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

Smit, C.

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.

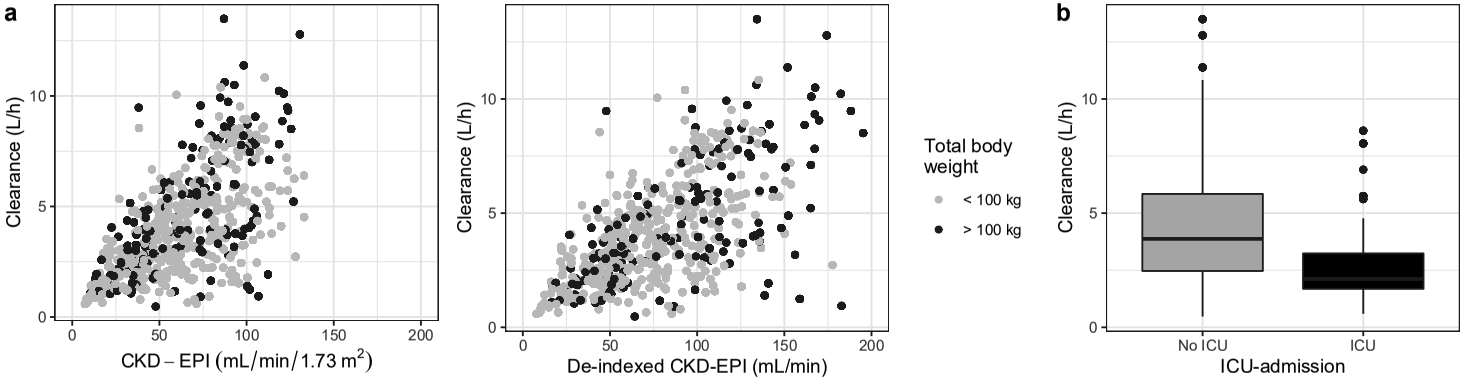

Figure 1. Individual *post-hoc* estimates of gentamicin clearance (from the structural model without covariates) versus (a) CKD-EPI (in mL/min/1.73 m2, left panel) or de-indexed CKD-EPI (in mL/min, right panel), with de-indexation being done by multiplication of CKD-EPI with BSA/1.73 and versus (b) ICU-admission. 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.

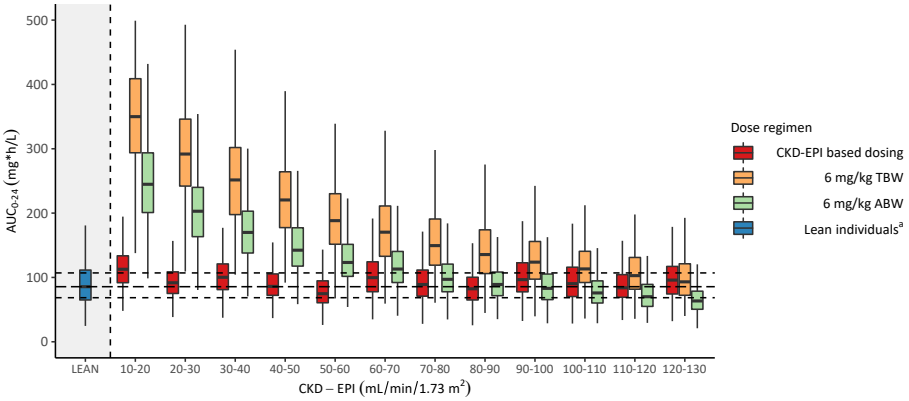

Figure 2. AUC_{0-24} values for different dose regimens versus CKD-EPI based on simulations using the final pharmacokinetic model (n = 10.000 per dose regimen). CKD-EPI based dosing follows the strategy as shown in Table 3. The boxplots show median and interquartile range of the AUC_{0-24} values for 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

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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.

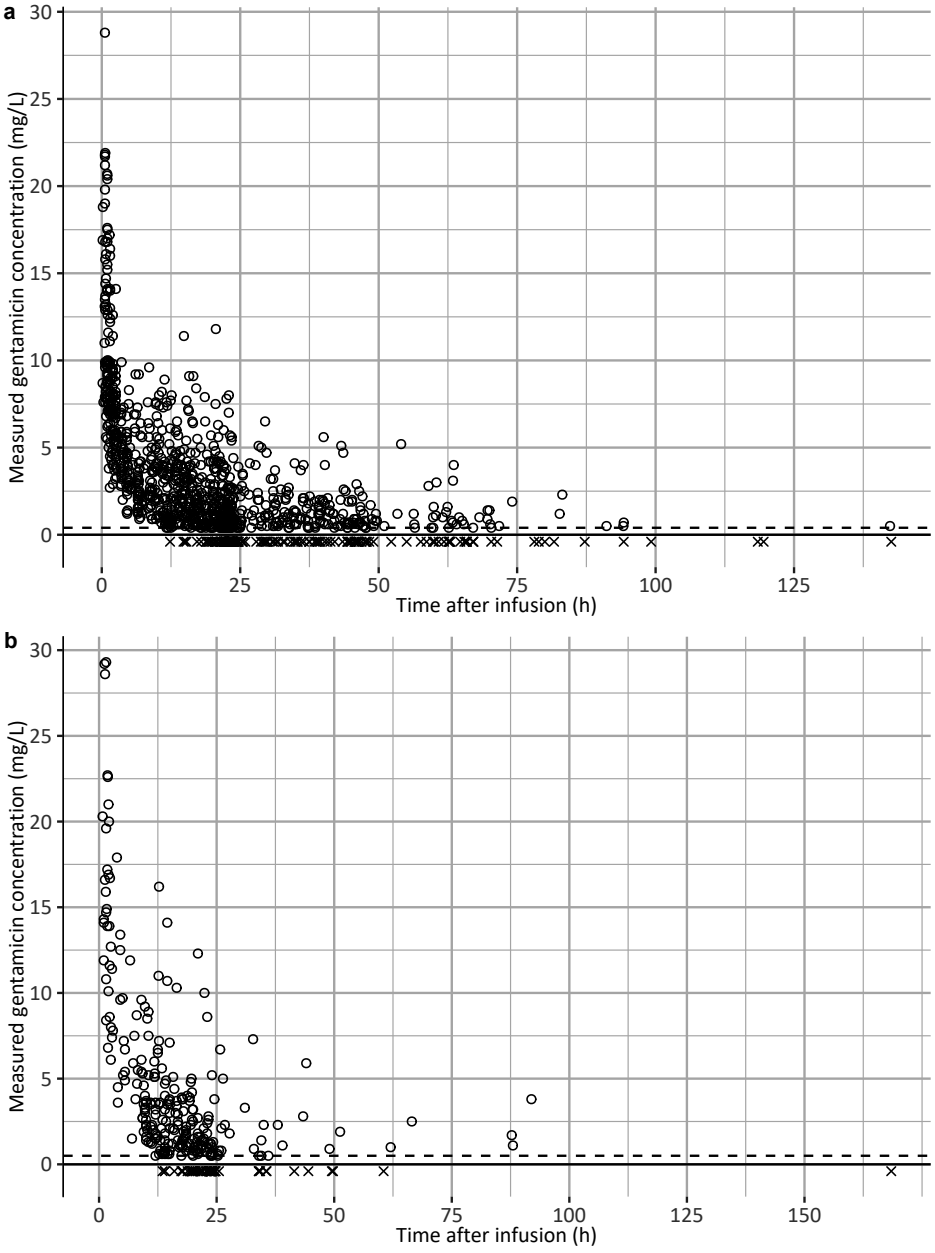

Figure S1. Observed gentamicin concentrations (open circles) versus time after start of the last gentamicin dose for (a) the training dataset (n = 542 individuals, 1187 samples) and (b) the external validation dataset (n = 208 individuals, 321 samples). Values below lower limit of quantification (LLOQ,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

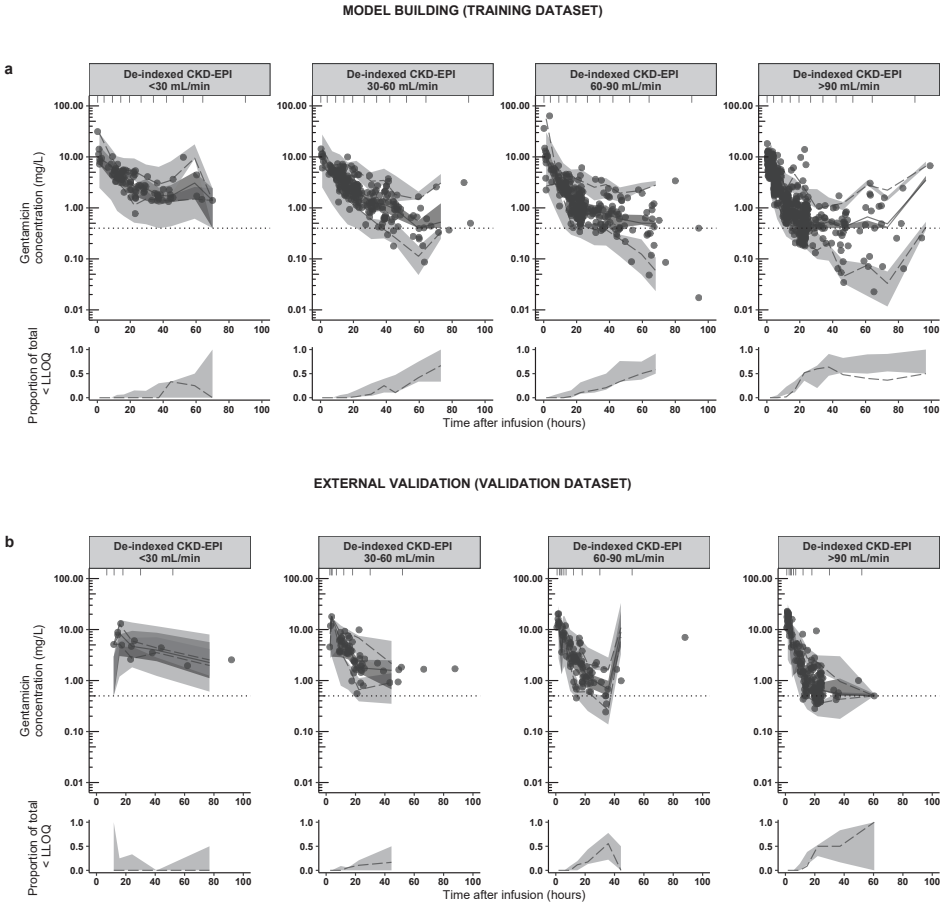

Figure S2. Prediction and variability corrected visual predictive checks (pvcVPC) of the final model , split for de-indexed CKD-EPI subgroup, based on (a) the training and (b) the external validation dataset. In the upper panels, the median, 2.5th and 97.5th percentiles of observed concentrations are 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.

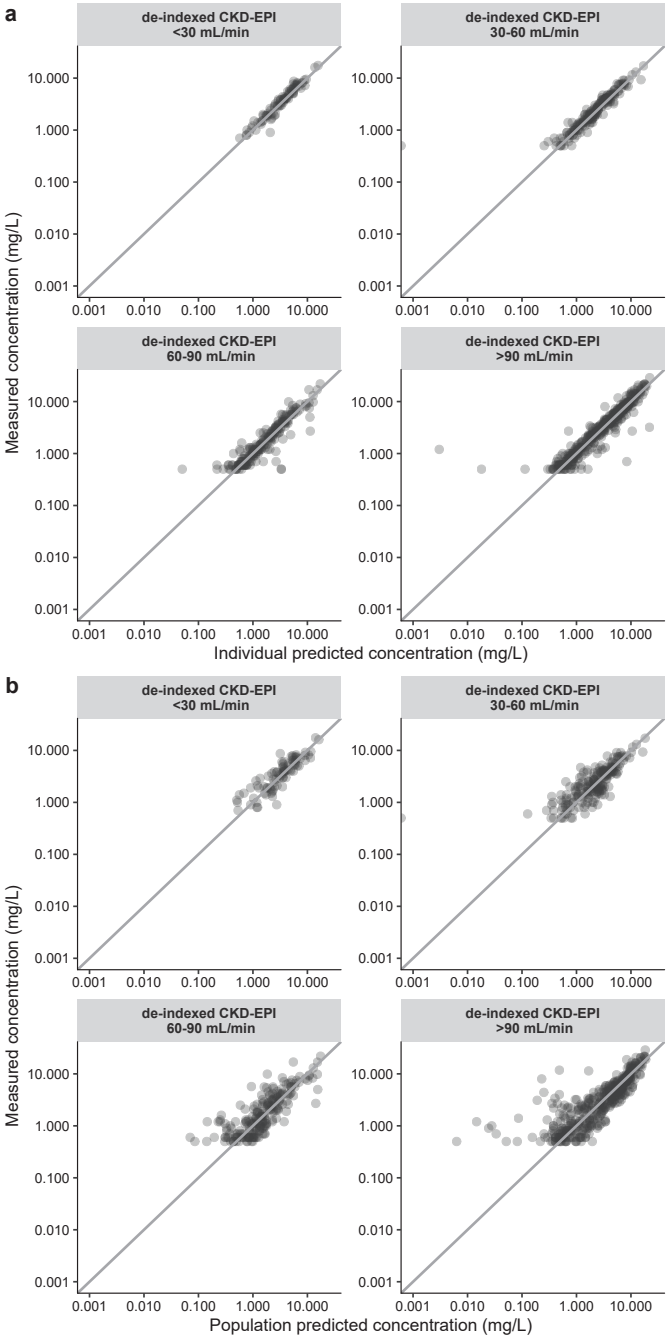

Figure S3. Goodness-of-fit plots of the final model with *the training dataset*. Observed versus individual (a) or population (b) predicted gentamicin concentrations, split for renal function groups (based on de-indexed CKD-EPI). The grey lines represent the line of identity (x = y). *CKD-EPI* Chronic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

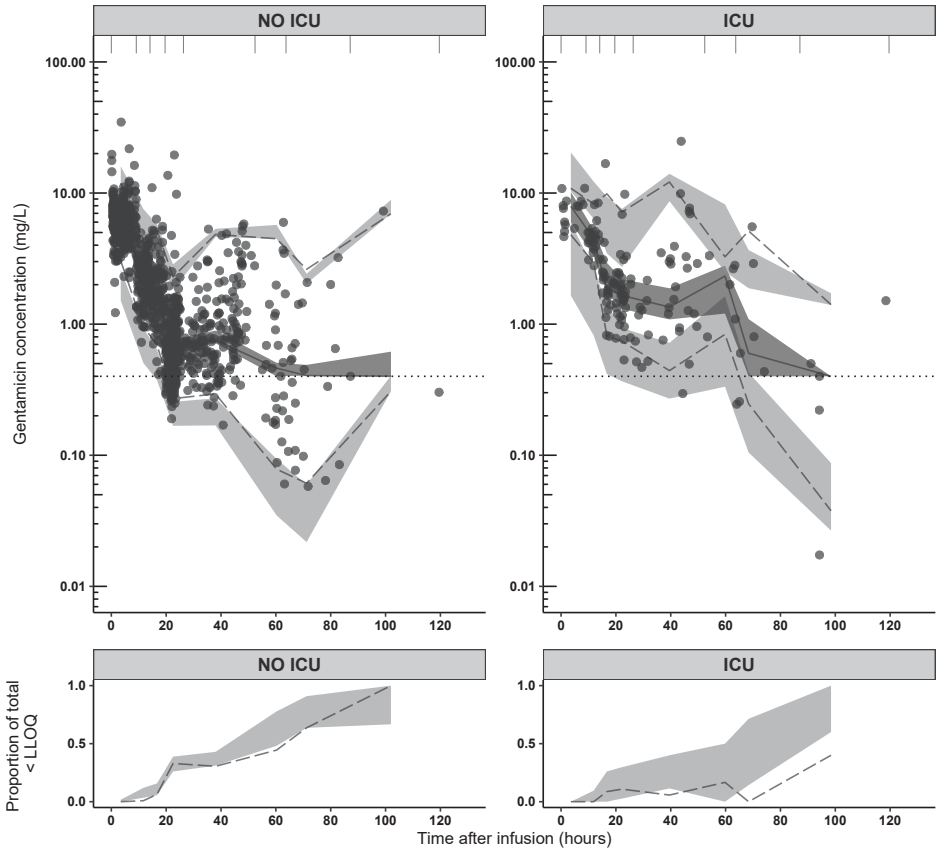

Figure S4. Prediction and variability corrected visual predictive checks (pvcVPC) of the final model, split for ICU-admission status, based on *the training dataset*. In the upper panels, the median, 2.5th and 97.5th percentiles of observed concentrations are shown as solid, lower and upper dashed lines. 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.

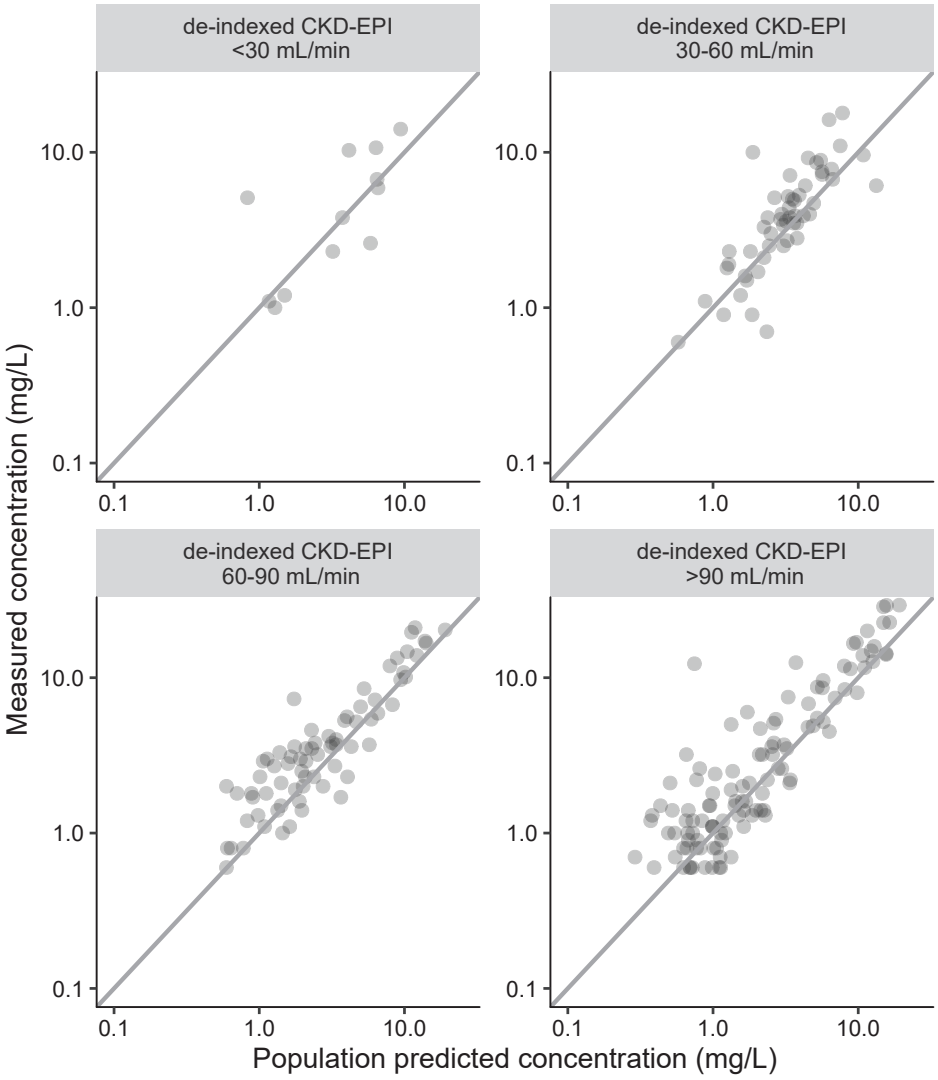

Figure S5. Goodness-of-fit plots of the final model with *the external validation dataset* using MAXEVAL = 0. Observed versus population predicted gentamicin concentrations, split for renal function groups (based on de-indexed CKD-EPI. The grey lines represent the line of identity (x = y).

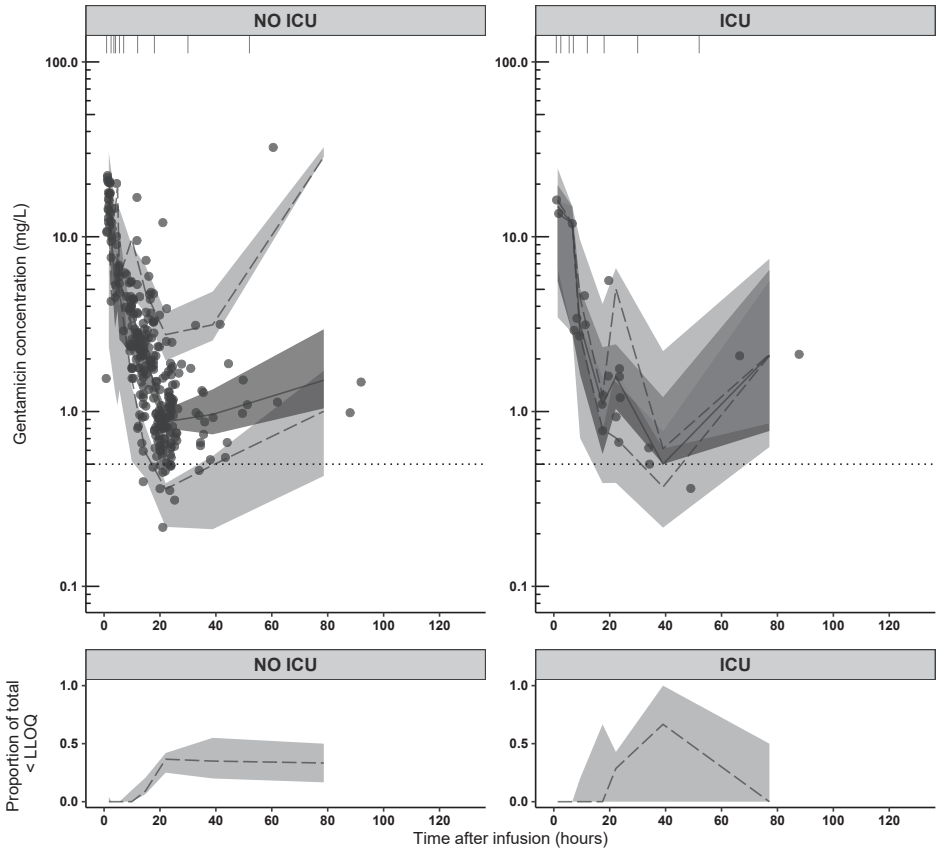

Figure S6. Prediction and variability corrected visual predictive checks (pvcVPC) of the final model, split for ICU admission status, based on *the external validation dataset*. In the upper panels, the median, 2.5th and 97.5th percentiles of observed concentrations are shown as solid, lower and upper 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.

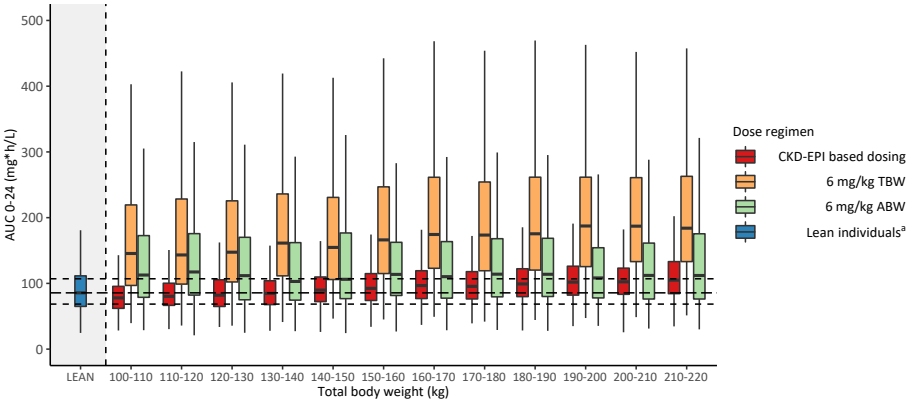

Figure S7. $AUC_{0\text{-}24h}$ values for different dose regimens versus total body weight based on simulations using the final pharmacokinetic model (n = 10.000 per dose regimen). CKD-EPI based dosing follows the strategy as shown in Table 3 in the main article. The boxplots show median and interquartile 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.

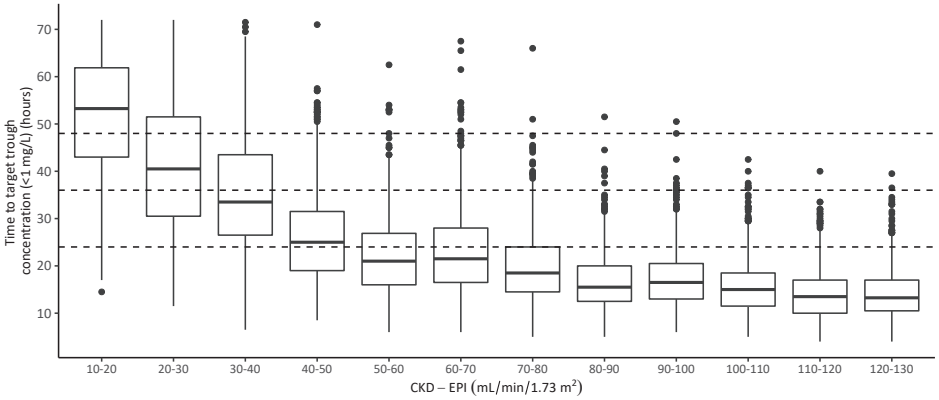

Figure S8. Time after dose to reach target trough concentration (<1 mg/L) for each CKD-EPI subgroup after a single gentamicin dose using the CKD-EPI guided dose strategy for obese individuals (shown in Table 3 in the manuscript). Predicted time to reach target concentration is based on simulations using 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