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

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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.

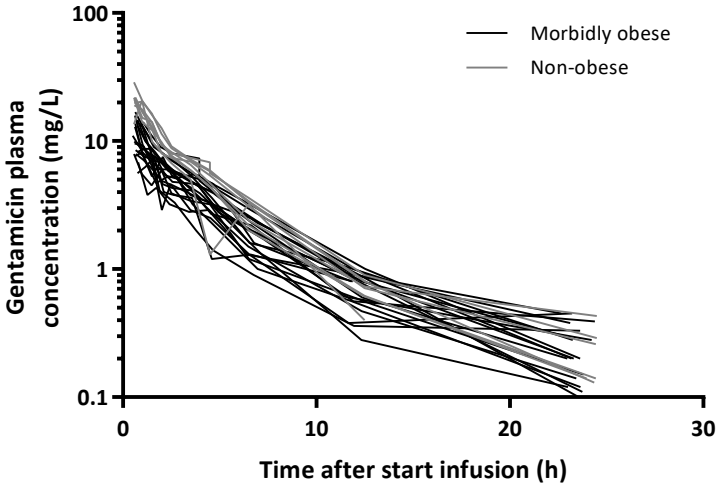


**Figure 1.** Observed gentamicin plasma concentrations (mg/L) versus time after start of infusion (h) for morbidly obese (receiving 5 mg/kg lean body weight, black lines) and non-obese (receiving 5 mg/kg total body weight, grey lines). Each line represents one individual.

### 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.

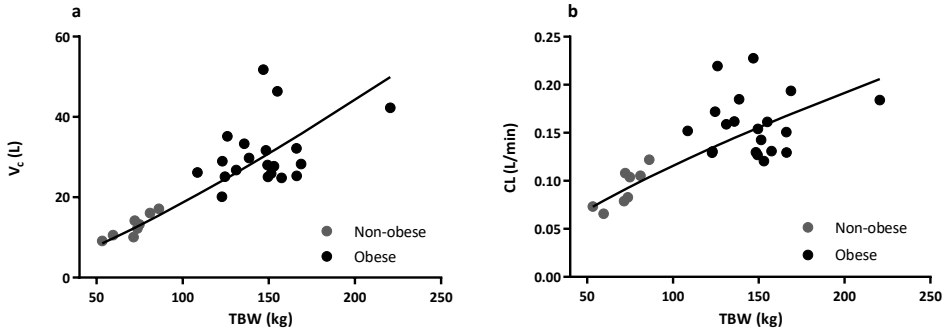


**Figure 2.** Individual values (n = 28) for (a) central volume of distribution (in L) and (b) clearance (in L/min) versus total body weight from the base model. Obese individuals are depicted using black dots and non-obese individuals using grey dots. The black line represents the covariate relation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

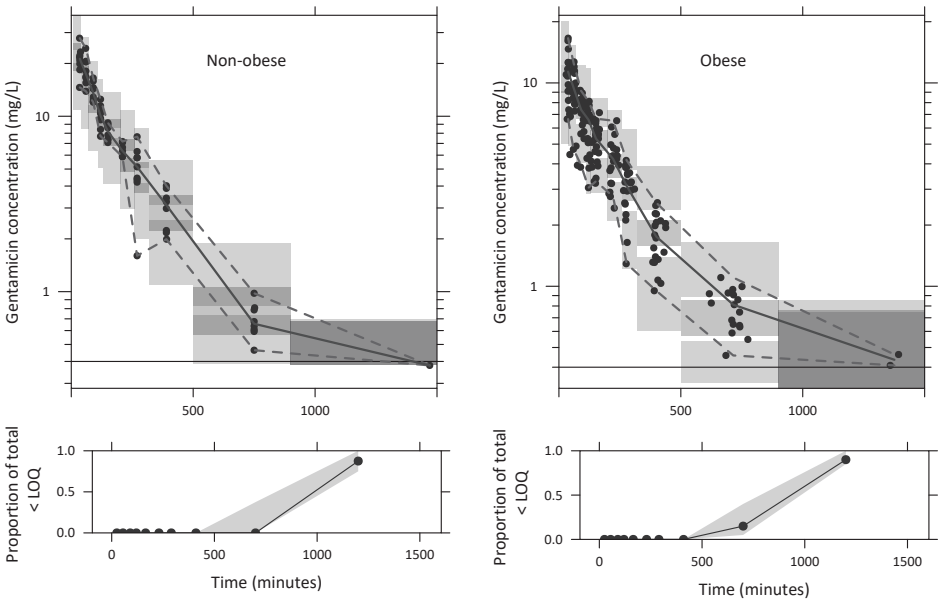


**Figure 3.** Prediction corrected visual predictive checks (pcVPC) of the final model for non-obese (upper left panel) and obese (upper right panel) individuals. The observed concentrations are shown as black circles, median, 2.5$^{th}$ and 97.5$^{th}$ percentiles of the observed data are shown as solid and the lower and upper dashed lines. The grey shaded area's show the 95% confidence intervals of the median (dark grey) and 2.5$^{th}$ and 97.5$^{th}$ 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.

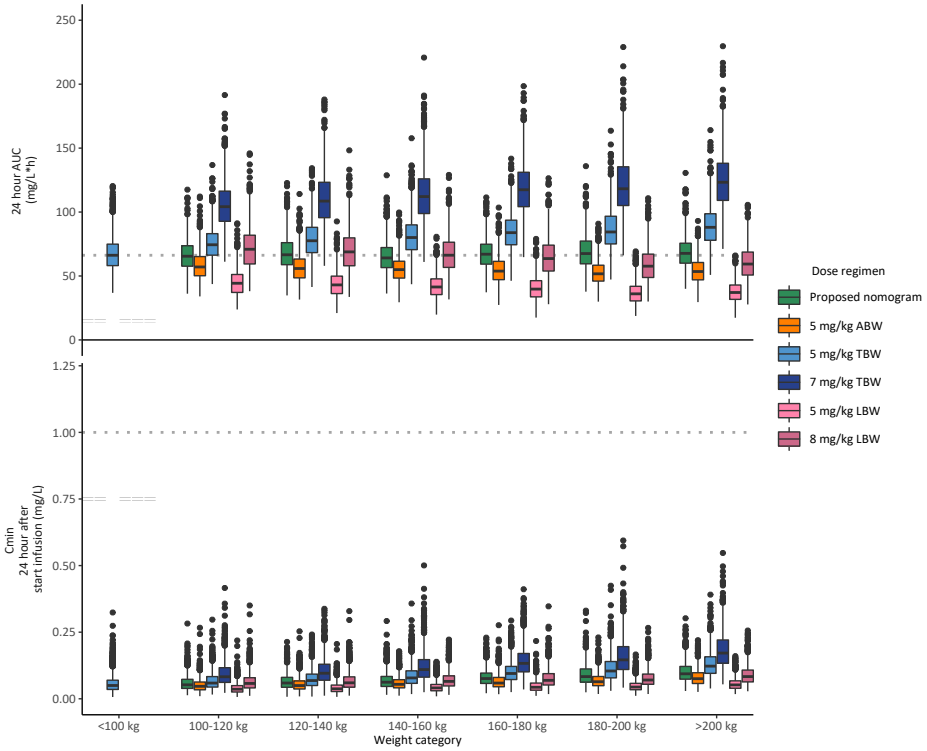


**Figure 4.** Boxplots (median and 95% confidence interval) representing gentamicin $AUC_{0\text{-}24h}$ (upper panel) and $C_{min}$ (lower panel) for different weight categories based on Monte Carlo simulations with six different TBW-, LBW- (calculated with the Janmahasatian formula [18]) and ABW (calculated 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 ($\theta_i$) was modelled according to equation (1):

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

where $\theta_{mean}$ is the population mean parameter value, and $\eta_i$ is a random variable for the ith individual with a mean of zero and variance of $\omega^2$, 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 $\varepsilon_2$ or $\varepsilon_1$ 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.

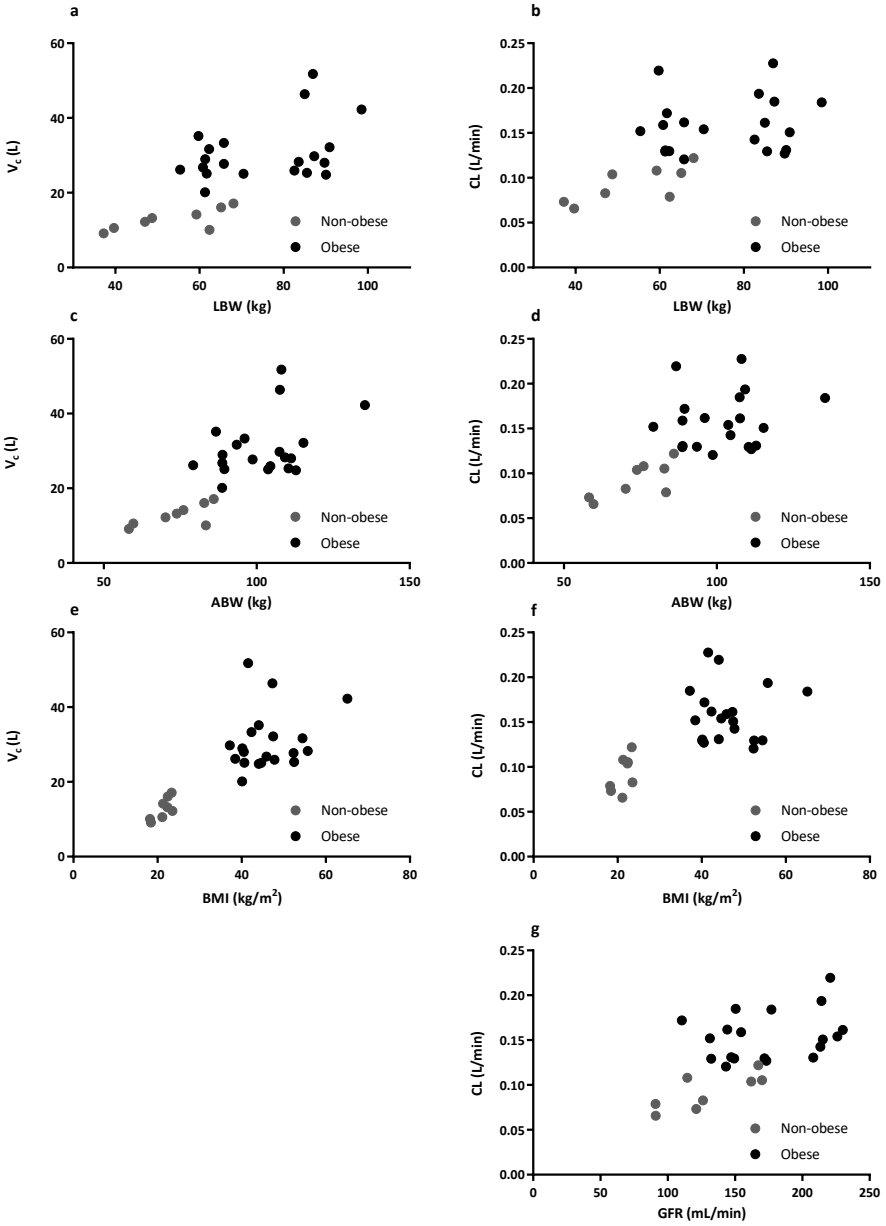


**Figure S1.** Individual values (n = 28) for (a, c and e) for central volume of distribution (L) and (b, d, f and g) clearance from the central compartment (in L/min) versus lean body weight, adjusted body weight, body mass index and glomerular filtration rate from the base model. Obese individuals 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.

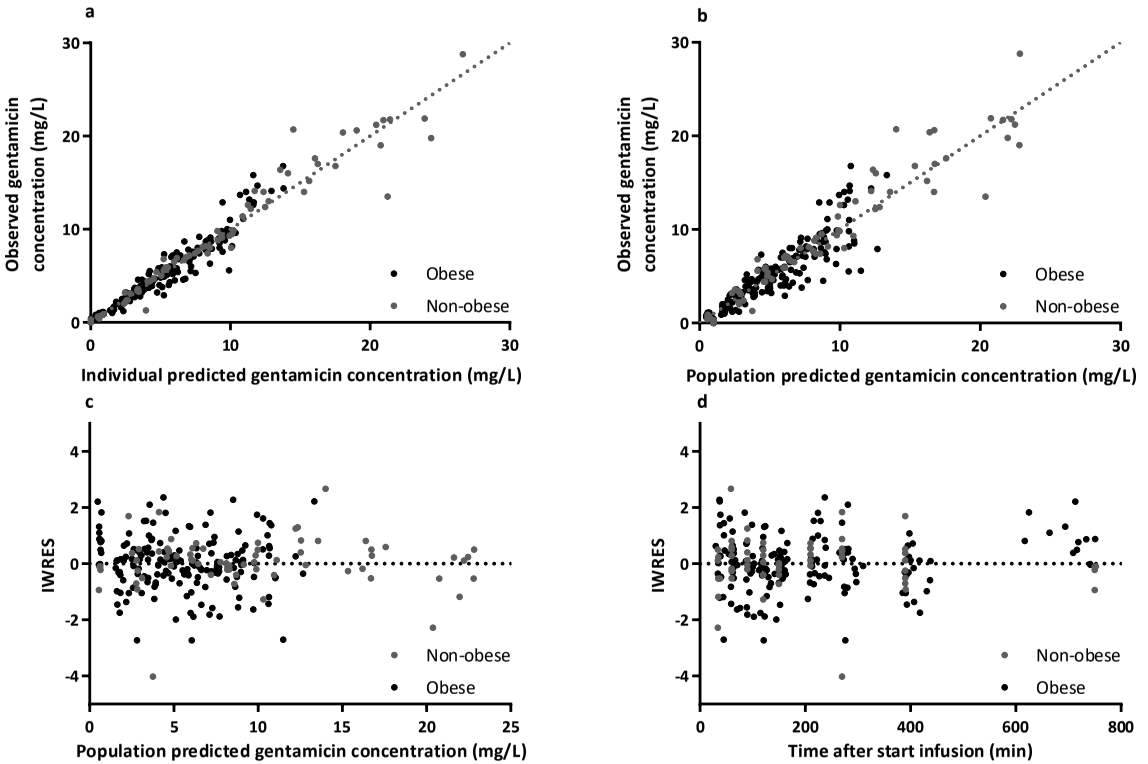


**Figure S2.** Goodness-of-fit plots of the final model for morbidly obese individuals (n = 20, black dots) and non-obese individuals (n = 8, grey dots): observed versus individual predicted gentamicin concentrations (a), observed versus population predicted gentamicin concentrations (b), individual 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.

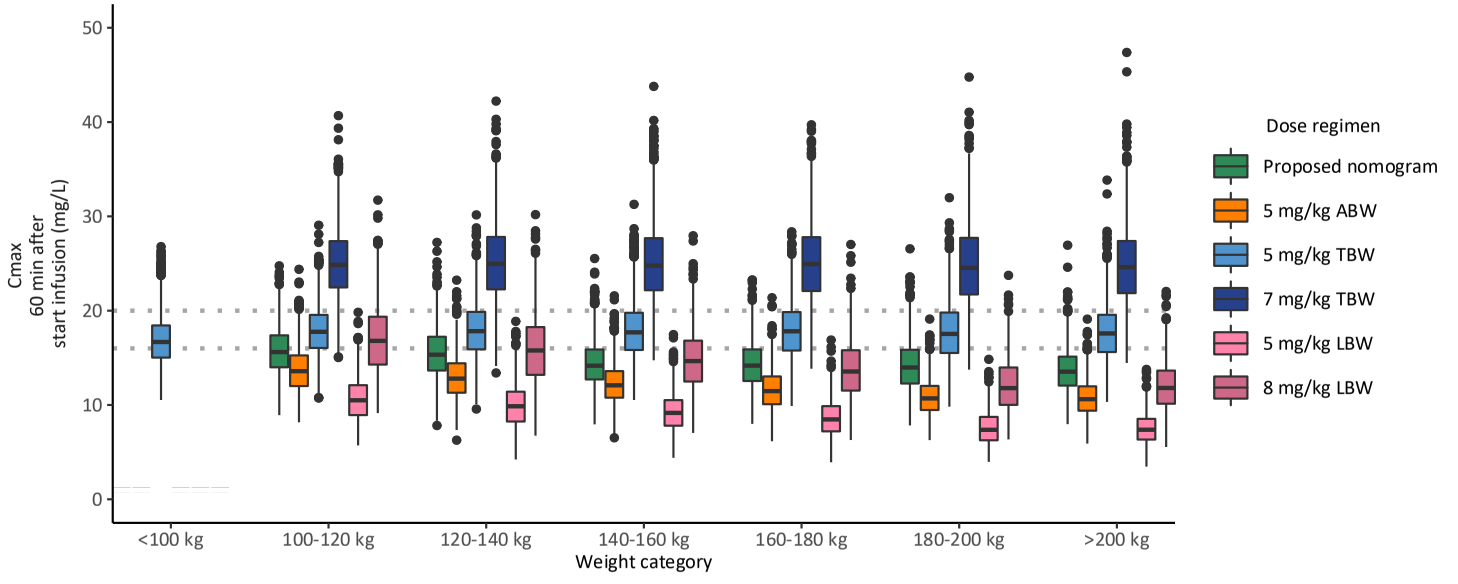


**Figure S3.** Boxplots (median and 95% confidence interval) representing gentamicin $C_{max}$ for different weight categories based on Monte Carlo simulations with six different TBW-, LBW- (calculated with the Janmahasatian formula [18]) and ABW (calculated as IBW + 0.4 x [TBW – IBW])-based dosing regimens (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
```