI naar de waarde voor totaal lichaamsoppervlak (door vermenigvuldiging met lichaamsoppervlak/1.73), in dit proefschrift 'de-indexatie' genoemd, of door LBW in plaats van totaal lichaamsgewicht te gebruiken in de CG-formule. Deze laatste methode lijkt de beste en meest rationele optie, gezien de sterke relatie tussen creatinine en spierweefsel, welke, in obese personen, het beste correleert met LBW [19]. Als maat voor de GFR wordt door sommigen voorgesteld om de klaring van renaal geklaarde geneesmiddelen te gebruiken. Dit is in het verleden reeds toegepast bij kinderen en kritisch zieke IC-patiënten [20–22]. Een beperking is hierbij echter dat veel renaal geklaarde geneesmiddelen niet alleen door glomerulaire filtratie worden geklaard, maar ook via allerlei andere (actieve) processen in de nieren. Dit geldt hoogstwaarschijnlijk ook voor gentamicine, tobramycine en vancomycine. Derhalve is het de vraag of de 'beste' methode voor het schatten van de GFR in de obese populatie ook de optimale methode is voor het schatten van de klaring van renaal geklaarde geneesmiddelen. Om deze reden kozen we in deze thesis voor een empirische methode waarbij we de voorspellende waarde van verschillende methodes, zoals de-indexatie, gebruik van LBW in de CG-formule en het verzamelen van een 24-uurs creatinine klaring, hebben onderzocht. Hierbij vonden we voor tobramycine en gentamicine (Hoofdstukken 5 en 6) dat de-indexatie van MDRD of CKD-EPI de originele, geïndexeerde MDRD of CKD-EPI, dan wel de CG met LBW overtrof in het voorspellen van de geneesmiddelklaring. Dit wijst er mogelijk op dat, wellicht door actieve renale secretie, de klaring groter is dan de GFR voor deze geneesmiddelen, waarbij deze actieve processen mogelijk beïnvloed worden door lichaamsgewicht. Dit zagen we reeds bij de gentamicine in non-obese en obese proefpersonen zonder nierfunctiestoornissen (Hoofdstuk 3), waarbij totaal lichaamsgewicht de beste voorspeller was van de gentamicine klaring, mogelijk door een beïnvloeding van OCT2. Dit is een renaal transporteiwit waarvoor aanwijzingen zijn dat de activiteit met toenemend lichaamsgewicht hoger is. Deze resultaten vormen een belangrijke eerste stap in de vertaling van de exacte renale klaringsroute naar veranderingen in geneesmiddelklaring in de obese populatie.

In het slot van Hoofdstuk 8 bespraken we strategieën om de klinische implementatie van de farmacokinetische modellen en doseerrichtlijnen uit dit proefschrift te maximaliseren. Het gebruik van farmacokinetische modellen voor het bepalen van de geneesmiddeldosering wordt *model informed precision dosing* (MIPD) genoemd. Het is mogelijk om binnen zo'n MIPD-raamwerk farmacokinetische modellen direct van nut te laten zijn voor de behandeling van een individuele patiënt. Hiertoe wordt vaak gebruik gemaakt van speciale farmacokinetische software, zoals het in Nederland veel toegepaste pakket MwPharm++. Dergelijke software is in staat om patiënt specifieke karakteristieken en geneesmiddelspiegels te integreren met een farmacokinetisch model om individuele doseeradviezen te kunnen genereren. Om het gebruik van onze modellen direct beschikbaar

te stellen voor een dergelijke toepassing hebben we de afgelopen jaren nauw samengewerkt met de ontwikkelaars van MwPharm++ en zijn de ontwikkelde modellen via dit platform beschikbaar gesteld voor haar gebruikers. Overigens is door *open-access* publicatie van de modelparameters in internationale wetenschappelijke literatuur, in principe verzekert dat elk MIPD-software pakket onze farmacokinetische modellen kan implementeren. Een ander aspect dat het gebruik van onze resultaten kan bevorderen is een externe validatie van de ontwikkelde populatie modellen. Dit betekent dat de voorspellende waarde van de modellen wordt getest in een tweede populatie die niet is gebruikt voor de initiële ontwikkeling van het model. Dit wordt door velen gezien als een belangrijkste stap in het garanderen van betrouwbare, reproduceerbare resultaten [23]. In dit proefschrift hebben we verschillende bronnen gebruikt voor een externe validatie. Voor vancomycine hebben we bijvoorbeeld gebruikt gemaakt van eerder gepubliceerde ruwe data van een andere obese populatie (Hoofdstuk 5) [24]. In Hoofdstuk 6 hebben we het ontwikkelde populatie model extern gevalideerd in een vergelijkbare dataset van een tweede ziekenhuis. Hoewel zulke validaties het vertrouwen in de ontwikkelde modellen kunnen versterken, dient hier te worden opgemerkt dat ook doseeradviezen die zijn gebaseerd op studies zonder externe validatie, maar wel een klinisch relevant effect vinden van bijvoorbeeld een covariaat, nog steeds zoveel mogelijk geïmplementeerd dienen te worden in de klinische praktijk. Natuurlijk dienen deze studies in zo'n geval wel van voldoende kwaliteit te zijn. Tenslotte is een cruciale stap in de implementatie van de studieresultaten de integratie hiervan in de fungerende richtlijnen. Om dit mogelijk te maken, hebben we vanaf het begin nauw samengewerkt met instanties en verenigingen die verantwoordelijk zijn voor het ontwikkelen van dergelijke richtlijnen, zoals de Koninklijke Nederlandse Maatschappij ter bevordering van de Pharmacie (KNMP), de Stichting Werkgroep Antibiotica Beleid (SWAB) en de Nederlandse Vereniging van Ziekenhuisapothekers (NVZA). Op dit moment zijn de doseeradviezen reeds grotendeels geïmplementeerd in het *Informatorium Medicamentorum*, onder redactie van de KNMP. Het *Informatorium* vormt de primaire informatiebron voor geneesmiddelinformatie voor Nederlandse (ziekenhuis)apothekers en huisartsen. Verder implementatie van de doseeradviezen in nationale en internationale richtlijnen is een prioriteit voor de nabije toekomst.

Concluderend, hebben we in dit proefschrift getracht meer inzichten te verkrijgen in de farmacokinetiek van de renaal geklaarde geneesmiddelen in (morbide) obese volwassenen, adolescenten en kinderen met gentamicine, tobramycine en vancomycine als typische, veelgebruikte geneesmiddelen binnen deze groep. Hiertoe hebben we de populatie farmacokinetiek van deze drie geneesmiddelen in de obese populatie gekarakteriseerd en op basis hiervan eenvoudige, praktische doseerrichtlijnen voor deze patiënten ontwikkeld. We lieten zien dat de farmacokinetiek van deze geneesmiddelen aanzienlijk wordt beïnvloed door obesitas, waarbij in het algemeen de klaring goed kan worden voorspeld

met een combinatie van lichaamsgewicht en een schatting van de nierfunctie, terwijl verdelingsvolume voor alle onderzochte geneesmiddelen toenam met lichaamsgewicht. Tevens leidde ons onderzoek tot enkele nieuwe inzichten wat betreft obesitas-gerelateerde veranderingen in farmacokinetiek, zoals de waarde van de-indexatie van veel gebruikte formules voor het schatten van de nierfunctie of de belangrijke invloed van geslacht bij het gebruik van *lean body weight* als doseerparameter. Met de resultaten van het in dit proefschrift beschreven onderzoek hebben we enkele belangrijke stappen gezet in het invullen van de huidige kennishiaten op het gebied van de farmacokinetiek in (morbide) obese volwassenen, adolescenten en kinderen.

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Part V



Appendices







Dose recommendations presented in this thesis

DOSE RECOMMENDATIONS PRESENTED IN THIS THESIS

Throughout this thesis, dose recommendations have been proposed for gentamicin, tobramycin and vancomycin based on studies in adult obese individuals with and without renal impairment (gentamicin) or without renal impairment (tobramycin and vancomycin), and in obese and non-obese children and adolescents with and without renal impairment (vancomycin). These dose recommendations are summarized in this appendix together with a short description of their applicability.

Gentamicin dose recommendations for adult obese individuals

Dose recommendations for gentamicin are based on studies in obese and non-obese healthy volunteers (Chapter 3) combined with a real-world population of obese individuals with and without renal dysfunction (Chapter 6). The final dose recommendation as presented in Chapter 6 are shown in Table 1. Included patients (n = 524) had a total body weight (TBW) between 53 and 221 kg and renal functions based on the Chronic Kidney Disease Epidemiology equation (CKD-EPI) between 5.1 and 141.7 mL/min/1.73 m^2. The developed pharmacokinetic model was externally validated in an additional dataset from a second hospital with similar weight and renal function ranges (n = 321, total body weight 69 – 180 kg, CKD-EPI 5.3 – 130.0 mL/min/1.73 m^2). With this data we designed dose recommendations in which mg/kg dose reductions and interval extensions were incorporated based on the renal function measured with CKD-EPI (Table 1). Monte Carlo simulations showed that using the dose recommendations from Table 1, similar exposure compared to lean individuals, receiving the EUCAST recommended dose of 6 mg/kg total body weight, is expected for all obese individuals regardless of renal function (Chapter 6, Figure 2).

Table 1. CKD-EPI based dosing for gentamicin in obese individuals with varying renal function (expressed as CKD-EPI), relative to standard dose of 6 mg/kg TBW for lean individuals with a normal renal function (> 60 mL/min/1.73 m^2). This table is also shown in Chapter 6, Table 3.

	Obese individuals >100 kg (non-ICU patients)[a]					Lean individuals <100 kg (reference)
CKD-EPI (mL/min/1.73 m^2)	>120	90 – 120	60 – 90	30 – 60	<30	>60
Gentamicin dose, mg/kg (based on TBW in kg)	6 (100 %)	4.8 (80 %)	3.6 (60 %)	2.4 (40 %)	1.8 (30 %)	6 (100 %)
Dose interval (h)[b]	24	24	24	24 – 36	36 – 48	24

[a] Consider 25% dose reduction in ICU patients for all CKD-EPI groups.

[b] Based on time to reach the target trough concentration (<1 mg/L). We recommend to individualize dosing using therapeutic drug monitoring

CKD-EPI Chronic Kidney Disease Epidemiology, *TBW t*otal body weight.

Tobramycin dose recommendations for adult obese individuals

Dose recommendations for tobramycin presented in this thesis are based on studies in non-obese and obese healthy volunteers (Chapter 4). Using a pharmacokinetic model that was developed using prospectively collected data from 28 individuals (TBW 57-194 with an estimated renal function >60 ml/min, using the Modification of Diet in Renal Disease [MDRD, non-obese] or LBW in the Cockcroft Gault formula [obese]) a dosing nomogram was developed (Figure 1). In this nomogram, the tobramycin dose was based on the de-indexed MDRD, where the individual's MDRD is multiplied by the body surface area (BSA)/1.73, while targeting an AUC_{24h} of 75 mg*h/L. This target has been proposed for tobramycin in treating pathogens with a MIC of 0.25 – 1 mg/L, as it has shown to have the best balance between effectiveness and toxicity. When this dose strategy is employed in the obese, a stable median AUC_{24} up to 190 kg without trends can be expected with outer ranges lying around ~75% to ~125% relative to the target of 75 mg*h/L (Chapter 4, Figure 4). Some remarks should be made regarding the dose nomogram. First, the tobramycin dose nomogram shows dose recommendations for de-indexed MDRD values between 30-250 mL/min. However, the model is based on a dataset with MDRD values of 77 to 171 mL/min and as such, dose recommendations outside of this MDRD-range (depicted with grey area's in the figure) should be interpreted with caution. Second, we have shown in the discussion (Chapter 8) that both the dosing guidelines from Table 1 (proposed for gentamicin based on individuals with and without renal impairment) and Figure 1 (proposed for tobramycin based on individuals without renal impairment) lead to similar doses with the exception of a subgroup of patients with CKD-EPI <50 ml/min/1.73 m^2, based on simulations in a population of 10.000 subjects with body weights from 100 – 220 kg, and randomly assigned CKD-EPI values varying from 7 – 133 ml/min/1.73 m^2. As such, it appears feasible to also use the gentamicin recommendations (Table 1) for tobramycin as well. However, this remains to be prospectively evaluated in future research.

Vancomycin dose recommendations for adult obese individuals

In Chapter 5, we present dose recommendations for vancomycin for adult obese individuals. These recommendations are based on a prospective study in non-obese and obese healthy volunteers (n = 28, TBW 60 – 235 kg). All individuals had an estimated renal function > 60 ml/min, calculated using the Cockcroft-Gault (CG) formula with lean body weight (LBW) for obese or with TBW for non-obese. With a population pharmacokinetic model based on this data we explored several dosing strategies, where best results (highest probability of having a AUC_{24h} between 400 – 700 mg*h/L on day 3) were obtained using a dose of 35 mg/kg TBW (maximized at 5500 mg/day) (Chapter 5, Figure 3). As these dose recommendations only apply to individuals without renal impairment, and they were based on single dose pharmacokinetics, the model could benefit from addition of TDM data from clinical practice similar to gentamicin.

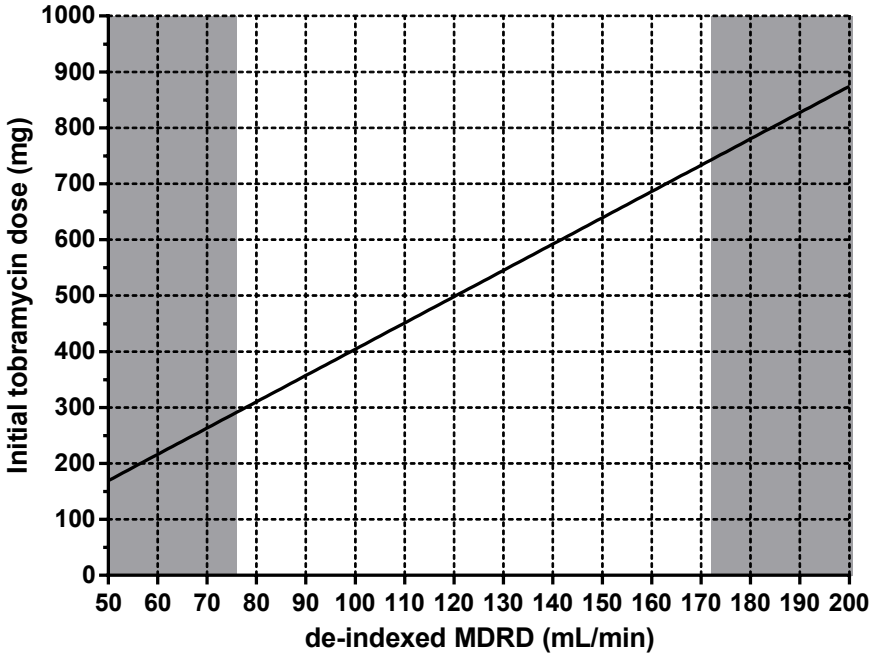


Figure 1. Dosing nomogram for tobramycin dose (in mg) based on the final tobramycin population PK model in non-obese and obese patients with body weights ranging from 57–194 kg and de-indexed MDRD values (calculated as MDRD * body surface area (BSA)/1.73) ranging from 77 to 171 mL/min, aiming for an AUC_{24} of 75 mg*h/L. The recommended tobramycin dose is calculated using equation: Dose (mg) = $AUC_{24, target}$ * 6.33 * (1 + 0.099 * [MDRD – 115]), where $AUC_{24, target}$ is the target AUC_{24} in mg*h/L of 75 and MDRD represents the de-indexed MDRD in mL/min. Since the PK data consists of MDRD values from 77 to 171 mL/min, dose recommendations extrapolation to values outside these should be interpreted with caution (grey area in the nomogram). This figure is also shown in Chapter 4, Figure 5. *MDRD* Modification of Diet in Renal Disease.

Vancomycin dose recommendations for non-obese and obese children and adolescents with and without renal impairment

A dosing guideline for vancomycin that can be used for all children and adolescents aged 1 – 18 years was presented in Chapter 7. For these recommendations a pharmacokinetic study was conducted using retrospectively collected data in 1892 children aged 1 – 18 years who were treated with vancomycin. This resulted in a population with a wide age and weight range, i.e. TBW between 6 – 188 kg, in which 13% and 16% was overweight or obese, respectively, and estimated creatinine clearance (based on the bedside Schwartz equation) was as low as 8.6 ml/min/1.73m^2. A dosing guideline was designed that bridges existing guidelines for non-obese children without renal impairment (i.e. the paediatric IDSA guideline recommending 15 mg/kg four times daily) and our earlier developed recommendations for obese adults without

renal impairment as presented in Chapter 5 (i.e. 35 mg/kg per day maximized at 3500 mg/day), with dose adaptations for renal impairment and obesity. The proposed guideline is shown in Table 2. Using this dosing strategy, we demonstrated that target exposure (AUC_{24h} 400 – 700 mg*h/L on day 3) can be expected throughout the entire population for any given weight and renal function (Chapter 7, Figure 5). One remark here is that in this study we included a relatively low number of individuals with renal functions <30 ml/min/1.73 m^2 (n = 12). As such, extra caution is necessary when the dose recommendations are used in this subpopulation.

Table 2. Dosing guideline for intermittent dosing of vancomycin in children and adolescents aged 1 – 18-years based on total body weight and renal function according to bedside Schwartz. This table is also shown in Chapter 7, Table 3.

Schwartz creatinine clearance (mL/min/1.73 m^2)	Total body weight (kg)			Relative daily dose (%)
	<30	30 – 70	>70	
>90	15 mg/kg every 6 h	15 mg/kg every 8 h	18 mg/kg every 12 h	100%
50 – 90	11 mg/kg every 6 h[a]	11 mg/kg every 8 h[a]	12 mg/kg every 12 h[a]	70%
30 – 50	5 mg/kg every 6 h[a]	5 mg/kg every 8 h[a]	6 mg/kg every 12 h[a]	35%
10 – 30	5 mg/kg every 12 h[a]	3 mg/kg every 12 h[a]	3 mg/kg every 12 h[a]	15%

[a] First dose is 15 mg/kg.





Curriculum vitae

CURRICULUM VITAE

Cornelis Smit was born in Menaldum, The Netherlands in 1988. After finishing secondary school at the Christelijk Gymnasium Beyers Naudé in Leeuwarden in 2006, he studied Pharmacy at the University of Groningen. During a research internship in 2010 at the Max-Planck-Institut für Molekulare Physiologie in Dortmund, Germany in 2010, he developed a special interest in conducting scientific research. After graduating as a PharmD cum laude in 2012 he started a residency in hospital pharmacy at the St. Antonius Hospital in Nieuwegein, The Netherlands, under mentorship of drs. M.M. Tjoeng, dr. E.M.W. van de Garde and Prof. dr. C.A.J. Knibbe. He combined this traineeship with a PhD research project, carried out at the St. Antonius Hospital, Radboudumc and Leiden University, supervised by Prof. dr. C.A.J. Knibbe, dr. H.P.A. van Dongen and dr. R.J.M. Brüggemann. Cornelis registered as a hospital pharmacist in 2017 and, following a traineeship under supervision of Prof. Dr. C.A.J. Knibbe, as a clinical pharmacologist in 2019. He currently holds a position as postdoctoral researcher and clinical pharmacologist at the University Children's Hospital (UKBB) in Basel, Switzerland, where he lives together with his wife Harriëtte and two children, Yfke and Karsjen.





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