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Hodiamont, C.J.

Publication date
2023

Document Version
Final published version

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Colofon
ISBN: 978-94-6483-249-5

Lay-out & cover design: Robin Weijland, persoonlijkproefschrift.nl
Printing: Ridderprint, the Netherlands

Improving antibiotic therapy in critically ill patients through pharmacokinetic dose optimization

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. P.P.C.C. Verbeek
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Aula der Universiteit
op vrijdag 1 december 2023, te 11.00 uur

door Caspar Jan Hodiamont
geboren te Nijmegen

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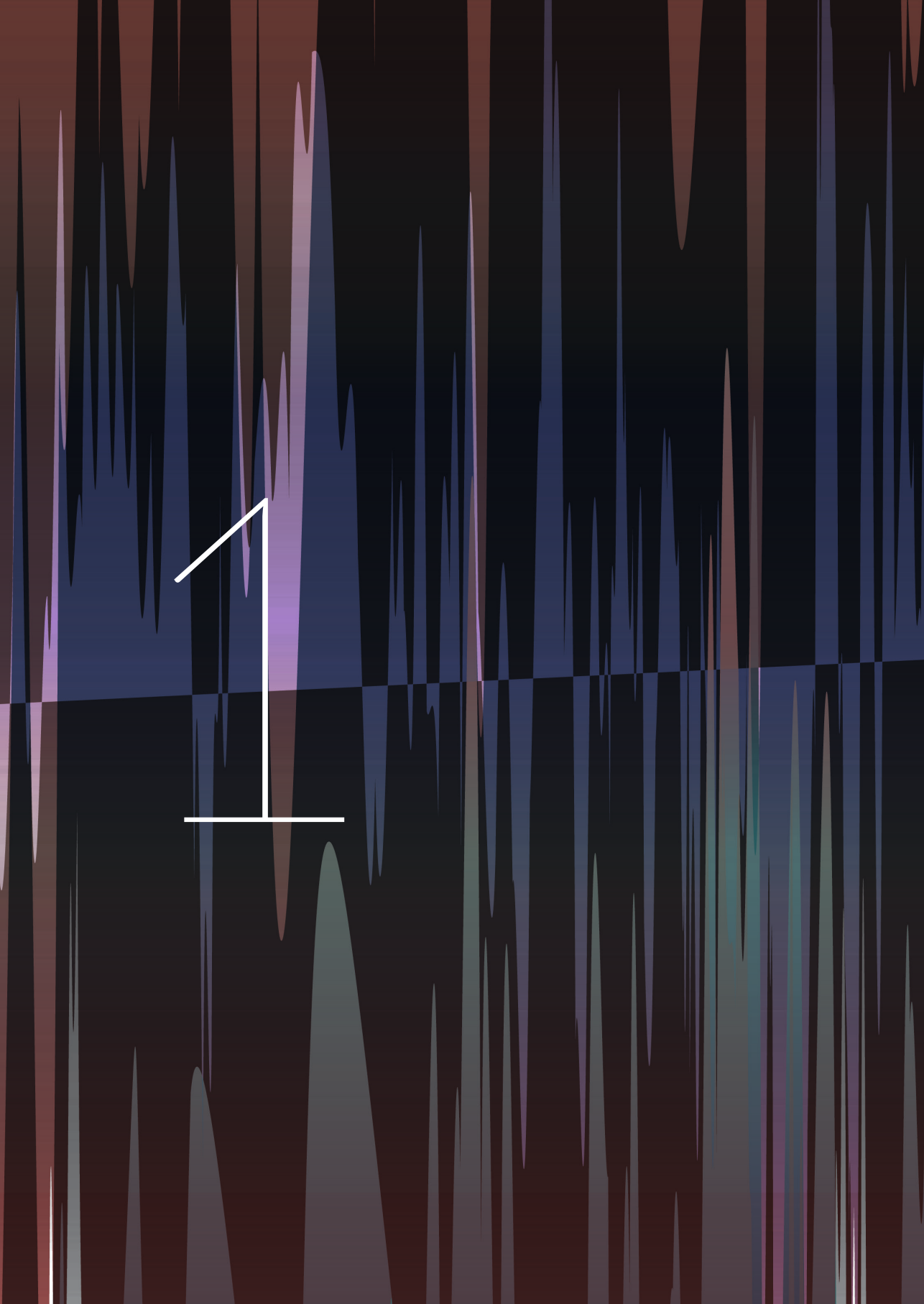

General introduction and outline of the thesis

Antibiotic therapy in the critically ill

Due to a high prevalence of infections, 70% of critically ill patients receive an antibiotic at any given point in time [1]. In the critically ill, infection is independently associated with mortality [2].

In these patients, early and adequate empirical antibiotic therapy has a greater impact on survival than any other intervention [3-5]. Three antibiotics that are commonly used in the treatment of sepsis are gentamicin, vancomycin and ceftazidime.

Gentamicin is an aminoglycoside antibiotic currently mostly used for the empirical treatment of sepsis as part of a combination regimen, usually with a broad-spectrum beta-lactam antibiotic. The main reason for the addition of gentamicin is to also cover gram-negative bacteria that may be resistant to the co-administered beta-lactam antibiotic [6].

Vancomycin is a glycopeptide antibiotic mainly used for treatment of suspected or proven infections with gram-positive bacteria that are resistant to beta-lactam antibiotics, usually methicillin-resistant staphylococci or ampicillin-resistant enterococci [7]. These bacteria are common causes of bloodstream infections in the critically ill, often associated with a central venous catheter or an intravascular prosthetic device.

Ceftazidime is a broad-spectrum cephalosporin antibiotic primarily used for treatment of suspected or proven infections caused by *Pseudomonas aeruginosa* [8], a common pathogen in ICU patients that is intrinsically resistant to many other antibiotics. *P. aeruginosa* infections are a major cause of morbidity and mortality in critically ill patients [9]. The Dutch sepsis guidelines therefore recommend to empirically treat *P. aeruginosa* in critically ill patients with sepsis due to hospital acquired pneumonia, ventilator associated pneumonia or suspected central venous catheter infection, or with sepsis of unknown origin in patients with prior infection or colonization with *P. aeruginosa* [6].

Antibiotic pharmacokinetics in the critically ill

Because of pathophysiological changes occurring in critically ill patients, the pharmacokinetics (PK) of antibiotics can be considerably altered [10, 11]. Two major changes that can alter PK in critically ill patients are an increase in

interstitial volume, which may affect the volume of distribution (Vd) of hydrophilic antibiotics, and a decrease in renal function, which potentially affects clearance (CL) of antibiotics that are eliminated through the kidneys.

Firstly, an increase in interstitial volume in critically ill patients can be caused by fluid extravasation into the interstitial space of tissues due to inflammation-induced capillary leakage [11]. While administration of resuscitation fluids represents the mainstay of sepsis treatment, this may lead to further increases in interstitial volume by continued extravasation [11]. For hydrophilic antibiotics like gentamicin, vancomycin and ceftazidime, such increases in interstitial volume may result in increases in Vd, hence leading to lower and potentially subtherapeutic antibiotic concentrations [10, 11].

Secondly, renal function is often decreased in critically ill patients due to acute kidney injury (AKI). AKI is a complication of shock due to infection, cardiac failure or severe inflammatory conditions or can be caused by nephrotoxic medication and is independently associated with mortality [12]. Many antibiotics are (mainly) cleared renally and are therefore administered in lower maintenance doses and/or longer dosing intervals to patients with reduced renal function. Despite these adjustments, however, there is still a substantial risk of supra-therapeutic concentrations [11].

In addition, several other pathophysiological changes, such as augmented renal clearance (due to enhanced renal function sometimes seen in critically ill patients), hepatic dysfunction and hypoalbuminemia may also influence antibiotic PK and may further complicate optimal dosing [11]. As a consequence, antibiotic concentrations might be substantially lower or higher than those achieved in non-critically ill patients, increasing the risk of sub- or supratherapeutic concentrations after administration of regular doses of antibiotics [10, 11]. Subtherapeutic concentrations increase the risk of clinical and microbiological failure [10, 11] and of antimicrobial resistance development [11], especially when treating infections with *Pseudomonas aeruginosa* [13]. Supratherapeutic concentrations increase the risk of drug-related toxicity when administering antibiotics with a narrow therapeutic index such as gentamicin and vancomycin, i.e. antibiotics with only a small difference between the minimum effective concentrations and the minimum toxic concentrations in the blood [10].

Pharmacokinetic optimization

To increase the likelihood that effective serum concentrations are reached, the use of optimized dosing strategies is recommended in critically ill patients [11]. These dosing strategies can vary between different antibiotics, depending on the PK and pharmacodynamic (PD) properties of the drug, whereby the PK properties determine how the body affects the antibiotic concentrations through absorption, distribution, biotransformation and excretion, and the PD properties determine how the antibiotic affects the targeted micro-organisms (activity) and the body (toxicity). Antibiotics can be classified according to the correlation between the antibacterial effect and three PK/PD indices, each of which uses the minimal inhibitory concentration (MIC, i.e. the lowest *in vitro* concentration of the antibiotic that inhibits visible growth of a microorganism) as the major PD marker [14]. These PK/PD indices are illustrated in figure 1.

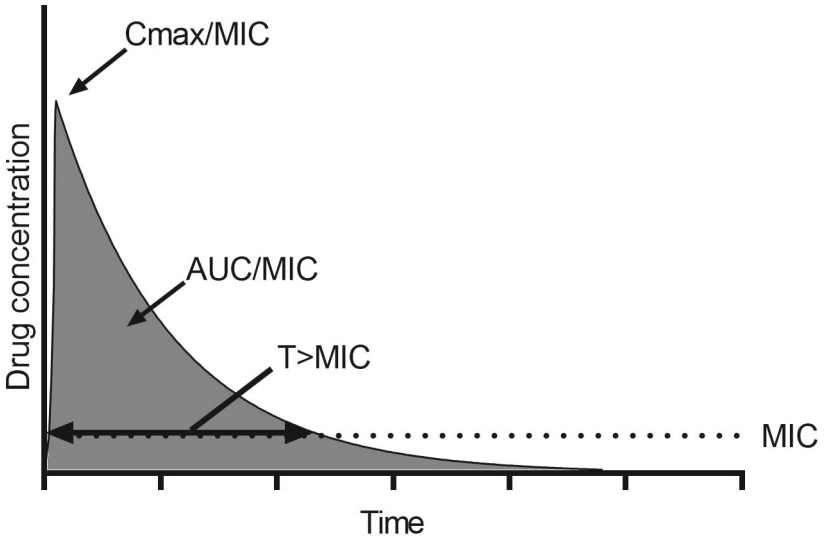

Figure 1
The three pharmacokinetic–pharmacodynamics indices correlating with antibacterial effect of antibiotics.

The first index is the ratio of the peak drug concentration to the MIC (Cmax/MIC). This is the main index for effect of gentamicin, for which achieving a target of Cmax/MIC of ≥10 is associated with efficacy [15, 16]. The second index is the ratio of the area under the drug concentration-time curve to the MIC (AUC/MIC), which is the main index for effect of vancomycin, for which achieving a target of AUC/MIC of ≥400 h is associated with efficacy [17]. The third index

is the percentage in a 24-hour time period during which the unbound drug concentration exceeds the MIC (T>MIC). This is the main index for effect of beta-lactam antibiotics like ceftazidime, for which the target associated with efficacy in critically ill patients is to achieve 100%T>MIC [18], although a higher target of 100%T>4xMIC may be needed for optimal bacterial killing and suppression of mutations leading to resistance [19].

Importantly, there are also PK targets for minimizing the risk of toxicity for antibiotics with a narrow therapeutic index. For gentamicin, a trough concentration (Cmin) <2 mg/L is associated with reduced risk of nephrotoxicity [20], while for vancomycin, an AUC <600 mg*h/L is associated with reduced risk of nephrotoxicity [21, 22].

There are several PK approaches to optimize dosing strategies, thereby increasing the probability that the PK/PD targets for efficacy are reached. Three of these PK approaches are investigated in this thesis. Firstly, the initial dosing scheme can be optimized for critically ill patient populations as a whole, in order to counter the effects of the altered antibiotic PK in this patient group (*a priori* optimization). For instance, the Dutch guidelines for empirical antibacterial therapy of sepsis recommend to use relatively high weight-based starting doses for gentamicin and suggest using a loading dose and continuous intravenous administration rather than intermittent administration for vancomycin and ceftazidime in critically ill patients [23]. Secondly, the initial dosing scheme can be tailored to specific patient characteristics (covariates) that are associated with decreased probabilities of target attainment, other than weight (also *a priori* optimization). For instance, patients with augmented renal clearance who are treated with antibiotics that are (mainly) cleared renally may need higher doses than patients with normal renal function [11]. Thirdly, doses can be adjusted during therapy using therapeutic drug monitoring (TDM). TDM uses measurement of antibiotic concentrations in serum to evaluate if doses should be increased or decreased in the individual patient in order to attain the pre-specified target concentration (*a posteriori* optimization). Early and rigorous TDM is strongly recommended for antibiotics with a narrow therapeutic index, mainly to reduce the risk of toxicity [11]. Dose modifications throughout treatment may be needed, since changes in Vd and CL in individual critically ill patients are often largest in the acute phase of sepsis and may gradually normalize during recovery from disease [11].

Non-linear mixed-effects modelling

For the most accurate estimation of individualized dosing requirements, measured concentrations combined with specific patient characteristics should be considered. If this is incorporated within a population PK model, which should be designed specifically for critically ill patients, this is called maximum *a posteriori* (MAP) Bayesian forecasting [24, 25]. MAP Bayesian forecasting uses an alternative approach of statistics that can integrate prior knowledge, such as the population PK model, and new information, such as information on characteristics and measured concentrations of the patient at hand, in a systematic way, in contrast to the more traditional frequentist approach that does not integrate prior knowledge [26]. As a result, the individual PK can be characterized based on only a few measured concentrations or even a single concentration. Population PK models describe the average time course of antibiotic exposure in a patient population and describe the extent and sources of variability in antibiotic exposure both between patients and within a patient over time [27]. For development of a population PK model, non-linear mixed-effects modelling (NONMEM) software can be used [28]. NONMEM can estimate typical, population PK parameters and can identify sources of variability in exposure in a specific population. By analyzing these sources of variability, predictive covariates can be identified that form a risk for overdosing or underdosing [27]. By combination of observations from an individual (concentrations and specific covariates) and information from the population PK model, individual PK parameter estimates can be obtained by MAP Bayesian analysis. Based on these individual PK parameters, antibiotic concentrations can be predicted for individual patients after each dosing regimen of interest. This makes NONMEM a powerful tool for accurate estimation of antibiotic dosing requirements, both for specific patient populations as well as for individual patients within that population.

Aim of the thesis

In conclusion, although adequate antibiotic therapy is of paramount importance in critically ill patients, these patients are at increased risk of not reaching the PK/PD targets that are associated with efficacy, safety and suppression of resistance development compared to non-critically ill patients. In this thesis, we apply three PK approaches to gentamicin, vancomycin or ceftazidime to investigate whether these approaches increase the probability of PK/PD target attainment in critically ill patients treated with these antibiotics.

Outline of the thesis

In *chapter 2*, we describe a population PK model for gentamicin in critically ill patients, which was developed to identify covariates that influence gentamicin peak concentrations (which are associated with efficacy) and to determine which measure of renal function best predicts gentamicin trough concentrations (which are associated with toxicity) [29]. The aim of this model was to evaluate whether certain patient characteristics are suitable for *a priori* dose optimization.

In *chapter 3*, we studied the predictive performance of the gentamicin population PK model described in chapter 2 in two independent populations of critically ill patients, to evaluate if this model can be used for dose optimization in other western ICU populations [30].

In *chapter 4*, we evaluated whether routine TDM of gentamicin peak concentrations as a tool for dose optimization increases the probability of PK/PD target attainment for efficacy in critically ill patients [31]. A population PK model was developed to estimate gentamicin peak concentrations after the first administration of a standard weight-based dose (before TDM) and after subsequent administrations using doses based on TDM, to evaluate if more patients attained the PK/PD target after TDM. In addition, Monte Carlo simulations were used to study the effect on PK/PD target attainment of higher starting doses.

Chapter 5 provides a literature review on the clinical PK of gentamicin and the consequences for optimal dosing of gentamicin for infections caused by Gram-negative bacteria. This review was focused on the general adult population and several subpopulations where PK can differ from PK in the general adult population: obese patients, critically ill patients, pediatric patients, neonates, elderly patients and patients on dialysis [32].

In *chapter 6*, we evaluated whether the use of a vancomycin loading dose leads to improved attainment of the PK/PD target for efficacy during the first 24h in critically ill patients. In addition, we investigated whether this loading dose results in a higher risk of acute kidney injury [33].

In *chapter 7*, we describe a population PK model for ceftazidime in critically ill patients with a proven or suspected *Pseudomonas aeruginosa* infection. This model was developed to identify the dosing regimen that maximizes the

probability of PK/PD target attainment for efficacy [34]. In addition, we evaluated if PK/PD target attainment correlated with a reduced risk of antimicrobial resistance development.

In *chapter 8*, we discuss the main findings, possible applications in clinical practice and future perspectives of these studies.

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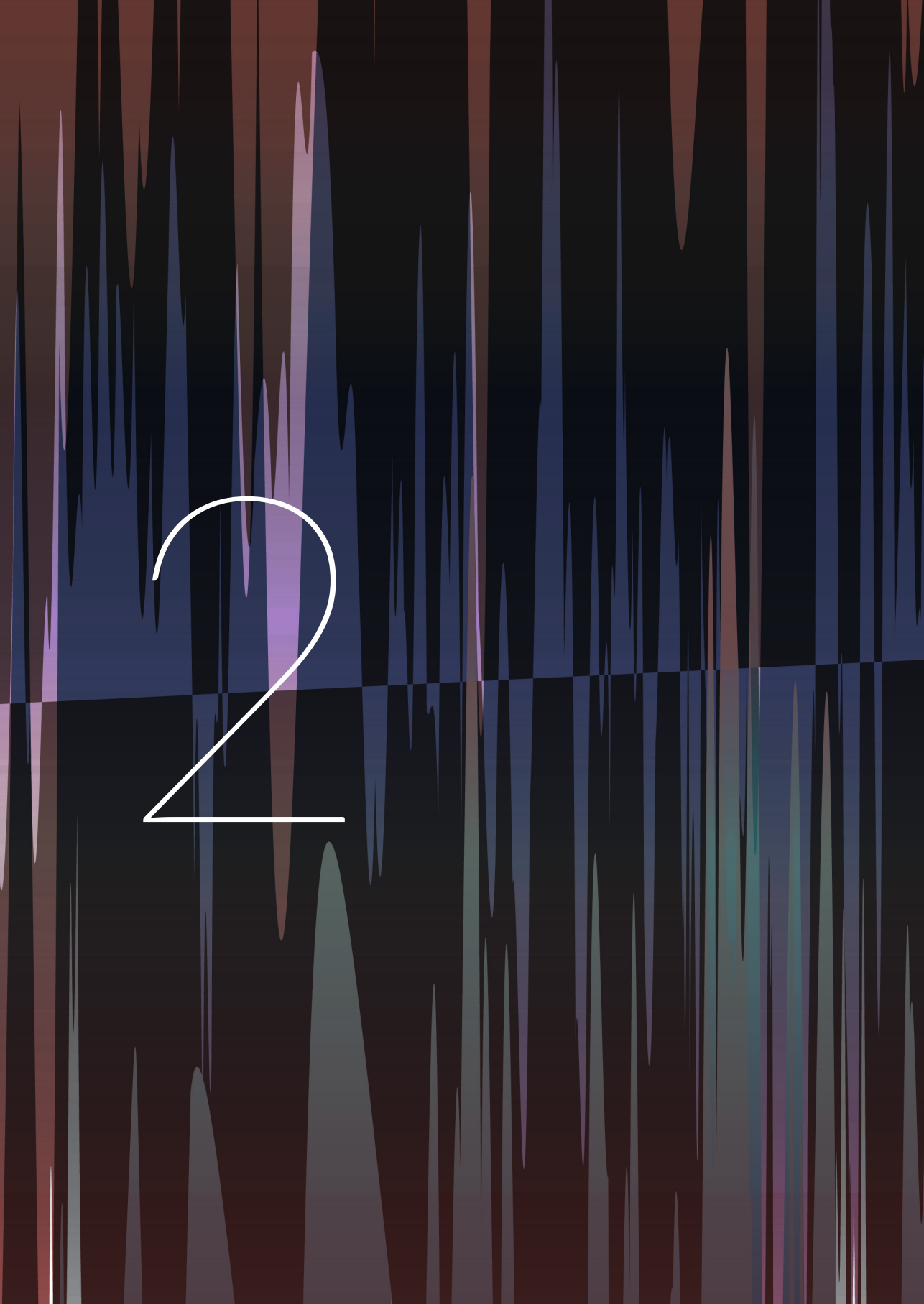
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Determinants of gentamicin concentrations in critically ill patients: a population pharmacokinetic analysis

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Int J Antimicrob Agents. 2017;49(2):204-211. DOI: 10.1016/j.ijantimicag.2016.10.022.

Abstract

When treating critically ill patients with gentamicin for severe infection, peak concentrations (Cmax) determine clinical efficacy and trough concentrations (Cmin) determine toxicity. Despite administration of body weight-standardised starting doses, a wide range of Cmax is generally observed. Furthermore, in therapeutic drug monitoring, several measures of renal function are used to predict appropriate Cmin and gentamicin dosing intervals, but the most accurate predictor is not known. This study aimed to quantify the impact of several patient parameters on gentamicin Cmax values and to determine which measure of renal function best predicts gentamicin clearance (CL). Clinical data and serum gentamicin levels were retrospectively collected from all critically ill patients treated with gentamicin at our intensive care unit between 1 January and 30 June 2011. Data were analysed using non-linear mixed-effects modelling (NONMEM v.7.1.2). A two-compartmental model was developed based on 303 gentamicin concentration-time data from 44 critically ill patients. Serum albumin levels explained 25% of interindividual variability in the volume of distribution (Vd). Creatinine clearance calculated from the creatinine concentration in a 6 h urine portion (CalcCLCr) resulted in acceptable estimation of gentamicin CL, whilst serum creatinine (SCr) and creatinine clearance estimated by the Cockcroft–Gault formula (CGCLCr) overestimated gentamicin CL and therefore underestimated Cmin. In conclusion, low albumin concentrations resulted in a larger Vd and lower Cmax of gentamicin. These results suggest that use of a higher gentamicin starting dose in critically ill patients with hypoalbuminaemia may prevent underdosing. Urinary CalcCLCr is a better predictor of Cmin than SCr or CGCLCr.

Introduction

In the treatment of sepsis in critically ill patients, early and appropriate antibiotic therapy has been shown to have a greater impact on survival than any other intervention [1–3]. Therefore, adequate dosing of antibiotics is of paramount importance in these patients. Gentamicin is often included in empirical treatment regimens for sepsis, with dosing schedules aimed at obtaining a ratio of peak concentration over minimum inhibitory concentration (Cmax/MIC) of >10 for optimal clinical efficacy [4, 5]. According to Dutch guidelines on therapeutic drug monitoring (TDM), a Cmax of 15–20 mg/L is considered to be therapeutic [6]. However, an evidence-based strategy for selecting optimal gentamicin starting doses to achieve this target in critically ill patients has not been established [7]. Body weight-standardised starting doses result in a wide range of Cmax, indicating large interindividual variability (IIV) in this patient group [8–10]. Depending on the MIC of the causative micro-organism, the likelihood of achieving Cmax/MIC >10 when using a starting dose of 5 mg/kg ranges from only 27.3% for an *Escherichia coli* strain with an MIC_{90} of 1 mg/L to 0% for a *Pseudomonas aeruginosa* strain with an MIC_{90} of 4 mg/L [8]. IIV in Cmax is largely caused by variability in the volume of distribution (Vd) of gentamicin in critically ill patients, which is reported to range from 16% to 64% [8, 11, 12]. This variability in Vd is partially determined by body weight [11], the severity of disease [13], administration of total parenteral nutrition (TPN) [14] and several other determinants that are correlated to a certain extent with the capillary leak syndrome that occurs during sepsis [15]. However, the contribution to variability in Vd of each separate determinant is unknown at present.

Whilst a high gentamicin Cmax is associated with efficacy, a high trough level (Cmin) is associated with toxicity, hence TDM is indicated to minimise the risk of nephrotoxicity [16, 17]. According to Dutch guidelines, a Cmin of <1.0 mg/L should be aimed for. Gentamicin Cmin is strongly associated with renal function, and measures of renal function, such as serum creatinine (SCr), total daily diuresis and creatinine clearance estimated according to the Cockcroft–Gault equation or calculated from a urine portion, are widely used to predict appropriate dosing intervals, with [18] or without [19] the use of a pharmacokinetic (PK) model. In critically ill patients, however, these measures of renal function are known to poorly predict actual renal function [20] and may lead to poor prediction of Cmin.

In this study, a population PK model for gentamicin in critically ill patients was developed to identify which parameters explain the IIV in Vd and to quantify the

impact of these parameters on Cmax. Moreover, the measure of renal function that best predicts gentamicin clearance (CL) and thus Cmin was investigated. Such knowledge is essential for optimising gentamicin dosing schedules in critically ill patients, thereby maximising efficacy and minimising toxicity.

Materials and methods

Patients and data

These retrospective analyses were performed using clinical data and serum gentamicin levels obtained as part of routine clinical care in critically ill patients admitted to the intensive care unit (ICU) of the Academic Medical Center in Amsterdam (The Netherlands). Data from all patients treated with gentamicin between 1 January and 30 June 2011 were included. According to Dutch law on medical research (WMO, article 1), no ethical approval is required when using anonymous data from routine diagnostic databases, as was done for the data analysed in this study. Routine clinical care at our institution includes measurement of gentamicin Cmax drawn within 1 h after infusion of the first dose, which is infused over 30 min. To determine the half-life, a second sample is collected the next morning at 06:00 h, regardless of the time the first dose was administered. Subsequently, gentamicin concentrations are routinely measured three times a week while on treatment in order to monitor Cmin and to adjust the dosing interval according to Dutch TDM guidelines [6]. The starting dose during the study period was 4 mg/kg total body weight (TBW), except for patients treated for endocarditis due to Gram-positive micro-organisms, who were treated with 3 mg/kg for synergistic effect in combination with a cell wall targeting antibiotic.

The following data were retrieved from the electronic Patient Data Monitoring System (PDMS): dose and timing of gentamicin; age; sex; TBW, ideal body weight (IBW) [21] and adjusted body weight (ABW) [22]; height; and severity of disease as assessed by the Acute Physiology and Chronic Health Evaluation (APACHE) II score [23]. During therapy, daily SCr, urinary creatinine concentration in a 6 h urine portion (00:00–06:00 h), daily diuresis and fluid balance, daily albumin level, administration of TPN, and application of continuous venovenous hemofiltration (CVVH) were noted. Both daily and total fluid balance were automatically calculated from data in the PDMS, in which all intravenous and oral input of fluids as well as all urine and non-urine outputs were monitored every hour in the PDMS. Creatinine clearance was estimated according to the Cockcroft–Gault equation (CGCLCr) [24] and was calculated from a 6 h urine portion by the

formula {CalcCLCr = [creatinine$_{urine}$ (mg/dL)/creatinine$_{serum}$ (mg/dL)] * [(volume$_{urine}$ (mL)/(time (h) × 60]}. CVVH was performed using a NxStage System One Cycler (NxStage Medical Inc., Lawrence, MA) and a high-flux polysulfone dialyser (FX80 CorDiax; Fresenius Medical Care, Bad Homburg, Germany) with a 1.8 m^2 surface. The blood flow rate was 150–180 mL/min and replacement fluid was infused by post-dilution at 35 mL/kg/h. The flow rate of ultrafiltrate during CVVH was calculated as:

Eq. (1) $$\text{Flow rate of ultrafiltrate} = [(F_{subst} * t_{di}) + UF_{vol}] / t_{di}$$

where F_{subst} is the flow rate of the replacement fluid, t_{di} is the time (h) within the dosing interval during which CVVH was applied, and UF_{vol} is the net ultrafiltrate volume (L) within the dosing interval.

Gentamicin concentrations were measured using fluorescence polarisation immunoassay (FPIA) technology on an AxSYM System (Abbott Diagnostics, Abbott Park, IL). The limit of detection was 0.49 mg/L. Accuracy at concentrations of 1, 4 and 8 mg/L was 108.2%, 110.7% and 106.9%, respectively. Intraday precision at concentrations of 1, 4 and 8 mg/L was 6.1%, 2.9% and 4.9%, respectively, and interday precision at these concentrations was 5.9%, 4.6% and 5.0%, respectively.

Population pharmacokinetic data analysis

Gentamicin concentration–time data were analysed using nonlinear mixed-effects modelling (NONMEM v.7.1.2; Icon Development Solutions, Ellicott City, MD) [25]. A three-step approach was undertaken during the modelling process.

During the first step, a compartmental population PK model was developed, quantifying gentamicin Vd and CL. For models with two or more compartments, these parameters were central and peripheral volume(s) of distribution (V1, V2, V3, etc.) and CL and intercompartmental clearance (Q1, Q2, etc.). Moreover, IIV was estimated in the PK parameters assuming a log-normal distribution. In addition, interoccasion variability (IOV) was estimated since the pharmacokinetics of gentamicin in a critically ill patient can vary substantially over time [26]. Residual variability was estimated by testing additive, proportional and combined error models. TBW, IBW and ABW were tested as a covariate for allometric scaling. Since IBW resulted in the best fit, PK parameters were allometrically scaled to 70 kg IBW [21, 22, 27]. The effect of CVVH was taken into account as shown in Eq. (2), not only allowing an estimation of different

values for CL in an individual patient (CL_i) on or off CVVH, but also allowing the estimation of IIV in CL when on CVVH (CL_{CVVH}) and when off CVVH (CL_{noCVVH}):

Eq. (2) Off CVVH $CL_{ij} = \theta_{noCVVH} * (IBW_i/70)^{0.75} * \exp(\eta_{noCVVHi} + \kappa_{noCVVHj})$

On CVVH $CL_i = \theta_{CVVH} * (IBW_i/70)^{0.75} * \exp(\eta_{CVVHi})$

where CL_{ij} is the gentamicin CL for individual *i* on occasion *j*, θ_{noCVVH} and θ_{CVVH} are population values for CL when off and on CVVH, respectively, $\eta_{noCVVHi}$ and η_{CVVHi} are estimates of IIV in CL when off and on CVVH, respectively, both with mean 0 and variance ω^2, and $\kappa_{noCVVHj}$ is the estimate for IOV in CL when off CVVH with mean 0 and variance π^2 [26].

During the second step, different covariates other than IBW and CVVH were tested for their correlation with gentamicin Vd (V1 and/or V2) and CL. First, the following variables were tested using univariate analysis: age; sex; height; SCr; CGCLCr; CalcCLCr; total daily diuresis, fluid balance of the concerning day; fluid balance since ICU admittance; albumin level; APACHE II score; administration of TPN; and flow rate of ultrafiltrate during CVVH. If covariate data were not available from the same day that the sample was drawn for gentamicin concentration measurement, they were considered missing. Handling of missing covariate data was done in such a way that concentration–time data from patients for whom covariate data were missing were ignored in estimating the correlation between PK parameter and covariate, as described previously [28]. This yielded estimation of a missing-data parameter for every covariate effect. When renal function was evaluated as a covariate on gentamicin CL, SCr, CGCLCr and CalcCLCr values were ignored (counted as missing) when a patient received CVVH in the preceding week, as SCr (which is used in these values) reflects creatinine clearance by CVVH and not renal function in the first period after CVVH.

Subsequently, an intermediate covariate model was constructed with all statistically significant covariates, after which a backward elimination procedure was performed. This yielded the final model prior to refinement.

During the third step, the model resulting from the second step was validated and refined based on visual predictive checks (VPCs) [29]. Four separate VPCs were performed with SCr, CGCLCr, CalcCLCr and total daily diuresis, respectively, as measures of renal function, to visualise which measure best predicts CL. VPCs

were performed prediction-corrected [30], with time after dose as independent variable and with the binning array 0.98, 1.21, 2.83, 8.50, 12.4, 23 and 36 h. These last two bins were chosen since selection of the dosing interval for gentamicin is often based on the concentration at 24 h or 36 h after administration. In addition, the model was validated using 1000 bootstrap replicates.

The first-order conditional estimation method with interaction was used throughout the modelling process. Whether addition of a parameter to the model resulted in improved fit was judged by a decrease of the objective function value (OFV) of at least 3.8 points, corresponding to a $P < 0.05$ in a χ^2 distribution with one degree of freedom. During the backward elimination procedure, an increase of at least 10.8 points ($P < 0.001$) was required for a covariate not to be rejected. In addition to a change in OFV, improvement in goodness-of-fit plots, as judged by visual inspection, was an important factor for selecting one model over another. Moreover, the precision with which parameters were estimated was taken into consideration (<30% for fixed-effects parameters and <80% for random-effects parameters) as well as the shrinkage of random effects parameters (which should be <30% [31]). Pirana v.2.7.1 (Pirana Software & Consulting BV, The Netherlands) [32] was used for model management, Xpose v.4.3.2 (Uppsala University, Uppsala, Sweden) [33] was used for the creation of goodness-of-fit plots, and PsN v.3.5.3 (Uppsala University) [34] was used for the performance VPCs.

Results

Data from 44 ICU-admitted patients who received a total of 174 doses of gentamicin (median 4 doses per patient; range 1–11 doses) were included in the analysis. Of these patients, 8 patients had two treatment episodes and 1 patient had three treatment episodes. In these 44 patients, gentamicin levels were routinely measured in a total of 303 serum specimens, of which 81 were taken after the first dose of the first treatment episode, 17 after the first dose of a subsequent treatment episode and 205 after subsequent doses. On average, 1.7 samples were taken in each dosing interval (range 0–5 samples). Baseline characteristics of critically ill patients receiving gentamicin are shown in Table 1. Of the 303 specimens, 76 (25%) were collected during CVVH. The median gentamicin starting dose was 4.0 mg/kg TBW (range 2.0–6.6 mg/kg TBW, reflecting deviations from the guidelines in clinical practice as well as lower dosing for synergistic effect in endocarditis in five patients). The

concentration–time data as shown in Fig. 1 illustrate the high variability in Cmax and concentrations at 24 h after infusion and beyond.

Table 1

Baseline characteristics of critically ill patients receiving gentamicin (N = 44)

Characteristic	Median (range)[a]
Sex male [N (%)]	20 (45)
Age (years)	61 (20 - 78)
Total body weight (kg)	70.5 (42.0 - 116)
Ideal body weight (kg)	68.2 (55.6 - 87.5)
Height (cm)	170 (154 - 195)
Admission category [N (%)]	
Medical	19 (43)
Surgical	25 (57)
Trauma	0 (0)
APACHE II score	17 (6 - 33)
SCr (μmol/L)	115 (36 - 1719)
CGCLCr (mL/min)	54.9 (4.0 - 150)
CalcCLCr (mL/min)	48.3 (0 - 130)
Patients on CVVH [N (%)]	5 (11.3)
Albumin level (g/L)	21.5 (10 - 36)

APACHE = Acute Physiology and Chronic Health Evaluation; SCr = serum creatinine; CGCLCr = creatinine clearance estimated by the Cockcroft–Gault formula; CalcCLCr = creatinine clearance calculated from the creatinine concentration in a 6 h urine portion; CVVH = continuous venovenous hemofiltration.

[a] Data are median (range) unless otherwise stated.

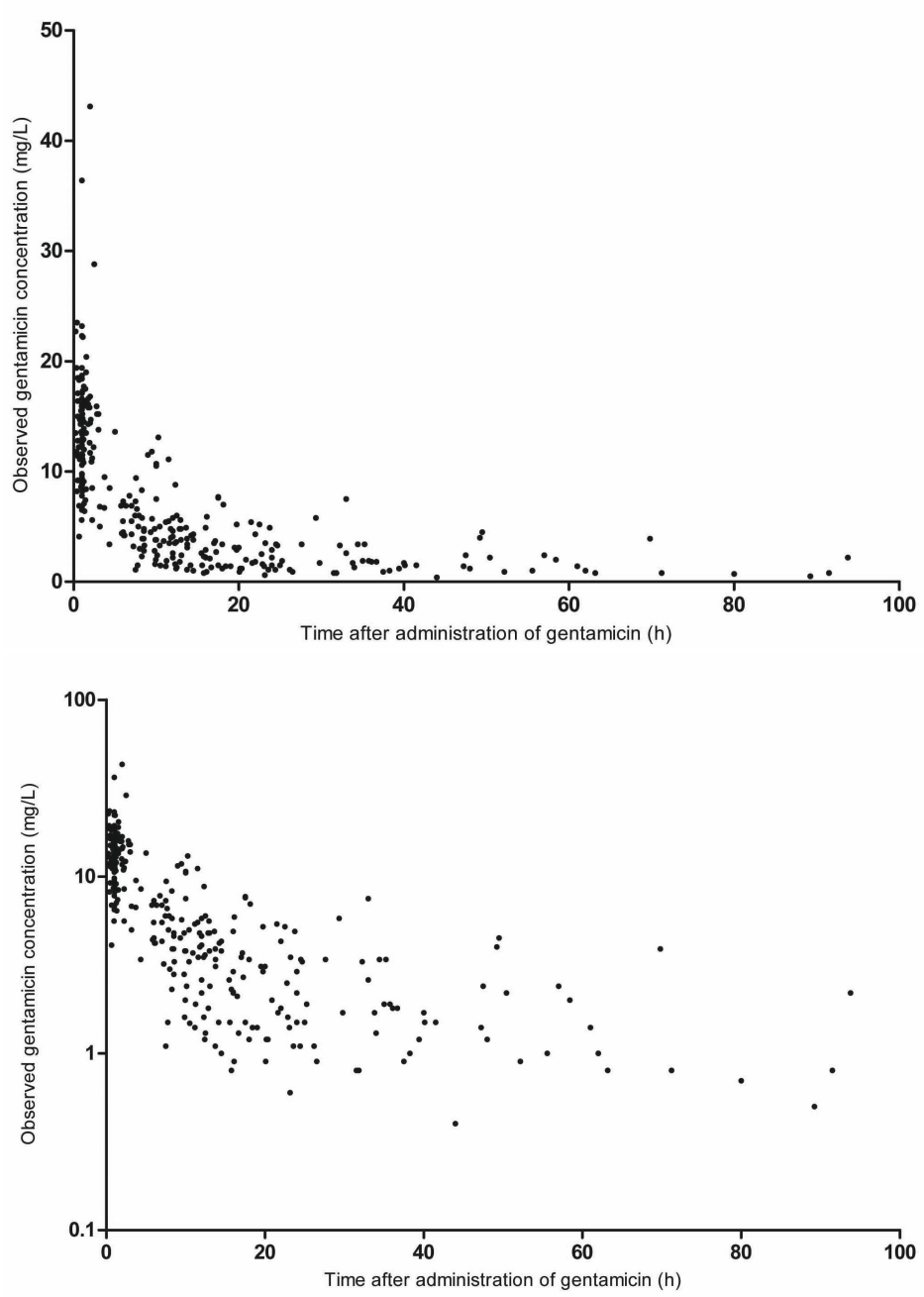

Fig. 1 Concentration-time data: (A) linear scale, illustrating the variation in gentamicin peak levels; and (B) logarithmic scale, illustrating the variation in gentamicin trough levels.

During the first step of the data analysis, the data best fitted a two-compartment model with first-order elimination. IIV could be estimated for CL_{noCVVH}, CL_{CVVH} and V1. IOV could be estimated for CL_{noCVVH}. A proportional error model best described the residual variability. Parameter estimates of this structural model are presented in Table 2. The parameters were estimated with acceptable precision, with a relative standard error of <30% for fixed-effects parameters and <80% for random-effects parameters.

Table 2

Parameter estimates of the structural model.

Parameter	Basic model		Final model		Bootstrap of final model	
	estimate	RSE (%)	estimate	RSE (%)	estimate	95% CI
CL_{noCVVH} (L/h/70 kg)	1.92	24	1.15	14.9	1.17	0.868 - 1.58
CL_{CVVH} (L/h/70 kg)	2.08	8.8	2.13	7.9	2.13	1.76 - 2.50
V1 (L/70 kg)	21.2	4.6	21.2	5.4	21.0	18.6 - 23.6
Q (L/h/70 kg)	2.25	26.5	1.96	20.7	1.97	1.22 - 3.34
V2 (L/70kg)	18.9	8.5	18.4	9.5	18.4	14.8 - 23.2
Interindividual variability (IIV)[a]						
CL_{noCVVH} (CV%)	76.6	46.1	42.5	27	45.0	20.4 - 76.5
CL_{CVVH} (CV%)	27.0	72.8	29.5	30.8	28.3	11.0 - 47.9
V1 (CV%)	21.6	41.4	17.2	25.3	17.1	7.91 - 25.7
Correlation (*r*) between IIV CL_{noCVVH} and V1	0.54	67	0.54	91	0.46	- 1 - 0.69
Interoccasion variability (IOV)[a]						
CL_{noCVVH} (CV%)	38.6	48.9	-	-	-	-
Residual variability						
Proportional error (%)	29.6	8	33.8	8	33.4	28.2 - 38.9
Covariate effects						
Albumin level on V1	-	-	-0.833	21	-0.859	- 1.27 - -0.515
CalcCLCr on CL_{noCVVH}	-	-	0.0132	39	0.0124	0.00497 - 0.0227
Correction parameter when CalcCLCr is missing	-	-	1.39	16	1.42	0.968 - 2.17

RSE = relative standard error; CI = confidence interval; CL_{noCVVH} = gentamicin clearance when patient is off CVVH; CVVH = continuous venovenous hemofiltration; CL_{CVVH} = gentamicin clearance when patient is on CVVH; V1 = gentamicin central volume of distribution; Q = gentamicin intercompartmental clearance; V2 = gentamicin peripheral volume of distribution; CV = coefficient of variation; CalcCLCr = creatinine clearance calculated from a 6 h urine portion.

[a] Calculated as the square root of $(e^{\omega}-1) * 100$.

During the second step, using univariate analysis, the covariates SCr, CGCLCr, CalcCLCr, albumin level, APACHE II score and total daily diuresis were associated with gentamicin CL (P <0.05) in patients not on renal replacement therapy. SCr, CGCLCr, CalcCLCr, albumin level and administration of TPN showed statistically significant (P <0.05) univariate correlations with CL_{CVVH}, and albumin level and fluid balance since ICU admittance with V1. After the backward elimination procedure, the correlation between albumin level and V1 and between each of the four measures of renal function (SCr, CGCLCr, CalcCLCr and total daily diuresis) and CL_{noCVVH} were retained in four separate models (one for each renal function measure), as exclusion of these correlations resulted in a significant increase of the OFV of >10.8 units (P <0.001). With inclusion of the correlation between a measure of renal function and CL_{noCVVH}, it appeared that exclusion of IOV CL_{noCVVH} did not result in a worsening of the OFV of >3.8 units or of the goodness of fit. This parameter was therefore rejected from the model. All tested covariate data were 100% available, except the CalcCLCr data, of which 71.0% were available for modelling.

During the third step, final model selection out of the four models resulting from the second step took place by creating VPC plots: model 1 included SCr; model 2 included CGCLCr; model 3 included CalcCLCr; and model 4 included total daily diuresis as measure of renal function. All measures of renal function underestimated observed gentamicin levels obtained >36 h after administration to some extent, i.e. in patients with the most severely impaired renal function (Table 3). The VPC plots show that CalcCLCr gives the best prediction of gentamicin CL for patients not on CVVH (Fig. 2c), leading to the smallest underestimation of observed gentamicin levels obtained >36 h after administration, whilst SCr results in the largest underestimation (Fig. 2a) (prediction-corrected median difference of 0.26 mg/L using CalcCLCr vs. 0.68 mg/L using SCr).

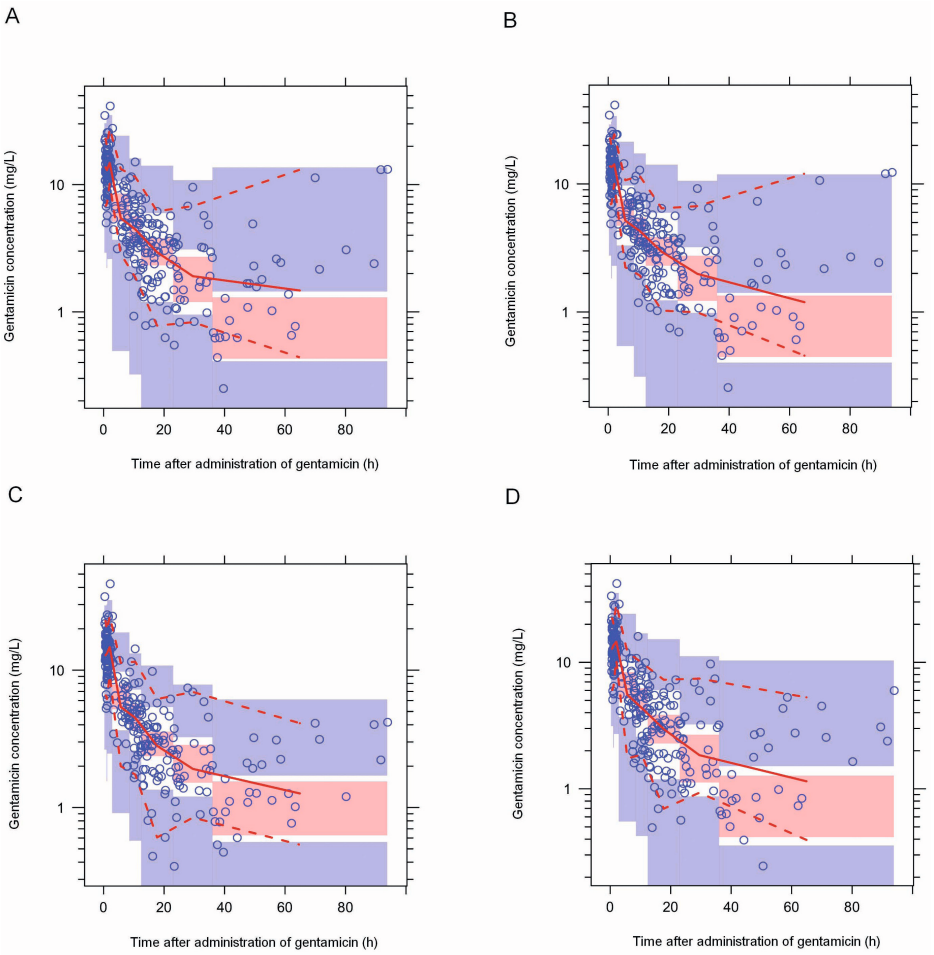

Fig. 2 Visual predictive checks (VPCs) of the two-compartmental model of gentamicin with one of the following measures of renal function as covariate on gentamicin clearance in patients not on continuous venovenous hemofiltration: (A) serum creatinine (SCr); (B) creatinine clearance estimated according to the Cockcroft–Gault formula; (C) creatinine clearance calculated from a 6 h urine portion; and (D) total daily diuresis. Solid and dotted lines are the observed median and 5th and 95th percentiles per bin, respectively. The red area is the 95% confidence interval (CI) around the simulated median, and the blue areas are the 95% CIs around the simulated 5th and 95th percentiles. Solid lines above a red area and dotted lines above a blue area indicate underestimation of observed gentamicin levels.

Table 3

Bias of the simulated gentamicin level relative to the observed level.

Time frame after administration	Measure of renal function	Observed level (mg/L)	Simulated level (95% CI) (mg/L)
23-36 h	SCr	1.91	1.87 (1.20 - 2.71)
	CGCLCr	1.98	1.89 (1.22 - 2.75)
	CalcCLCr	1.91	2.09 (1.52 - 2.86)
	Total daily diuresis	1.84	1.79 (1.12 - 2.68)
>36 h	SCr	1.47	0.79 (0.43 - 1.30)
	CGCLCr	1.19	0.80 (0.45 - 1.34)
	CalcCLCr	1.26	1.00 (0.63 - 1.54)
	Total daily diuresis	1.15	0.77 (0.41 - 1.27)

CI = confidence interval; SCr = serum creatinine; CGCLCr = creatinine clearance estimated according to the Cockcroft–Gault formula; CalcCLCr = creatinine clearance as calculated from a 6 h urine portion.

Values are prediction-corrected medians.

Thus, the final model included separate estimates for CL on or off CVVH, a correlation between albumin level and V1, and a correlation between CalcCLCr and CL_{noCVVH}, as shown in Equations 3 and 4 (the latter is derived from Eq. 2):

Eq. (3) $$V1_{ij} = 21.2 * (IBW_i/70) * (ALBM_{ij} / 22)^{-0.833}$$

where $V1_{ij}$ is the estimated gentamicin V1 of individual *i* on occasion *j*, IBW*i* is the estimated IBW of individual *i*, and ALBM*ij* is the albumin level of individual *i* on occasion *j*.

Eq. (4) Off CVVH

$$CL_{ij} = 1.15 * (IBW_i/70)^{0.75} * [1 + 0.0131 * (CalcCLCr_{ij} - 30) * FLAG_{ij}] * 1.39^{(1-FLAGij)} * \exp(\eta_{noCVVHi})$$

On CVVH

$$CL_i = 2.13 * (IBW_i/70)^{0.75} * \exp(\eta_{CVVHi})$$

where $FLAG_{ij}$ is 1 when CalcCLCr data were present and 0 when CalcCLCr data were missing for individual *i* on occasion *j*.

According to Eq. (3), a 'typical' patient with all median characteristics of the study population and an IBW of 70 kg will have a gentamicin V1 of 16.3 L when the albumin level is 30 g/L but a V1 of 29.2 L when the albumin level is 15 g/L ($P < 0.001$). This means that almost all patients with a serum albumin level of <15 g/L and approximately one-half of the patients with a serum albumin level between 15–25 g/L suffer from subtherapeutic gentamicin Cmax. Albumin level explained 25% of IIV in V1. Fig. 3 shows the association of albumin level with V1 (Fig. 3a) and Cmax (Fig. 3b).

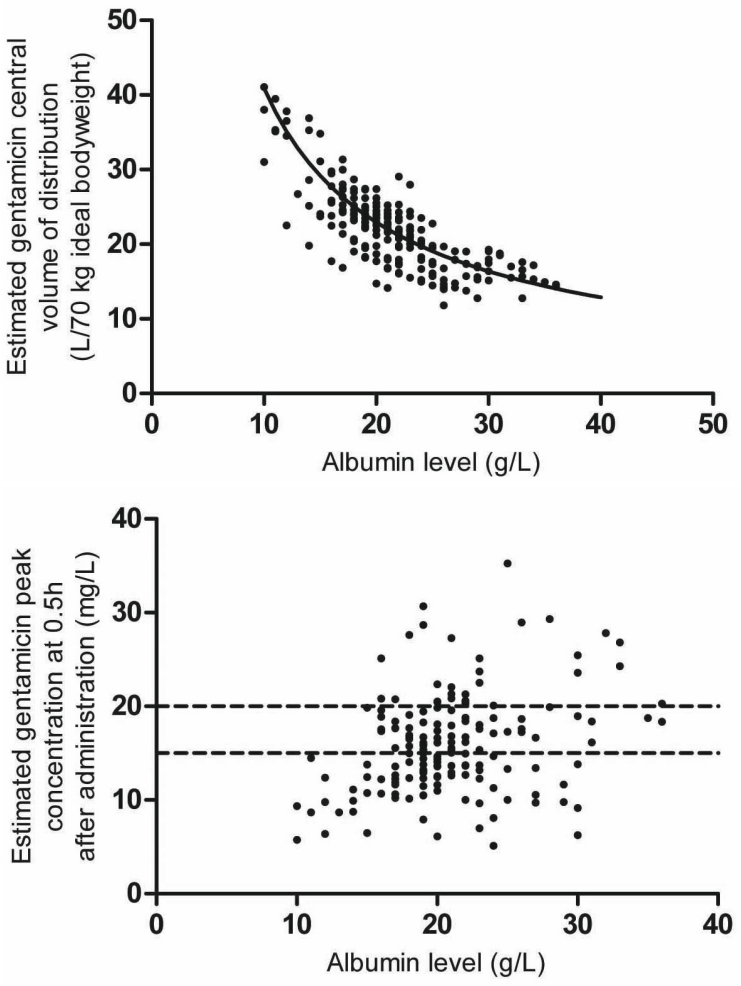

Fig. 3 Correlations between albumin level and (a) central volume of distribution (V1) and (b) peak concentration (Cmax).

Eq. (4) shows that with every unit increase in CalcCLCr, gentamicin CL_{noCVVH} will increase by 0.0131 L/h. So, a typical patient, not receiving CVVH and with an

IBW of 70 kg, will have a CL of 1.90 L/h when CalcCLCr is 80 mL/min but a CL of 0.92 L/h when CalcCLCr is 15 mL/min. This correlation explained 36% of IIV in V1 and 64% of IIV in CL_{noCVVH} (calculated based on the estimated values for ω^2). Eq. (4) also shows that CL_{noCVVH} was estimated to be 39% higher for patients and at moments when CalcCLCr data were missing compared with when CalcCLCr data were present, although this parameter was not significantly different from 1 [1.39, 95% confidence interval (CI) 0.94–1.84]. To check whether the inclusion of gentamicin concentrations with missing CalcCLCr data influenced the results, we have repeated the population PK analysis using the final model, but including only the concentrations for which CalcCLCr data were available. This analysis provided parameter estimates comparable with those obtained with the whole data set: the fixed-effects parameters (CL_{CVVH}, CL_{noCVVH}, V1, V2, Q and the parameters describing the covariate effects) estimated with the reduced data set were all within the 95% CIs of those for the complete data set, and differences between these estimates were all <30%.

The results of the final model matched the results of the bootstrap of the final model.

Discussion

We developed a population PK model of gentamicin in critically ill patients to quantify the impact of several patient parameters on gentamicin Vd (which is correlated with Cmax, which is in turn correlated with treatment success) and to address which measure of renal function best predicts gentamicin CL (to avoid accumulation and its associated toxicity). Serum albumin level was significantly associated with Vd. Critically ill patients with albumin levels of <15 mg/L may be at risk for Cmax below the target range of 15–20 mg/L. Gentamicin CL was estimated reasonably well by using CalcCLCr, but was overestimated using SCr or CGCLCr.

The finding that patients with hypoalbuminaemia demonstrate an expanded Vd confirms the observations of previous studies [35, 36]. Hypoalbuminaemia may be caused by intravascular volume expansion due to resuscitation fluid administered in case of septic shock, or to loss of albumin due to endothelial leakage during sepsis. We recommend that especially for critically ill patients with hypoalbuminaemia, Cmax should be measured immediately after the first dose to facilitate adequate dosing of the second gentamicin administration, which is likely to be a higher dose than the starting dose. At least a 150% higher starting dose may be necessary to achieve a therapeutic Cmax in patients

with albumin levels of <15 mg/L. However, this remains to be determined in a prospective setting.

Because gentamicin is a hydrophilic molecule, one would expect fluid balance to have an impact on Cmax. Surprisingly, fluid balance was not associated with gentamicin Vd in the multivariate analysis. However, fluid balance, although based on the best possible data that can be collected in routine clinical care, remains difficult to assess. Moreover, measurement of fluid balance was started only after ICU admittance, so the influence of fluid administration in other hospital departments could not be taken into account. Therefore, we cannot rule out an effect of fluid balance.

When estimating the ability of different measures of renal function to predict gentamicin CL, CalcCLCr was found to perform best, showing the least underestimation of Cmin (Table 3; Fig. 2). The investigated measures of renal function that are commonly used in clinical practice (e.g. CGCLCr) are known to overestimate renal function in critically ill patients [11, 20, 37], thereby underestimating the gentamicin Cmin (Fig. 3b), potentially leading to selection of inappropriately short dosing intervals [38]. This is especially true for SCr as a measure of renal function (Fig. 3a). We therefore discourage using these parameters for determining gentamicin dosing intervals in critically ill patients. Possible future rapid and affordable glomerular filtration rate measurement techniques may help to accurately measure renal function in these patients [39].

There are some limitations to this study, inherent to its retrospective design. IOV in CL was not included in the final model because it did not significantly improve the predictions. However, since the clinical situation in a critically ill patient can change considerably during the course of gentamicin therapy, it is likely that IOV in CL does exist. It is possible that more measurements per patient over different dosing intervals would result in a more reliable estimate of the IOV.

Another limitation may be that the median gentamicin dosage used during the study period was relatively low (4 mg/kg). Currently, higher doses of 5–8 mg/kg are used in The Netherlands. Moreover, the targeted concentrations based on Dutch guidelines are lower than in many other countries [40]. However, for modelling purposes, this relatively low dose results in reliable results because gentamicin is consistently reported as exhibiting linear pharmacokinetics. Obviously, dosing at 4 mg/kg provides a lower probability of achieving the target gentamicin Cmax in critically ill patients compared with the current doses.

In addition, the CVVH modality as used at our ICU was included in the analysis. The resulting parameter estimate for CL_{CVVH} is likely not to be applicable in patients who are treated with other forms of CVVH.

Moreover, the correlation between CalcCLCr and gentamicin CL was based on 215 concentration–time data points out of 303 samples (71.0%). To calculate the strength of this correlation, the samples for which CalcCLCr was unavailable were ignored and an adjustment factor was introduced. Inclusion of data from patients without any renal information was considered to be useful as associations between PK parameters and other covariates could be investigated. Additional population PK analysis using only the gentamicin concentrations for which CalcCLCr data were available provided parameter estimates comparable with those obtained with the whole data set.

A final limitation of this study may be data on timing of gentamicin administration and sample collection, which were used as registered during routine care. Probably, there are differences between the registered and actual timing of dose administration and sample collection. This may have hampered accurate estimation of PK parameters and may explain the relatively high residual variability of 33.8%.

A strength of this study is the routine measurement of gentamicin Cmax following the first dose, with subsequent follow-up trough samples. As a result, concentrations were available during the whole dosing interval, from 0 to 94 h after administration (Fig. 1). These data allowed us to model the complete concentration–time curve, also taking into account the patients with low CL that reached target Cmin levels (<1 mg/L) far beyond 24 h after drug administration.

Conclusion

For critically ill patients with hypoalbuminaemia, a peak serum concentration (Cmax) should be measured immediately after the first dose to facilitate adequate dosing of the second gentamicin administration. A higher starting dose should be considered for these critically ill patients. Also, gentamicin CL was overestimated by using SCr level or CGCLCr, whilst calculation of creatinine clearance from a urine portion (CalcCLCr) resulted in acceptable estimation of gentamicin CL. The former two measures of renal function might lead to application of inappropriately short dosing intervals with subsequent toxicity and are therefore not recommended for guidance of the gentamicin dosing interval in critically ill patients.

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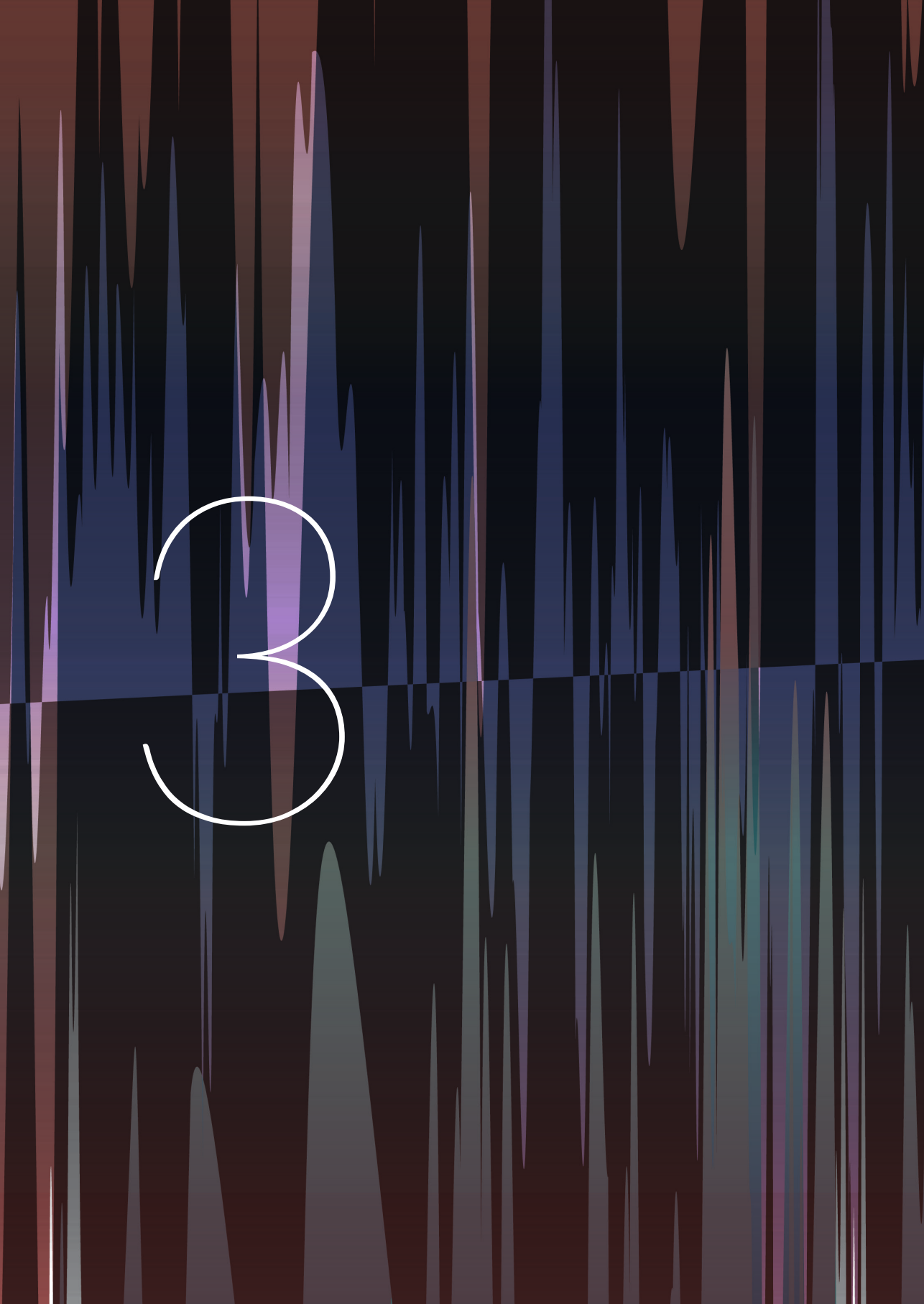
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Predictive performance of a gentamicin population pharmacokinetic model in two western populations of critically ill patients

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Int J Antimicrob Agents. 2018 Aug;52(2):218-225. DOI: 10.1016/j.ijantimicag.2018.04.016.

Abstract

External validation of population pharmacokinetic (PK) models is warranted before they can be clinically applied to aid in antibiotic dose selection. The primary objective of this study was to assess the predictive performance of a gentamicin population PK model in intensive care unit (ICU) patients in two independent western populations of critically ill patients.

Methods: Data were collected from the ICU where the model was developed (Academic Medical Center, Amsterdam [AMC]) and from the Centre Hospitalier Universitaire de Nîmes (CHU Nîmes). Primary end-points were bias and accuracy. The model was regarded as valid if bias was not significantly different from 0 and accuracy was equal to or less than 2.5 mg/L. Non-linear mixed-effects modelling (NONMEM) was used for data analysis.

Results: The AMC validation dataset consisted of 192 samples from 66 ICU patients and the CHU Nîmes dataset of 230 gentamicin samples from 50 ICU patients. The structural model predicted the gentamicin plasma concentrations in the AMC population with a non-significant bias (0.35, 95% CI: -0.11–0.81) and a sufficient accuracy of 2.5 mg/L (95% CI: 2.3–2.8). The gentamicin plasma concentrations were overpredicted in the CHU Nîmes population with a significant bias of 4.8 mg/L (95% CI: 4.00–5.62) and an accuracy of 5.5 mg/L (95% CI: 4.7–6.2).

Conclusion: The model is valid for use in the AMC ICU population but not in the CHU Nîmes ICU population. This illustrates that caution is needed when using a population PK model in an external population.

Introduction

Aminoglycosides, particularly gentamicin, are often included in empirical broad-spectrum antibiotic therapy for treatment of severe sepsis. Administering an effective dose of the correct drug as soon as possible to a septic patient has been shown to decrease mortality rate [1–3]. In the case of gentamicin, the dose is considered appropriate when a maximum gentamicin plasma concentration (Cmax)/minimum inhibitory concentration (MIC) ratio of 8–10 is classically targeted, leading to faster clinical response and an increased probability of cure [4–6]. According to Dutch therapeutic drug monitoring (TDM) guidelines, a gentamicin Cmax of 15–20 mg/L is considered therapeutic, whereas French gentamicin dosing guidelines recommend targeting 30–40 mg/L [7–9]. There is large interindividual variability (IIV) in gentamicin pharmacokinetics (PK) in intensive care unit (ICU) patients, which means the probability that a Cmax/MIC ≥8–10 is reached with a starting dose of 5 mg/kg is only 27% for organisms with an MIC of 1 mg/L [10, 11].

Population PK models can be used to interpret the complex PK in critically ill patients and identify covariates that explain part of the IIV. Such models can aid in selecting the correct starting dose and optimising individual dosing regimens. Previously, Hodiamont et al. developed a population PK model for gentamicin in ICU patients [12]. Plasma albumin concentrations were identified as a significant covariate on the central volume of distribution. Continuous venovenous hemofiltration (CVVH) and creatinine clearance calculated based on a 6 h urine portion (CalcCLcr) as a measure of renal function were identified as covariates on clearance [12]. External validation of this model is necessary to confirm whether it can be used reliably for calculation of the appropriate gentamicin (starting) doses. The primary objective of this study was to externally validate the previously developed population PK model by evaluating its predictive performance in cohorts from two different ICUs. A secondary objective of the study was to validate the effect of albumin on volume of distribution of gentamicin in ICU patients to ascertain whether this covariate could aid in selecting the initial dose.

Materials and methods

Patients and data

Datasets from two ICU populations were used for external validation of the population PK model. For the first cohort, data were collected from the

department where the model was developed, the ICU of the Academic Medical Center (AMC) Amsterdam, The Netherlands. Data were collected between November 7, 2016 and March 15, 2017 in a prospective observational design. All adult (≥18 years) patients admitted to the ICU who were receiving gentamicin were included, provided that at least one gentamicin concentration measurement was available. Pregnant patients and patients on hemodialysis were excluded. The AMC Institutional Review Board reviewed the study and waived informed consent as therapeutic drug monitoring (TDM) is routinely conducted at the ICU of the AMC and only anonymous data obtained during routine clinical care were used in this study.

Patients received a gentamicin starting dose of 5 mg/kg total body weight if sepsis of unknown origin was suspected or 3 mg/kg total body weight as part of endocarditis treatment. Part of the samples for the dataset originated from TDM. To verify whether the Cmax was therapeutic (15–20 mg/L), a sample was drawn 30 min after ending the first gentamicin administration, which was infused over 30 min. A follow-up blood sample was drawn the next morning around 06:00 hours; this was used to estimate when the gentamicin concentration dropped below 1 mg/L and thus when the next dose could be administered. Follow-up samples were collected at least three times a week to check whether the dosing interval was still appropriate. Samples of waste material from blood gas samples drawn from the ICU patients treated with gentamicin were also collected to assure random sampling. Samples were stored at room temperature for a maximum of 96 h and centrifuged at 2750 x g for 5 min to separate the blood plasma, which was stored at -80 °C and analysed within 100 days [13]. Time points of gentamicin administration and blood sample collection were witnessed during the day where possible and otherwise collected as registered in the electronic patient data information system of the hospital. Moreover, the duration of infusion was witnessed, as this duration often differs from the 30 min infusion prescribed in the protocol.

Gentamicin plasma concentrations were measured with a Fluorescence Polarization Immunoassay (Cobas Integra 400+ autoanalyser). The Cobas has a lower limit of quantification (LLOQ) of 0.5 mg/L and the accuracy was 96.1%, 104.0% and 103.1% at concentrations of 2.16, 4.86 and 7.88 mg/L, respectively.

The following patient characteristics were collected from the electronic patient data information system of the hospital: age, sex, total body weight (TBW), height, creatinine level, albumin serum concentration, total daily diuresis (TDIU),

application of CVVH and the severity of disease described by the sequential organ failure assessment (SOFA) score. TDIU data were collected as a measure for renal function as data on CalcCLcr levels were not available and TDIU was found to be the second-best parameter predicting gentamicin clearance in the previously developed model [12]. An albumin level was denoted as missing when no albumin level was known 24 h before or after a gentamicin infusion or a gentamicin sample collection, whereas all other parameters, such as SOFA score and TDIU, were denoted as missing when no value was recorded 12 h before or after a gentamicin infusion or a gentamicin sample collection. The ideal body weight (IBW) was calculated according to equations (1) and (2). The dataset thus created is referred to as the AMC data.

Eq. (1) IBW_{men} (kg) = 50 + 0.91 * (height (cm) − 152)

Eq. (2) IBW_{women} (kg) = 45 + 0.91 * (height (cm) − 152)

The second dataset came from the Centre Hospitalier Universitaire (CHU) in Nîmes, France [7, 14]. As this is an observational study, the Institutional Review Board approved the study and waived the need for consent. The data were collected in ICU patients (≥18 years) who received gentamicin in one of the following two periods: June 2 until November 29, 2013 or October 30, 2014 until March 10, 2015. The data from the two periods were combined into one dataset as there were statistically significant differences ($P < 0.05$) between both periods in only age and SOFA score, which were not identified as significant covariates in the previously developed model, thus no influence on the predictive performance was expected. In the first inclusion period, patients received a starting dose of at least 3 mg/kg gentamicin based on their TBW at admission. During the second period, 8 mg/kg body weight gentamicin was administrated as starting dose. During both periods, gentamicin was administrated in a 30 min intravenous infusion and Cmax, 30 min after the end of infusion, and trough levels were routinely collected and measured with an automated Immunoassay with a Cobas C system. The LLOQ was 0.4 mg/L and three levels of quality control were performed daily (1.7, 4.5 and 6.8 mg/L). Information for this study on albumin concentrations, application of CVVH, creatinine concentrations, TDIU, SOFA score, weight, height, age and sex were collected retrospectively from the electronic patient files. IBW was calculated using equations (1) and

(2). Missing data were handled as in the AMC dataset. This dataset is referred to as the CHU Nîmes data.

Data analysis

Using the two datasets, the previously developed population PK model for gentamicin [12] was validated using Bayesian estimation in NONMEM (v7.3.0, Icon Development Solutions, Ellicott City, USA) [15]. The population PK parameters were fixed to the final estimates of the previously developed model and maximum evaluations (MAXEVAL) was set to 0. The predictive performance of this model without covariates (the structural model) and with covariates (the final model) was examined.

The structural population PK model is a two-compartment model with allometrically scaled PK parameters to an IBW of 70 kg. A clearance parameter was estimated separately for patients on and off CVVH. IIV was estimated on the central volume of distribution and on both clearance parameters, using a log-normal distribution. Interoccasion variability (IOV) was estimated on the clearance parameter off CVVH. The final model included a negative association between albumin level and central volume of distribution and a positive correlation between TDIU and clearance off CVVH. The model including TDIU as covariate on clearance off CVVH was used as CalcCLcr data were not available. Details on the structural and final model can be found in [12].

The predictive performance of the model was evaluated by comparing the population predicted concentrations (Cpred) with the observed concentrations in the datasets (Cobs). Primary end-points for the predictive performance were the mean error (ME, equation (3)) and mean absolute error (MAE, equation (4)) calculated as measurements for bias and accuracy [16, 17].

Eq. (3)
$$ME = \frac{1}{n}\sum_{j=1}^{n}(Cpred - Cobs)$$

Eq. (4)
$$MAE = \frac{1}{n}\sum_{j=1}^{n}|Cpred - Cobs|$$

Where n represents the number of observations of all individuals. If 0 was included in the 95% confidence interval (CI) of ME, no significant bias was present. When this was the case and a MAE of ≤2.5 mg/L was obtained, the model was regarded valid. The MAE cut-off of 2.5 mg/L was chosen because

a deviation of 2.5 mg/L from 17.5 mg/L, the middle of the therapeutic window of Cmax (15–20 mg/L), still results in a therapeutic Cmax and there is a less than 50% chance of a false positive indication for dose adjustment. To visualise the predictive performance, Bland-Altman plots and Visual Predictive Checks (VPCs) were created [18]. PsN (v3.5.3, Uppsala University, Sweden) was used for the creation of VPCs [19]. Pirana (v2.9.4., Software & Consulting BV, The Netherlands) was used for model management.

The PK of gentamicin from the present validation study was compared with the PK of gentamicin in the ICU population in which the model was developed. Both validation datasets were fitted (MAXEVAL >0) to the structural model using the first-order conditional estimation method with interaction in NONMEM (FOCE + I). The final population parameter estimates from the previously developed model served as initial estimates. The newly estimated PK parameters of the two validation data sets were compared with the parameter estimates of the previously developed structural model and their 95% CI.

For the secondary objective of this study, the data from the cohorts were fitted to the previously developed final model with and without albumin as a covariate on central volume of distribution (V1), using FOCE + I. A correction for missing albumin values was applied, as described earlier [20]. When the objective function value (OFV), calculated based on the likelihood ratio test, increased by 3.84 units or more [15] for the final model without albumin relative to the final model with albumin, albumin was regarded as having a statistically significant association with V1 ($P < 0.05$ based on a χ^2-distribution with 1 degree of freedom). Furthermore, an increase in the estimate of IIV in V1 was considered as an indication that less IIV was explained without this covariate. When albumin was found to significantly influence V1, Cmax and V1 after the first dose (Cmax after subsequent doses are affected by TDM) were plotted against albumin to visualise this association. Cmax was calculated as the individual prediction of the gentamicin concentration 30 min after the end of gentamicin administration.

Statistics

Statistical tests were performed using SPSS Statistics (v23, IBM, USA). Continuous variables were tested with the unpaired T-test if normally distributed. The Mann Whitney U test was executed when continuous variables were non-normally distributed. Categorical variables were analysed using the Chi-square test. A P-value <0.05 was regarded as statistically significant.

Results

Data

Sixty-six patients receiving a total of 122 gentamicin administrations were included in the AMC dataset. One patient was excluded because of hemodialysis treatment. A median of 1 dose was administered per patient with a range of 1 to 7. The AMC data consisted of 192 gentamicin concentration-time samples. Of these, 131 (68%) were routinely collected samples during TDM and 61 (32%) were collected from waste material blood samples. An average of 2.9 samples were measured per patient, with a median of 1 sample per dose interval (range 1 to 8). The number of concentrations below the limit of quantification (BLQ: <0.5 mg/L) was 15, i.e. 7.8% of all samples, and these were excluded. Fifty-six patients received gentamicin for the treatment of sepsis and 8 for endocarditis. Two patients were treated with gentamicin because of pneumonia risk after submersion in or aspiration of freshwater. The parameters IBW, CVVH, albumin and TDIU that were used in the previously developed model were available in 80%, 100%, 79% and 100% of patients, respectively.

The CHU Nîmes data consisted of 50 patients who received a total of 149 gentamicin administrations (median 3 doses/patient; range 1 to 6). This dataset consisted of 230 gentamicin concentration-time samples. The number of samples ranged from 1 to 11 per patient (median 5), with a median of 2 samples per dose interval (range 1 to 5). Of these concentrations, 26 (11.3%) were BLQ (<0.4 mg/L) and were excluded. The covariates IBW, CVVH, albumin and TDIU that were used in the final model were available in 100%, 100%, 29% and 86% of patients, respectively. Table 1 shows the patient baseline characteristics from the AMC data and the CHU data.

Table 1

Patient characteristics at baseline.

	Original model (N = 44) [12]	**Validation cohorts**		
		AMC Amsterdam (N = 66)	**CHU Nîmes (N = 50)**	**P-value***
Female [N (%)]	24 (55)	13 (20)	21 (42)	0.091
Age (years)	61 (50-68)	64 (55-73)	62 (49-75)	0.614
Mean dose (mg/kg body weight)	4 (3.8-4.5)	4.8 (4.7-5.1)	6.3 (5.2-7.5)	<0.001
Total body weight (kg)	70.5 (60-85.8)	77.6 (67.4-89.5)	72.0 (59.1-87.5)	0.198
Ideal body weight (kg)	68.2 (63.6-70.6)	69.1 (60.5-74.6)	62.3 (57.0-66.4)	0.001
Height (cm)	170 (165-175)	174 (168-180)	168 (161-170)	0.01
SOFA score	-	9 (6-11)	5.5 (3-9)	<0.001
APACHE II score	17 (12-23)	-	-	-
CVVH [N (%)]	5 (11.4)	9 (14)	1 (2)	0.027
Serum creatinine (µmol/L)	115 (89.3-179)	112.5 (77.8-181.8)	87 (57-114.5)	0.02
Total daily diuresis (mL)	785 (350-1690)	1125 (503 -2128)	1422 (721 -2150)	0.22
Albumin (g/L)	21.5 (19-25.3)	25 (19-31)	28.7 (25.1-32.8)	0.002
Death during ICU admission [N (%)]	-	12 (18)	4 (8)	0.098

Values are expressed as median (interquartile range), unless stated otherwise. SOFA = Sequential Organ Failure Assessment, APACHE = Acute Physiology and Chronic Health Evaluation, CVVH = continuous venovenous hemofiltration, ICU = intensive care unit.

* The P-values represent if there was a statistical difference between the two validation cohorts.

Predictive performance

Table 2 presents the ME (bias) and the MAE (accuracy) for the structural and final models of the AMC data and the CHU data. The validation of the structural model using the AMC data yielded a statistically non-significant bias of 0.35 mg/L (95% CI: -0.11–0.81). The MAE was 2.54 mg/L (95% CI: 2.26–2.82) and thus equalled the prior set cut-off. For the final model (addition of the covariates albumin and TDIU) a small significant bias of 0.81 mg/L was found but the accuracy remained the same.

Validation of the structural model with the CHU data resulted in an upward bias of 4.81 mg/L, which was significantly different from 0 (95% CI: 4.00–5.62). Furthermore, accuracy was 5.45 mg/L. The predictive performance of the final model was no better as it yielded a bias of 6.89 mg/L (95% CI: 5.92–7.81) and an accuracy of 7.17 mg/L.

Table 2

Predictive performance of the model using population predictions.

	AMC Amsterdam (N = 66)		CHU Nîmes (N = 50)	
	Structural model	**Final model**	**Structural model**	**Final model**
Mean Error (mg/L)	0.35 (-0.11–0.81)	0.81 (0.33–1.30)	4.81 (4.00-5.62)	6.89 (5.92–7.81)
Mean Absolute Error (mg/L)	2.54 (2.26–2.82)	2.54 (2.21–2.86)	5.45 (4.72-6.17)	7.17 (6.27–8.07)

Values are expressed as mean (95% confidence interval).

The predictive performance is visualised in the Bland-Altman plots in Fig. 1. These plots and the VPCs in Fig. 2 indicate that the model can estimate the gentamicin concentrations without bias and with reasonable accuracy in the AMC population, but that the concentrations are overpredicted in the CHU population. The VPC also shows that in both populations the models overestimate the IIV. However, this overestimation is greater in the CHU population.

The results of the comparison of the PK of gentamicin from the present validation cohorts with the PK of gentamicin in the ICU population in which the model was developed are presented in Table 3. Mean CL (both off and on CVVH) and the mean central volume of distribution (V1) as estimated with the CHU data were higher and outside the 95% CI of the corresponding parameter estimates from the previously developed model. This is consistent with the overprediction seen when validating the model with the CHU data.

Table 3

Pharmacokinetic parameter estimates of the prospective AMC ICU and CHU ICU population when the collected data are fitted with the previously developed structural model.

	Structural Model [12]		**Validation**			
			AMC Amsterdam		**CHU Nimes**	
Parameter	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
CL not on CVVH (L/h/70 kg)	1.92	1.47–2.37	2.39	1.933–2.85	3.93	2.99–4.87
CL on CVVH (L/h/70 kg)	2.08	1.79–2.37	1.60	1.22–1.97	2.46	2.37–2.55
V1 (L/70 kg)	21.2	19.39–23.01	23.9	21.20–26.61	28	24.90–31.10
Q (L/h/70 kg)	2.26	1.58–2.94	0.625	0.17–1.08	1.68	0.02–3.34
V2 (L/70 kg)	18.9	16.12–21.68	6.47	3.02–9.92	12.8	7.06–18.54

Estimates are expressed as means. CI = Confidence interval, CL = clearance, CVVH = continuous venovenous hemofiltration, V1 = central volume of distribution, Q = intercompartment clearance, V2 = peripheral volume of distribution.

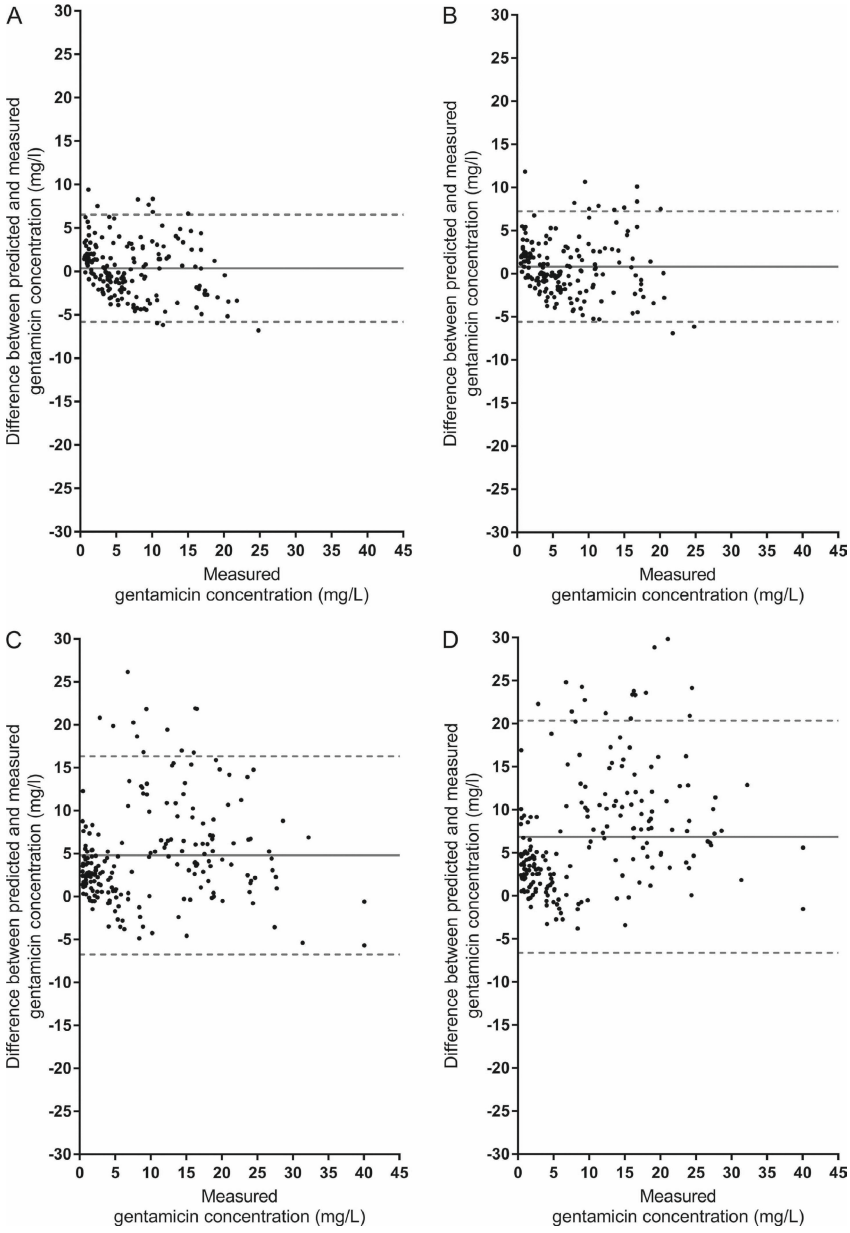

Fig. 1

Bland Altman plots of the predictive performance of the previously developed model based on (A) the AMC data predicted by the structural model, (B) the AMC data predicted by the final model, (C) the CHU data predicted by the structural model and (D) the CHU data predicted by the final model. The differences between the population predicted and measured concentrations are plotted against the measured gentamicin concentration. The dotted lines represent the ±1.96 standard deviation and the solid line the mean error.

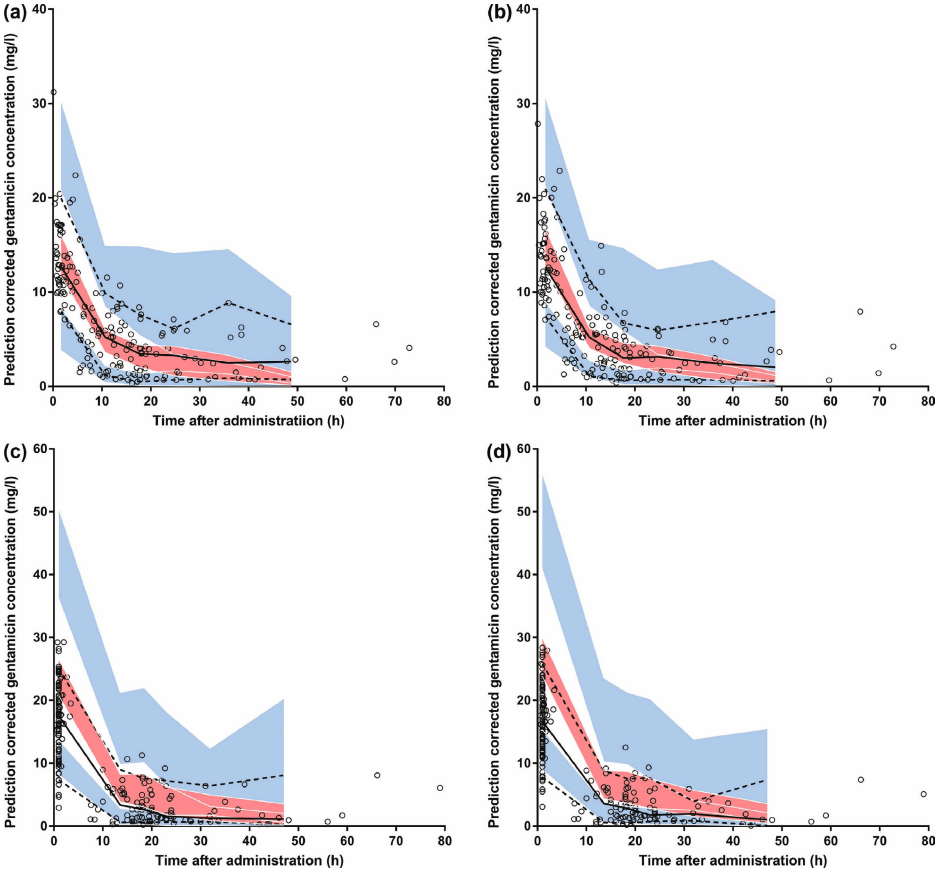

Fig. 2
Prediction corrected visual predictive checks of the validation of the original model with (a) the data from the AMC ICU population using the structural model, (b) the data from the AMC ICU population using the final model, (c) the data from the CHU ICU population using the structural model and (d) the data from the CHU ICU population using the final model. The solid and dotted red lines show the median, 5 and 95 percentiles of the measured concentrations, respectively. The red box indicates the 95% CI of the median of the predicted concentrations and the blue boxes the 95% CI of the 5 and 95 percentiles of the predicted concentrations. A model shows adequate predictive performance when the solid and dotted lines in the VPC run through the red and blue boxes, respectively. IIV is overestimated when less than 5% of the concentration points are outside the blue boxes on both sides.

Influence of serum albumin concentrations

When the AMC data were fitted to the final model, the OFV was 7.782 units higher in the model without albumin concentration as a covariate on V1 (P <0.01). Furthermore, an increase in the estimate of the IIV in V1 from 32.4% to 36.3% was observed. The association between albumin concentration and

V1 and the resulting effect on Cmax is shown in Fig. 3. This figure shows that serum albumin concentrations <20 g/L are associated with a low and often subtherapeutic Cmax. The association between albumin concentration and V1 was not validated with the CHU data as 71% of the albumin data were missing.

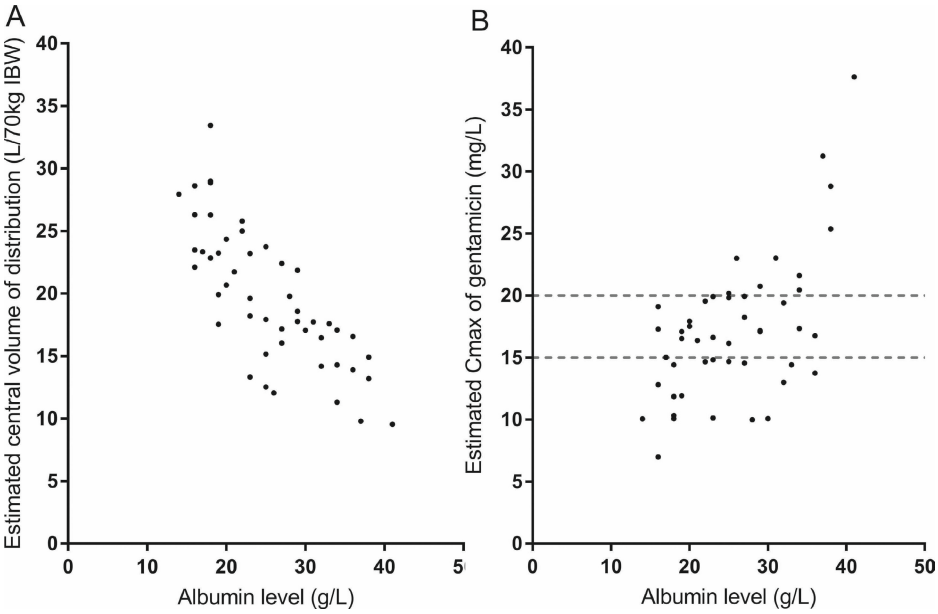

Fig.3
Albumin concentration in relation to (a) the estimated central volume of distribution (V1) of gentamicin and the (b) estimated peak concentration (Cmax) at 30 min after the end of gentamicin administration, after fitting the AMC data to the final model. Only the Cmax and V1 of the first administration are shown. The dotted lines represent the therapeutic window for Cmax of 15 to 20 mg/L.

Discussion

The predictive performance of a previously developed population PK model of gentamicin in ICU patients was tested in two different populations of ICU patients. The prospectively collected AMC data could be sufficiently predicted by the structural model, as shown by an ME that was not statistically significantly different from 0 and an MAE of 2.5 mg/L. However, an overprediction was observed when predicting the concentrations of the CHU data set. In addition, the negative association between gentamicin central volume of distribution and albumin level that was identified during development of the previous model could be confirmed with the collected AMC data.

A strength of this validation study was that two independently collected datasets including patients from different countries with a different case mix were used. These datasets were selected with the assumption that they would be representative of the western ICU population. A valid model would predict both the AMC and the CHU Nîmes data appropriately.

A limitation of this study was that creatinine clearance data, calculated based on a 6 h urine portion (CalcCLcr) and identified as the best measure for kidney function to predict gentamicin CL off CVVH in the previously developed model, was not available for both validation cohorts and therefore could not be used. Instead, TDIU was used as a measure for renal function, as this covariate had the second-best association and data were available. However, TDIU is likely to reflect the renal function less reliably, as the use of diuretics was not accounted for. This could explain why ME and MAE were not better when the concentrations were calculated with the final model instead of the structural model (Table 2). Another limitation was that the CHU data had a low percentage (29%) of available albumin levels, making this dataset unsuitable for verification of the association between V1 and albumin level. Albumin level was not often available in the CHU data as this covariate is not usually measured on a routine basis and this covariate was not captured in the context of the study during which the CHU database was built.

Whether the observed bias and accuracy with the CHU Nîmes data can be regarded as high or low is difficult to assess as no previous studies that externally validated a population PK model for gentamicin in critically ill patients could be identified. However, the bias of 4.81 mg/L when predicting the gentamicin concentrations of the CHU Nîmes cohort with the structural model indicates a statistically significant overestimation, which may preclude necessary dose adjustments.

The statistically significant ME and large MAE observed with the CHU Nîmes data may be caused by the fact that this ICU population was too different from the AMC ICU population. This is illustrated in Table 1 where the ICU patients in the CHU data set have lower SOFA-scores, lower mortality rates and lower serum creatinine levels, which indicates a less ill population. However, this only seems to be part of the explanation as the expectation would then be that the CHU cohort would have a lower total, central plus peripheral, volume of distribution than the more severely ill AMC population instead of the higher volume of distribution that was found (Table 3).

In theory, the high volume of distribution in the French population could be explained by low albumin values that were missing (negative association). However, the limited albumin samples that were available in the CHU population (29%) are in the same range as or higher than in the model-building population and the new, prospectively collected AMC population. In addition, higher albumin levels are expected in this less ill population. Therefore, the missing albumin values are unlikely to be responsible for the differences in volumes of distribution between the two ICU populations.

Another part of the explanation might be that the PK of gentamicin in the CHU Nîmes ICU population is indeed different from the AMC ICU population. Also, a high V1 was found in the CHU Nîmes population compared with the literature [10, 21, 22]. In addition, gentamicin CL off CVVH in the AMC population seems relatively low compared with the CHU Nîmes population (Table 3) and with the literature [10, 21].

The results of this validation study show that the previously developed model cannot simply be used in other ICU populations. This underscores the importance of external model validation because a seemingly good model may not perform adequately in other institutions, particularly if the model did not originate from a sufficiently heterogeneous population. Prior validation of the model is recommended with data from the population in which the model is intended to be used.

Addition of serum albumin concentrations as a covariate significantly improved the fit of the model when using the AMC data and the previously identified association between the central volume of distribution of gentamicin and albumin concentration could be confirmed [12]. The previous study showed that patients with very low albumin concentrations of <15 g/L are prone to developing subtherapeutic Cmax values [12]. Although these very low Cmax values were barely observed in our study population, an association was confirmed. As such, consideration of the albumin level of an ICU patient may improve gentamicin dosing, e.g. by measuring the Cmax early in the course of treatment in ICU patients with serum albumin concentrations <20 g/L to ascertain Cmax target exposure, or by prescribing at least 6 mg/kg in patients with albumin levels <20 g/L, particularly when TDM of Cmax levels are not conducted. This recommendation is strengthened by the fact that previous studies have also observed a negative association between the volume of distribution of aminoglycosides and serum albumin concentrations [12, 23, 24].

Conclusion

This external validation study shows that the previously developed structural population PK model for critically ill patients receiving gentamicin can predict gentamicin concentrations without bias and with acceptable accuracy in the ICU population admitted to the hospital where the data for model development originated. However, the model overpredicts gentamicin concentrations in an ICU population from another western hospital. Therefore, the model may not easily be used in other western ICU populations. Prior validation of population PK models with data from the population in which the model is intended to be used is recommended.

In addition, the negative association between the central volume of distribution of gentamicin and albumin concentrations in ICU patients was confirmed. This association implies that hypoalbuminemia may result in a Cmax below the targeted range.

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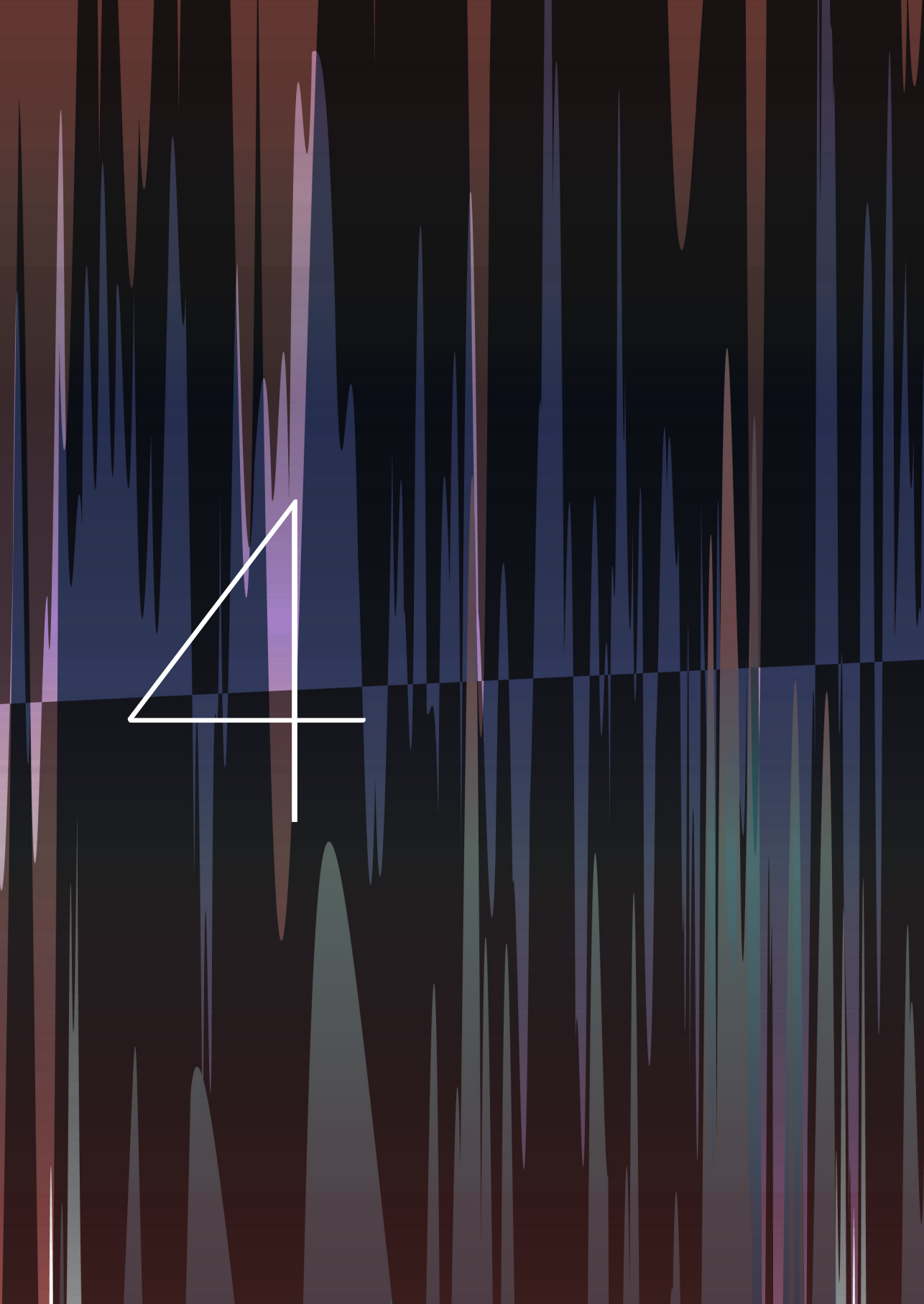

Therapeutic drug monitoring of gentamicin peak concentrations in critically ill patients

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This is a non-final version of an article published in final form in Ther Drug Monit. 2017;39(5):522-530. DOI: 10.1097/FTD.0000000000000432.

Abstract

Background: Adequate gentamicin peak concentrations (Cmax) are important for optimal clinical efficacy. Within a critically ill patient, substantial variability in Cmax can occur over time, hampering the usefulness of therapeutic drug monitoring (TDM). The aim of this study was to evaluate the effect of gentamicin dosing based on Cmax after the first dose on gentamicin target attainment in critically ill patients.

Methods: From gentamicin-treated critically ill patients, dosing information, clinical parameters, and serum concentrations were collected prospectively. A population pharmacokinetic model was developed using nonlinear mixed-effects modeling to estimate Cmax after each dose. To evaluate the usefulness of routine TDM, percentages of Cmax within (%Cther, 15–20 mg/L), above (>20 mg/L), and below (%Csubther, <15 mg/L) the therapeutic range after the first and second doses were compared. In addition, simulations were performed to evaluate the impact of TDM.

Results: Four hundred sixteen measurements from 59 patients receiving 130 gentamicin doses were included. In the 30 patients who received >1 dose, TDM increased %Cther from 40% after a first median dose of 5.0 mg/kg to 50% after the second dose, and decreased %Csubther from 47% to 30%. Simulations using a 5 mg/kg starting dose revealed %Cther after the second dose of 28.4% without and 36.8% with TDM and %Csubther of 56.9% and 29.3%, respectively. Increasing the simulated starting dose to 6 mg/kg increased %Cther after the first dose from 27.7% to 33.5% and decreased %Csubther from 58.6% to 35.6%. TDM after a first dose of 6 mg/kg had no substantial effect on %Cther or %Csubther after the second dose.

Conclusions: Gentamicin dosing based on Cmax after the first dose increased %Cther and decreased %Csubther, but did not result in therapeutic Cmax in half of the patients. When simulating a higher starting dose, %Csubther after the first dose decreased, and TDM showed no additional influence. These data suggest that a starting dose of 6 mg/kg should be considered and that repeated Cmax measurements are not of added value.

Introduction

Critically ill patients often have severe infections, presenting an important challenge in intensive care units (ICUs). In a 1-day point prevalence study including 13,796 patients admitted to ICUs from 75 countries, 51% of patients were classified as having an infection. Infections were associated with increasing incidence of antibiotic-resistant bacteria and a greater risk of hospital mortality, with an adjusted odds ratio of 1.51 [1]. Early and adequate empirical antimicrobial treatment of patients admitted to the ICU for sepsis has a greater impact on survival than any other intervention [2-4].

Gentamicin is often used in empirical antimicrobial regimens for sepsis because of its rapid bactericidal activity and because of the relatively low rates of resistance [5, 6]. For optimal clinical efficacy, the aim is to obtain a ratio of gentamicin peak concentration (Cmax) over minimum inhibitory concentration (MIC) of greater than 10 [7–12]. A Cmax of 15–20 mg/L is considered sufficient for susceptible *Enterobacteriaceae* [13]. Gentamicin trough concentrations (Cmin) higher than 0.5–2 mg/L have been associated with nephrotoxicity because of drug accumulation [14, 15]. Thus, for optimal therapy, high Cmax and low Cmin concentrations are desirable [8, 16]. To achieve optimal gentamicin levels, therapeutic drug monitoring (TDM) is recommended [17]. Monitoring of Cmin is often performed routinely to prevent toxicity, particularly in patients with decreased renal function. However, especially in critically ill patients, monitoring of Cmax is also important because pathophysiological characteristics associated with critical illness can result in an increased volume of distribution (Vd) of gentamicin and decreased Cmax [7, 18]. These changes usually occur during the first hours to days after admission. During recovery, these characteristics will reverse, which may again change the pharmacokinetics (PK) of gentamicin.

TDM can be used to correct for PK differences between patients (interindividual variability; IIV), but its efficacy is hampered by variability within the same patient over time, the interoccasion variability (IOV), reflecting the uncertainty in predicting drug concentrations in an individual [19, 20]. When IOV in Vd is large, the predictive value of one Cmax measurement for the next Cmax will be limited and effectiveness of TDM may be diminished. Rea et al. [12] estimated a high IOV in Vd of 40.9% and recommended evaluation of Cmax after the first administration. In a prospective study, model-based dosing of gentamicin using Cmax measurements resulted in higher antibiotic efficacy,

shorter hospitalisation, and reduced incidence of nephrotoxicity in patients on internal medicine and surgical wards [17]. However, to the best of our knowledge, gentamicin dose adjustment based on Cmax measurement has not been evaluated in critically ill patients.

The aim of this study was to evaluate the effect of gentamicin dose adjustment based on Cmax measurements after the first administration on gentamicin target attainment in critically ill patients.

Materials and methods

Patients

A prospective single-center observational cohort study was performed in critically ill patients admitted to the mixed medical and surgical ICU of the Academic Medical Center in Amsterdam, the Netherlands. The Human Research Ethics Committee of the Academic Medical Center has taken notice of the study protocol and has decided that no ethical approval is required, given that anonymous data from routine diagnostic databases are used. All patients receiving gentamicin were included if at least 1 blood sample was collected. Gentamicin was administered by a 30-minute intravenous infusion at a fixed first dose of approximately 5 mg/kg. Patients who were treated for endocarditis with 3 mg/kg of gentamicin in combination with a beta-lactam antibiotic for synergistic effect were included for population PK modelling but excluded for calculation of primary and secondary end points.

Data collection

Collected data included the dose administered, infusion duration, dosing interval, and exact time of gentamicin administration. Furthermore, the following patient-related parameters were collected from the electronic patient data monitoring system (PDMS) at the ICU or calculated from these parameters: age, sex, total body weight (TBW), ideal body weight (IBW) [21], adjusted body weight (ABW) [22], and creatinine clearance (CL) calculated according to Cockroft & Gault [23].

Blood sampling

Samples were prospectively collected between May 2013 and June 2013 and between April 2014 and June 2014. In our hospital, dosing recommendations after a first gentamicin dose of 5 mg/kg are based on Cmax and a second gentamicin concentration determined in a specimen collected at a random time point between 6 and 23 hours after the administration. Using Bayesian

forecasting with an ICU-specific population PK-model incorporated in the software package MwPharm (v3.60; Mediware, Groningen, the Netherlands) [24], individual concentration–time curves are estimated to calculate Cmax and the moment the concentration drops below 1 mg/L. Subsequently, a recommendation is generated by the hospital pharmacist for the next dose. After this first assessment, gentamicin concentrations are measured for specific clinical indication only, for example after dose adjustment or if renal function deteriorates. In this study, in addition to the samples routinely collected for TDM, blood samples from waste material used for blood gas analyses were collected for the measurement of gentamicin concentrations. This assured random sampling relative to the gentamicin administration. The exact time of sample collection (for both the TDM samples and the waste material) was recorded, and blood samples were stored at room temperature for a maximum of 3 days, followed by centrifugation (2750 g, 10 minutes, 20°C) and storage of serum at -80°C until further analyses. Gentamicin concentrations in blood samples remain stable at room temperature for at least 3 weeks [25].

Gentamicin measurement

Gentamicin serum concentrations were measured by auto-immunoassay using COBAS INTEGRA 400 plus (Roche Diagnostics, Basel, Switzerland). The limit of quantification was 0.5 mg/L, and the assay showed linearity from 0.5 to 10 mg/L. Concentrations greater than 10 mg/L were measured using 2- or 4-fold dilutions.

PK analysis

Population PK analysis, using nonlinear mixed-effects modeling as implemented in the software package NONMEM 7.2 (ICON Development Solutions, Ellicott City, MD) [26] was applied to develop a population PK model of gentamicin in critically ill patients, including the observed variability. To evaluate goodness of fit (GOF), the following criteria were used. A decrease in the objective function value (OFV) of ≥3.84, corresponding to a $P < 0.05$ in a χ^2-distribution with 1 degree of freedom ($P < 0.05$, $df = 1$) was considered a statistically significant improvement of the fit. Moreover, the precision with which the PK parameters were estimated and visual inspection of goodness-of-fit plots, generated using Xpose (version 4.3.2, Uppsala, Sweden) [27] and R version 3.03, were evaluated. Pirana (version 2.7.1, Pirana Software & Consulting BV, Denekamp, the Netherlands) [28] was used as the model environment. The first-order conditional estimate method with interaction was used throughout the modelling process. One-, 2-, and 3-compartment PK models were tested. Additive, proportional, and

combined error models were compared to describe the residual variability. IIV was separately tested for all PK parameters using Equation 1:

Eq. (1) $$\theta_i = \theta_{tv} * e^{\eta i}$$

where θ_i is the individual parameter estimate of the parameter, θ_{tv} is the typical value of the parameter in the population, and η_i corresponds to the estimate for interindividual variability in θ_{tv}, with mean 0 and variance ω^2.

A new occasion was defined with every new administration of gentamicin. To complete the structural model, IOV was tested for CL and V1 with Equation 2:

Eq. (2) $$\theta_{ij} = \theta_{tv} * e^{(\eta i + \kappa j)}$$

where θ_{ij} is the individual parameter estimate on the j^{th} occasion, and κ is the interoccasion random effect parameter with mean 0 and variance π^2 [19].

After the structural model was determined, the final model was developed by introducing the influence of body weight on all parameters using allometric scaling with TBW, IBW, or ABW, whichever gave the largest improvement of OFV and goodness-of-fit, according to Equation 3 [29]:

Eq. (3) $$\theta_i = \theta_{tv} * (W/70)^b$$

where W is the body weight parameter and *b* is a constant. For CL and intercompartmental CL (Q), *b* was set to 0.75 and for Vd *b* was set to 1 [30]. Moreover, TBW, IBW, and ABW were tested for their correlation with gentamicin Vd and CL using univariate analysis, in which *b* was estimated. A covariate effect of body weight was included in the final model if the OFV decreased with ≥3.84 units ($P < 0.05$, $df = 1$).

For the resulting final model, a visual predictive check (VPC) was performed by simulating 1000 patients to assess the predictive performance of the model. The VPCs were generated using Perl-speaks-NONMEM version 3.7.6 [31].

In addition, the bootstrap method with replacement (1000 samples) was used for determination of 95% confidence intervals of the parameters.

Evaluation of IOV in V1

Because IOV in Cmax is largely dependent on IOV in V1, we arbitrarily established an a priori cut-off of 15% for the coefficient of variation of IOV in V1 as an acceptable value below which efficient TDM can be performed. With an IOV of 15% and a Cmax of 15 mg/L, the Cmax for the next administration can be expected to range from ~10.5 to ~19.5 mg/L (15 ± 2 times the SD), providing a >50% chance that a Cmax within the required therapeutic range of 15–20 mg/L will still be there after the next administration without dose adjustment.

Analysis of gentamicin Cmax

Using the final model, gentamicin Cmax was calculated after every administration. Cmax was defined as the concentration 30 minutes after the end of gentamicin infusion, following the guidelines from the Dutch Association of Hospital Pharmacists [13].

The primary end point was the percentage of Cmax values within the therapeutic range of 15–20 mg/L (%Cther). Secondary end points were the percentage of subtherapeutic (%Csubther, <15 mg/L) and supratherapeutic (%Csuprather, >20 mg/L) Cmax values. These end points were calculated after the first administration to evaluate the effect of the starting dose of approximately 5 mg/kg on target attainment. To evaluate the effect of TDM, the same end points were calculated after the second administration for all treatment episodes that consisted of >1 administration.

Simulation of Cmax at different starting doses

In routine TDM, other factors than variability can influence the effect of dosing based on Cmax on gentamicin target attainment, such as omissions in sample collection or dose adjustment, or mistakes in interpretation of Cmax. This can result in patients receiving an identical subsequent dose, despite reaching a nontherapeutic Cmax and patients receiving an adjusted dose, despite reaching a therapeutic Cmax after the first administration. To exclude these imperfections and thus evaluate the best possible effect of TDM, multiple Monte Carlo simulations of Cmax were performed using NONMEM. For each simulation, 2 gentamicin administrations with subsequent Cmax were simulated for 1000 patients with a body weight of 70 kg. To eliminate the impact of low gentamicin CL (leading to accumulation if administration of the next dose is simulated before Cmin is close to 0), the serum concentration was reset to 0 at the start of the second dose. The primary and secondary end points as defined above were again calculated.

Using the final model, Cmax values without TDM were simulated for a starting dose of 350 mg (5 mg/kg) followed by a second dose of 350 mg.

To evaluate the effect of TDM, Cmax values were simulated for a gentamicin starting dose of 350 mg, followed by a second dose calculated as follows:

Eq. (4) $$D_{genta2}\ (mg) = C_{target}/C_{max1} * D_{genta1}$$

Where C_{max1} is the simulated peak concentration in mg/L after the starting dose (D_{genta1}) of 350 mg and C_{target} is the target Cmax, which was fixed at 17.5 mg/L. With the newly calculated gentamicin dose D_{genta2}, Cmax values were subsequently simulated for the second administration. Primary and secondary end points were again calculated to evaluate the effect of TDM on target attainment.

To evaluate the effect of a higher starting dose on target attainment, simulations and calculation of end points with and without TDM were repeated using a starting dose of 420 mg (6 mg/kg).

Statistical Analysis
Descriptive statistics were used to present the data. Data were presented as mean ± SD, unless stated otherwise.

Results

A total of 59 gentamicin-treated patients at the ICU were included, receiving 130 gentamicin administrations, after which 416 blood samples were collected. One patient had 2 treatment episodes and 1 patient had 3 treatment episodes, adding up to a total of 62 episodes, of which 4 episodes were for treatment of endocarditis. A mean of 6.7 (±5.9) samples were collected per treatment episode. Table 1 shows the patient characteristics and the data set for PK modeling.

The mean number of gentamicin administrations was 2.1 (±1.9) per patient. There were 33 treatment episodes with >1 administration, of which 3 episodes were for endocarditis. Hence, 30 episodes were used for calculation of primary and secondary end points. There were 3 episodes with >4 administrations.

Renal function showed a large between-patient variation in the study population but also in individual patients over time.

Table 1

Baseline characteristics of the included patients and model building data set

Demographic characteristics	Mean ± SD, unless otherwise stated
Males	N = 30 (51%)
Females	N = 29 (49%)
Age (years)	60.9 ± 17.2
TBW (kg)	79.2 ± 22.0
IBW (kg)	71.4 ± 11.6
ABW (kg)	74.6 ± 13.0
Creatinine clearance (Cockcroft & Gault) (mL/min)	
First administration (N = 62 treatment episodes)	87.0 ± 64.7
Second administration (N = 33 treatment episodes)	99.7 ± 59.3
Third administration (N = 13 treatment episodes)	133.0 ± 85.6
Patients treated with lower gentamicin doses for synergistic effect for endocarditis	N = 4 (7%)
Pharmacokinetic data	
Number of treatment episodes	
All treatment episodes	N = 62
Excluding patients treated for endocarditis	N = 58
Number of administrations	N = 130
Number of administrations per episode	2.1 ± 1.9
Total numbers of samples	N = 416
TDM collected (%)	44%
Waste material (%)	56%
Number of samples per episode	6.7 ± 5.9
Starting dose corrected for TBW (mg/kg), excluding patients treated for endocarditis	5.1 ± 1.1

TBW = total body weight, IBW = ideal body weight, ABW = adjusted body weight, TDM = therapeutic drug monitoring.

Model

The 2-compartment model was found to be superior to the 1- and 3-compartment models for description of the concentration–time profiles of gentamicin in ICU patients. A combined error model was found to best describe the residual error. IIV and IOV were estimated for CL and central volume of distribution (V1). Both provided a significant decrease in OFV of ≥3.84 units when added stepwise to the model, and GOF-plots showed a clear improvement of the model fit. This model provided a population CL estimate of 2.3 L/h and a population V1 estimate of 21.60 L. IIV in CL and V1 was 75% and 27%, respectively. IOV in CL was 24%. IOV in V1 was 25.1%, substantially higher than the a priori cut-off of

15%. Shrinkage for IIV in CL was 7%, but shrinkage for IIV in V1 and for IOV in CL and V1 was between 36% and 45%.

The results of the final model matched the results of the bootstrap of the final model (Table 2). Figures 1 and 2 show the GOF-plots and VPC of the provided structural model. Addition of associations (both using allometric scaling and using univariate analysis) between CL, intercompartmental CL, V1, and peripheral volume of distribution, and TBW, IBW, or ABW did not improve the fit: the drop in OFV was less than 3.84 and estimates for IIV increased. Other covariates were not tested because we wanted to estimate total IOV in gentamicin V1 after a body weight-based dose.

Table 2

Final Model Population Parameter Estimates and Bootstrap Results (N = 1000)

Parameter	Final model			Bootstrap of final model	
	Estimate	RSE (%)	Shrinkage (%)	Median	95% CI
CL (L/h)	2.3	8.9		2.28	1.64–2.71
V1 (L)	21.6	5.6		21.75	19.35–24.77
Q (L/h)	1.3	25.1		1.28	0.64–1.85
V2 (L)	10.2	13.8		10.68	7.70–53.76
Interindividual variability (IIV)					
CL (CV%)	75.0	16.4	7	75.46	59.86–120.58
V1 (CV%)	27.0	56.1	36	27.26	10.84–40.64
Correlation, r, between IIV CL and IIV V1	0.21	104.3		0.22	-0.62–0.31
Interoccasion variability (IOV)					
CL (CV%)	24.0	24.2	44	24.17	18.68–31.43
V1 (CV%)	25.1	52.9	45	23.44	8.16–39.92
Residual variability					
Proportional error (%)	19.4	11.4		19.16	12.72–23.36
Additive error	0.13	14.4		0.12	0.04–0.32

95% CI = 95% confidence interval, CL = gentamicin clearance, CV% = coefficient of variation, calculated as the square root of (e^{ω}-1) * 100%, Q = gentamicin intercompartmental clearance, RSE = relative standard error, V1 = gentamicin central volume of distribution, V2 = gentamicin peripheral volume of distribution.

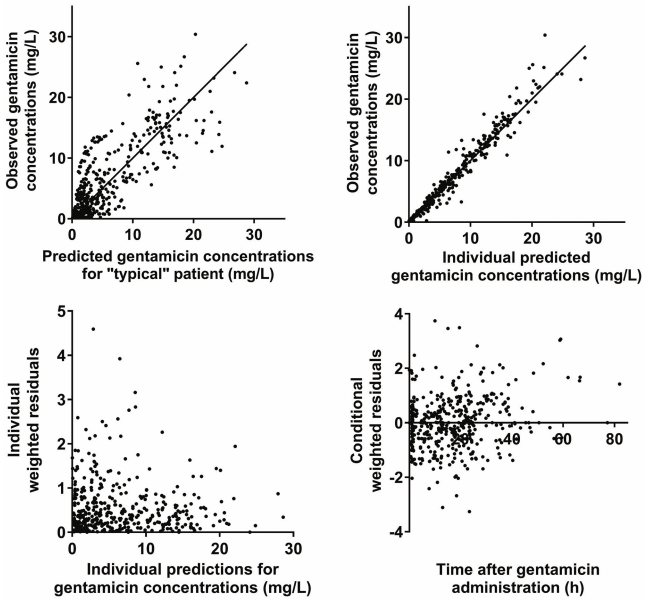

Fig. 1
Goodness-of-fit plots of the final model.

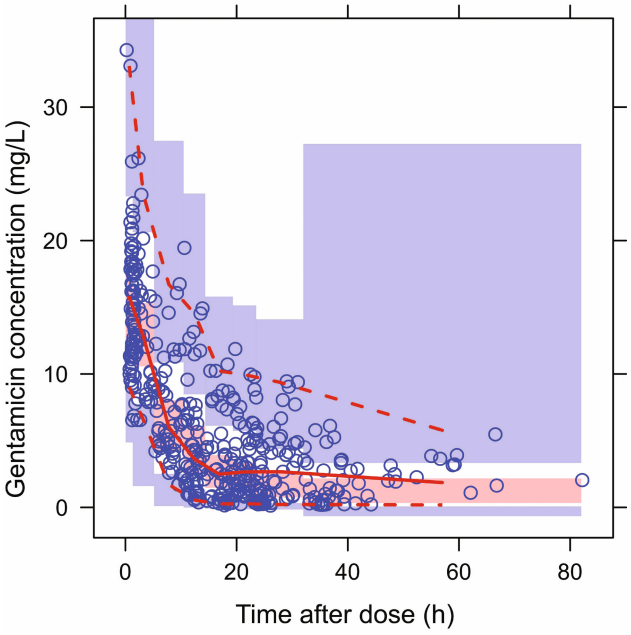

Fig. 2
VPC of the final model. The points represent the observed data. The solid line represents the median, and the dotted lines represent fifth and 95th percentiles of the observed data. The shaded regions summarize the predicted 95% confidence intervals of the median/percentile in that bin.

Analysis of gentamicin Cmax

Using the final model, individual gentamicin Cmax values were estimated. Figure 3 shows the time course of Cmax per treatment episode for the first 4 administrations.

After the first median dose of 5.0 mg/kg (N = 58 treatment episodes, because 4 episodes for endocarditis were excluded from analysis), %Cther was 46.5%, %Csubther was 34.5%, and %Csuprather was 19%. Considering only treatment episodes consisting of >1 gentamicin administration (N = 30), %Cther was 40%, %Csubther was 46.7%, and %Csuprather was 13.3% after the median first dose of 5.0 mg/kg (Fig. 4). Routine TDM increased %Cther to 50% after the median second dose of 5.1 mg/kg and decreased %Csubther to 30%.

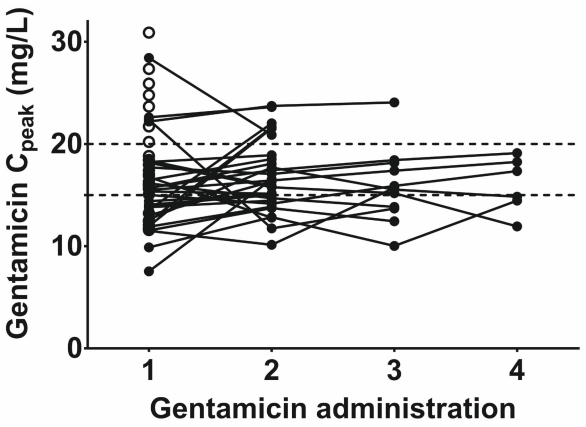

Fig. 3

Calculated gentamicin peak concentrations per patient for the first 4 administrations. The area between the striped lines represents the therapeutic range of 15–20 mg/L. The white dots represent patients who had only 1 administration.

Simulation of gentamicin Cmax at different starting doses

In the simulation of a 5 mg/kg gentamicin starting dose, %Cther was 27.7% after the first administration, %Csubther was 58.6%, and %Csuprather was 13.7% with a median Cmax of 14.0 mg/L. Increasing the starting dose to 6 mg/kg increased %Cther to 33.5% after the first administration, but decreased %Csubther to 35.6% and increased the median Cmax to 16.8 mg/L, but at the cost of an increase in %Csuprather to 30.9%.

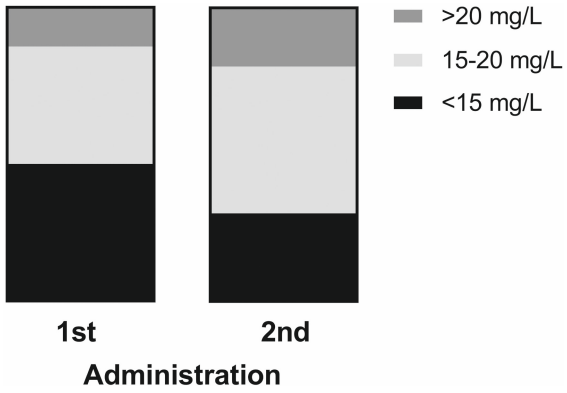

Fig. 4
Distribution of the calculated gentamicin peak concentrations after the first and second administrations for all patients with at least 2 administrations (N = 30).

Simulation of the effect of TDM on subsequent gentamicin Cmax
With a dose of 5 mg/kg and no TDM simulated, %Cther was 28.4% after the second administration, %Csubther was 56.9%, and %Csuprather was 14.7%, with a median Cmax of 14.3 mg/L (Fig. 5A). However, if TDM was applied, %Cther was 36.8% after the second administration and %Csubther was 29.3%, with a median Cmax of 17.5 mg/L, but %Csuprather increased to 33.9% (Fig. 5B).

With a dose of 6 mg/kg and no TDM simulated, %Cther was 33.8% after the second administration, %Csubther was 35.0%, and %Csuprather was 31.2%, with a median Cmax of 17.1 mg/L (Fig. 5C). If TDM was applied, these percentages were identical to those observed after TDM after a starting dose of 5 mg/kg: %Cther was 36.8% after the second administration, %Csubther was 29.3%, and %Csuprather was 33.9% (Fig. 5D).

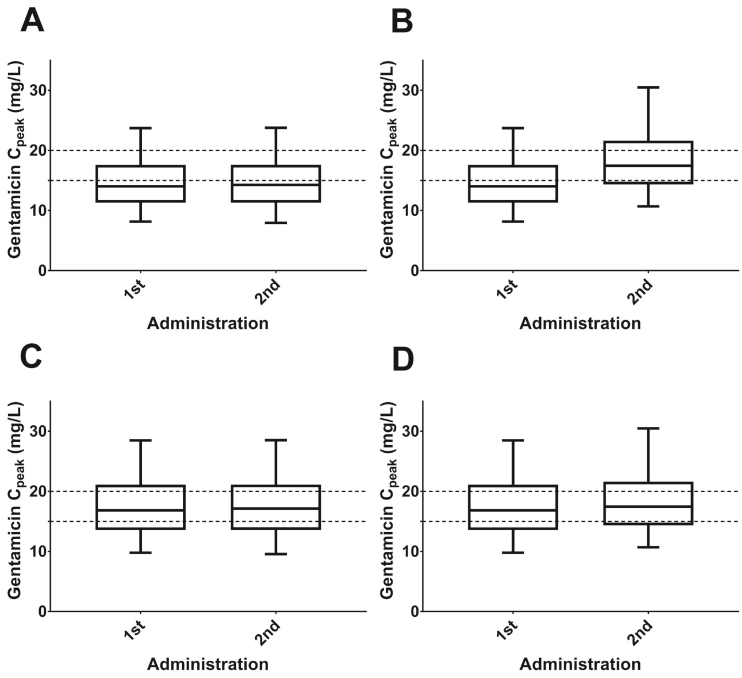

Fig. 5
Boxplots of the distribution of simulated gentamicin peak concentrations (N = 1000) per administration for the first 2 administrations of patients receiving 2 administrations of 5 mg/kg (A), of patients receiving a starting dose of 5 mg/kg followed by dose adjustment after the first Cmax measurement (B), of patients receiving 2 administrations of 6 mg/kg (C), and of patients receiving a starting dose of 6 mg/kg followed by dose adjustment after the first Cmax measurement (D). Whiskers represent the fifth and 95th percentiles. The area between the striped lines represents the therapeutic range of 15–20 mg/L.

Discussion

To evaluate the effect of gentamicin target attainment in critically ill patients of gentamicin dose adjustment based on Cmax measurements after the first administration, a population PK model of gentamicin in patients admitted to the ICU was developed. An IOV in gentamicin V1 of 25.1% was found exceeding the arbitrary a priori cut-off value of 15%, below which we consider that TDM can be performed effectively. Routine dose adjustment based on observed Cmax increased %Cther and decreased %Csubther, but also increased %Csuprather after the second administration. Even in the setting of TDM, therapeutic Cmax was not observed in half of the patients after the second administration. Simulation showed that increasing the starting dose modestly improved %Cther after the first administration from 27.7% using 5 mg/kg to 33.5% using 6 mg/kg,

but substantially decreased %Csubther from 58.6% to 35.6%. TDM did not result in a substantial increase in the percentage of patients reaching therapeutic Cmax after the second administration when a starting dose of 6 mg/kg was used (33.8% without TDM versus 36.8% with TDM).

A 2-compartment PK model with a combined proportional and additive residual error, IIV on V1 and CL, IOV on V1 and CL was found to be appropriate to describe the PK of gentamicin in patients admitted to the ICU. To validate the model, a bootstrap and VPC were conducted. The bootstrap results matched the results from the final model, and the VPC showed that the model adequately predicts the observed concentrations during the entire dosing interval. Nevertheless, the VPC shows an overestimation of the variability and an underestimation of the lowest concentration at the end of a dosing interval. In addition, shrinkage for IIV in V1 and for IOV in CL and V1 was between 36% and 45%. However, the VPC shows that Cmax values were estimated without bias. The model was therefore considered to be suitable to calculate and simulate Cmax.

This PK model showed a V1 of 21.6 L and a CL of 2.3 L/h, comparable with a previous, retrospective study at the same ICU, where V1 was 21.2 L and CL was 2.1 L/h during continuous venovenous hemofiltration and 1.9 L/h without continuous venovenous hemofiltration [32]. Increased Vd is also reported in previous studies [33–35]. One study found a Vd of 0.43 L/kg in critically ill patients [35], as compared to 0.40 L/kg (V1 and V2 combined) in this model.

In the present study, IIV in V1 and CL was found to be 27.0% and 75.0% respectively, and IOV in V1 and CL 25.1% and 24.0%. An earlier retrospective study found higher variability, with IIV in CL of 83.7% and IIV and IOV in Vd of 64.4% and 40.9%, respectively (IOV in CL could not be reliably estimated) [12]. There are several possible explanations for this difference. Our model was based on a higher number of measurements per patient (averaging 7.1 versus 2.1), enabling a more precise estimation of parameters. Moreover, our data were collected prospectively, including exact data on timing of drug administration and of sample collection.

With the developed population PK model, gentamicin Cmax values were estimated for all treatment episodes consisting of >1 administration. After the first administration, %Csubther was 46.7%, suggesting that higher doses (6–7 mg/kg) should be considered for critically ill patients, in accordance with the latest guidelines of the Dutch Association of Hospital Pharmacists [13].

Simulation showed that using a starting dose of 6 mg/kg would decrease %Csubther to 35.6% after the first administration.

A drawback of higher starting doses is that fewer patients will reach an adequate Cmin within 24 hours. This was indeed reported in a recent study using a starting dose of 8 mg/kg, where subsequent doses were withheld because of high Cmin in most patients [36].

It should be noted that the TDM Cmax target of 15–20 mg/L for patients with sepsis is defined for treatment of infections with *Enterobacteriaceae* (e.g., *E. coli*) for which the clinical breakpoint for susceptibility is 2 mg/L [37]. However, for *Pseudomonas* and *Acinetobacter* species, the clinical breakpoint for susceptibility is 4 mg/L; hence, Cmax levels higher than 15–20 mg/L would be needed for adequate treatment of infection with susceptible strains of these species. Therefore, some guidelines recommend using a target of 30–40 mg/L for critically ill patients [38]. Conversely, over 90% of all susceptible *E. coli* strains are inhibited by 1 mg/L, for which a Cmax of 10 mg/L would probably be sufficient. Ideally, one would base optimal dosing on Cmax/MIC targets for each individual case. Because one cannot postpone antibiotic treatment until susceptibility testing results have become available, it is important to be aware of local susceptibility patterns and MIC distributions.

After routine TDM was applied, that is, after the second administration, %Cther was only 50% and %Csubther was still 30%. This can at least in part be attributed to the 25.1% IOV in V1, as illustrated by the observation that 3 of 7 patients with a therapeutic Cmax after the first administration whose dose was not adjusted had a subtherapeutic Cmax after the second administration.

The modest usefulness of TDM could also be partly explained by incorrect dosing recommendations because TDM in critically ill patients can be complex. A small study on the quality of routine dosing recommendations during TDM that was performed concurrent with our study showed that agreement on dosing between professionals was under 80%, often because of incorrect interpretation of the routinely collected clinical information [39]. This was the reason why simulations, in which these imperfections have no influence, were used to assess the effect of TDM on gentamicin Cmax target attainment.

The strength of this study was its prospective nature, which ensured collection of reliable data with regard to the exact timing of gentamicin administration

and sample drawing. This resulted in a PK model with low residual error values compared with published population PK models for gentamicin [5, 12, 40].

A limitation may be that only body weight was tested as a covariate and other covariates (e.g., renal function, fluid balance, and use of inotropic agents) were not taken into account. The addition of covariates on V1 would likely result in a decreased estimate of IOV of V1. Because the aim of this study was to quantify the IOV as encountered when using TDM in routine clinical practice, where no covariates other than body weight are currently considered when prescribing gentamicin, we decided not to test covariates. Moreover, the developed population PK model seems to adequately estimate IOV, as judged by inspection of the GOF-plots and the VPC.

Another limitation might be that 17% of calculated Cmax values after the first administration were not based on an actual gentamicin concentration measured approximately 1 hour after the start of infusion. However, these calculated Cmax values are not expected to under- or overestimate actual Cmax because the GOF-plots and VPC showed that Cmax estimations were not biased.

Monte Carlo simulations were used to explore the best possible effect of TDM. Observed %Cther after the first administration was higher than %Cther simulated after a starting dose of 5 mg/kg (40% versus 27.7%), whereas %Csubther was lower (46.7% versus 58.6%). This could be explained by the fact that severely ill patients, with above average Vd and variability in PK, more often received >1 administration than patients who were less ill. Consequently, these patients predominantly determined the estimates for IOV and thus had more influence on the model and the simulation, leading to a higher %Csubther when compared with the observed data. However, observed and simulated Cmax showed the same trends when comparing TDM and no TDM, that is, TDM decreases the %Csubther but does not seem to decrease the range of Cmax. Of course, the results of these simulations should be confirmed prospectively in a clinical trial.

Based on the results of this study, one could question the added value of dose adjustment based on Cmax measurements in critically ill patients because the IOV in this patient category proved too large to achieve therapeutic Cmax in most patients. One possible solution could be to adjust the width of the therapeutic range because the current range does not seem to take the large IOV in this patient population into account. For example, one could define 20 mg/L as target concentration and accept all Cmax between 15 and 25 mg/L as therapeutic. In

addition, there may still be a role for Cmax measurements in detecting extremely high Cmax values, which are to be expected more frequently with a higher starting dose of 6 mg/kg, as well as in detecting extreme low Cmax values, which may still occur despite a higher starting dose. However, repeated Cmax measurement after subsequent administrations may not be of added value.

Conclusion

Dose adjustment based on Cmax measurements after the first administration modestly reduced the percentage of critically ill patients who were undertreated. However, despite TDM, half of the patients did not reach therapeutic Cmax. The likely explanation is the large IOV in Vd, which limits the predictive value of a Cmax for the next Cmax. Therefore, repeated Cmax measurement may not be of added value. Raising the initial gentamicin dose from 5 to 6 mg/kg should be considered in critically ill patients to improve target attainment after the first dose. Because our simulation showed that after a starting dose of 6 mg/kg, TDM may not substantially increase the percentage of patients reaching therapeutic Cmax after subsequent doses, the effect of Cmax measurements after the first administration may be limited. The usefulness of TDM for higher starting doses than 5 mg/kg should be evaluated prospectively.

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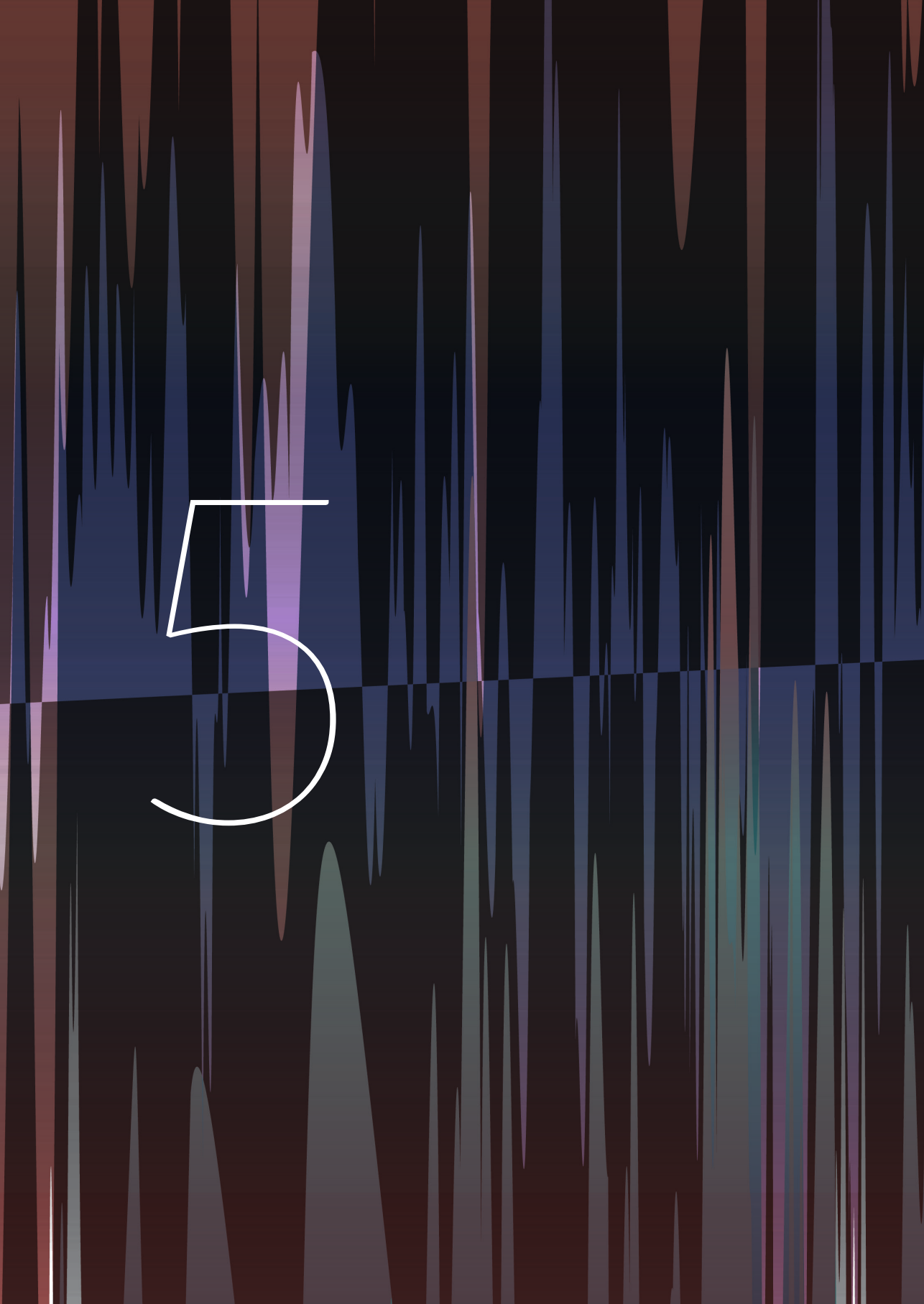
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Clinical pharmacokinetics of gentamicin in various patient populations and consequences for optimal dosing for Gram-negative infections: an updated review

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Clin Pharmacokinet. 2022;61(8):1075-1094. DOI: 10.1007/s40262-022-01143-0.

Abstract

Gentamicin is an aminoglycoside antibiotic with a small therapeutic window that is currently used primarily as part of short-term empirical combination therapy. Gentamicin dosing schemes still need refinement, especially for subpopulations where pharmacokinetics can differ from pharmacokinetics in the general adult population: obese patients, critically ill patients, paediatric patients, neonates, elderly patients and patients on dialysis. This review summarises the clinical pharmacokinetics of gentamicin in these patient populations and the consequences for optimal dosing of gentamicin for infections caused by Gram-negative bacteria, highlighting new insights from the last 10 years. In this period, several new population pharmacokinetic studies have focused on these subpopulations, providing insights into the typical values of the most relevant pharmacokinetic parameters, the variability of these parameters and possible explanations for this variability, although unexplained variability often remains high. Both dosing schemes and pharmacokinetic/pharmacodynamic (PK/PD) targets varied widely between these studies. A gentamicin starting dose of 7 mg/kg based on total body weight (or on adjusted body weight in obese patients) appears to be the optimal strategy for increasing the probability of target attainment (PTA) after the first administration for the most commonly used PK/PD targets in adults and children older than 1 month, including critically ill patients. However, evidence that increasing the PTA results in higher efficacy is lacking; no studies were identified that show a correlation between estimated or predicted PK/PD target attainment and clinical success. Although it is unclear if performing therapeutic drug monitoring (TDM) for optimisation of the PTA is of clinical value, it is recommended in patients with highly variable pharmacokinetics, including patients from all subpopulations that are critically ill (such as elderly, children and neonates) and patients on intermittent hemodialysis. In addition, TDM for optimisation of the dosing interval, targeting a trough concentration of at least <2 mg/L but preferably <0.5–1 mg/L, has proven to reduce nephrotoxicity and is therefore recommended in all patients receiving more than one dose of gentamicin. The usefulness of the daily area under the plasma concentration–time curve for predicting nephrotoxicity should be further investigated. Additionally, more research is needed on the optimal PK/PD targets for efficacy in the clinical situations in which gentamicin is currently used, that is, as monotherapy for urinary tract infections or as part of short-term combination therapy.

Introduction

Gentamicin is an aminoglycoside antibiotic that has been in use for parenteral administration since 1971 [1]. Despite 50 years of clinical experience, optimal dosing schemes still need further refinement [2], especially for subpopulations where population pharmacokinetic (PPK) studies have been relatively sparse, including paediatric, elderly and critically ill patients [3]. Additionally, adjusting the dosage to individual needs remains a challenge due to the narrow therapeutic window and substantial interindividual variability (IIV) of gentamicin pharmacokinetics [3]. Moreover, the optimal pharmacokinetic/pharmacodynamic (PK/PD) target for clinical efficacy is still under debate [4].

Gentamicin pharmacokinetics in specific subpopulations like obese patients, critically ill patients, paediatric patients, neonates, elderly patients and patients on dialysis can differ from gentamicin pharmacokinetics in the general adult patient population. This manuscript aims to narratively review the clinical pharmacokinetics of gentamicin in these patient populations and the consequences for optimal dosing of gentamicin for infections caused by Gram-negative bacteria, focussing on new insights from the past 10 years.

We searched PubMed for relevant articles from the past 10 years using the following search strategy: ((Pharmacokinetics [Mesh] OR Pharmacokinetics [Subheading] OR Monte Carlo Method [Mesh] OR Drug Monitoring [Mesh] OR Drug Dosage Calculations [Mesh] OR Pharmacokinetic*[tiab] OR Pharmacodynamic*[tiab] OR PK/PD[tiab] OR population Pk*[tiab] OR target attainment[tiab] OR target attainment[tiab] OR Drug monitoring[tiab] OR TDM[tiab] OR Dose calculation*[tiab] OR Drug dos*[tiab]) AND (“Gentamicins”[Mesh] OR gentamicin*[tiab])), limited to the last 10 years and to articles in English. Articles on aminoglycosides were included only if specific data on gentamicin were reported; data on other aminoglycosides (particularly tobramycin) were not extrapolated to gentamicin. Articles focusing exclusively on treatment for infections caused by Gram-positive bacteria (e.g. combination therapy for endocarditis) were not included. Articles were selected after reading titles and abstracts. In addition, references from selected articles were screened for relevance.

Pharmacokinetics in the general adult population

Pharmacokinetic parameters

The median clearance (CL) of gentamicin in adult patients with normal renal function (creatinine clearance [CLCR] >60 mL/min) is 4.58 L/h/70 kg (range 4.31–5.12) [3]. Gentamicin distributes mainly into the extracellular fluid compartment, the volume of distribution (Vd) in non-critically ill adult patients with normal renal function is approximately 19.5 L/70 kg [5, 6]. The ranges of pharmacokinetic parameters in several subpopulations are reported in Table 1.

Table 1

Ranges of pharmacokinetic parameters in several subpopulations.

Subpopulation	CL (L/h/70 kg)	Vd/V1 (L/70 kg)	IIV CL (%)	IIV Vd/V1 (%)
General adult population	4.31-5.12 [3]	13.3-24.5 [11,47,49,50,52]	18.5-36 [3]	5.8-11.9 [3]
Obese patients	4.3-4.6 [47-49]	10.5-20.3 [11,47,49,50,52]	17.4 [46]	18.5 [46]
Critically ill patients	1.15-5.7[a] [57]	19-53[b] [57]	29.3-83.7 [57]	10.9-64.4 [57,59]
Paediatric patients	5.6–9.1 [90-92]	17.5-24.5 [89,91,92]	16-39 [3]	21.6-49 [3]
Neonates	0.49-6.3 [89,112,114-117]	26.6-63.7 [89,111-117]	16.1-58.6 [3]	10.3-35 [3]
Elderly patients	3.0[b] [126]	14.6-25.9[b] [124,126]	20.5 [126]	10.5 [126]
Patients on IHD	4.68-6.96[a,c] [63,129-132]	12.4-23.1[b] [63,64,129-132]	0.3[d] [137]	50.7 [137]
Patients on PD	0.25[a,c] [141]	21.0 [141]	NR	NR

Not all studies have reported weight-normalised CL and Vd/V1. For studies reporting CL and Vd /V1 in L/h and L respectively, average patient weight was estimated to be 70 kg. To simplify comparison of the ranges of these pharmacokinetics parameters between subpopulations, weight-normalised CL and Vd /V1 are therefore reported in L/h/70 kg and L/70 kg, respectively, even for paediatric patients and neonates

CL = gentamicin clearance, IHD = intermittent hemodialysis, IIV = interindividual variability, NR = not reported, PD = peritoneal dialysis, Vd = volume of distribution, V1 = volume of distribution of the central compartment

[a] (Partly) reported in L/h instead of L/h/70 kg

[b] (Partly) reported in L instead of L/70 kg

[c] Total CL during IHD/PD session

[d] Non-IHD CL

Variability and causes

In five studies published between 1989 and 2006, included in a large review of PPK models of gentamicin that focused on patients from the general adult population (excluding patients on hemodialysis, cystic fibrosis, critically ill and elderly patients), IIV in CL ranged from 18.5 to 36% [3]. Two of these studies reported IIV in Vd or IIV in the volume of distribution in the central compartment (V1). In a one-compartment model, IIV in Vd was 11.9%. In a two-compartment model, IIV in V1 was 5.8% [3]. One study including 697 adult patients also reported 8% interoccasion variability (IOV) for CL and 19% IOV for volume of distribution in the peripheral compartment (V2) [5]. To the best of our knowledge, no new PPK studies focusing on the general adult population have been published in the last 10 years.

In the 14 studies on adults included in the aforementioned review, CLCR was the most common covariate found to have a significant impact on gentamicin CL (in 7/10 studies that tested it) [3]. Three studies that focused on the general population reported that addition of renal function as a covariate on CL decreased IIV in CL from 95 to 67%, from 55 to 27% and from 33.9 to 18.5%, respectively [5, 7, 8]. In several studies, the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) performed better than the Cockcroft-Gault equation (CRGT) or the Modification of Diet in Renal Disease equation (MDRD) for their association with gentamicin CL, and adjustment for individual body surface area improved the performance of CKD-EPI, especially for obese or cachectic patients [9–11].

In the aforementioned review, total body weight (TBW) was the most common covariate on gentamicin Vd (in 9/14 studies that tested it) [3]. The pharmacokinetics of gentamicin in obese patients will be described in more detail separately.

Dosing and pharmacokinetic/pharmacodynamic (PK/PD) targets

Although once-daily dosing (ODD) (or extended-interval dosing) of gentamicin has still not been universally implemented [12–14], there is consensus that this dosing scheme makes optimal use of the pharmacological characteristics of gentamicin, increasing the probability that the gentamicin concentration has dropped below the threshold for nephrotoxicity when the next dose is administered [2]. Pathophysiologically, ODD likely leads to less gentamicin accumulation in proximal renal tubular epithelial cells because of saturation of gentamicin uptake, which probably takes place through megalin-and cubilin-mediated endocytosis [2, 15, 16].

In recent decades, dosing of gentamicin has increased from 3 to 4.5 mg/kg/day and subsequently to 6 or 7 mg/kg/day to maximise the probability of target attainment (PTA) [17]. However, the optimal PK/PD target for clinical efficacy of aminoglycosides is still under debate [4]. Several clinical studies from the 1980s and 1990s found the ratio of peak concentration to minimal inhibitory concentration (Cmax/MIC) to be the PK/PD index that was primarily linked to clinical efficacy, with maximal efficacy at Cmax/MIC ≥8–10 (Fig. 1) [18–20]. A study analysing data from four earlier prospective studies including 236 patients with a Gram-negative bacterial infection receiving aminoglycosides, of which 103 received gentamicin, found increasing clinical response (a composite endpoint with clinical and/or microbiological parameters) with increasing Cmax/MIC [19]. All patients received combination therapy, but no concomitant antibiotics that had an antibiotic effect against the causative Gram-negative micro-organisms. A retrospective study including 78 patients treated with aminoglycosides for hospital-acquired pneumonia with a Gram-negative micro-organism (predominantly *Pseudomonas aeruginosa*), of which 38 received gentamicin, found that Cmax/MIC >10 in the first 48 hours of therapy was associated with a 90% probability of defervescence and normalisation of leucocyte count. Of the included patients, 94% received combination therapy with a β-lactam, of which 72% had a causative micro-organism that was also susceptible to the β-lactam antibiotic [18].

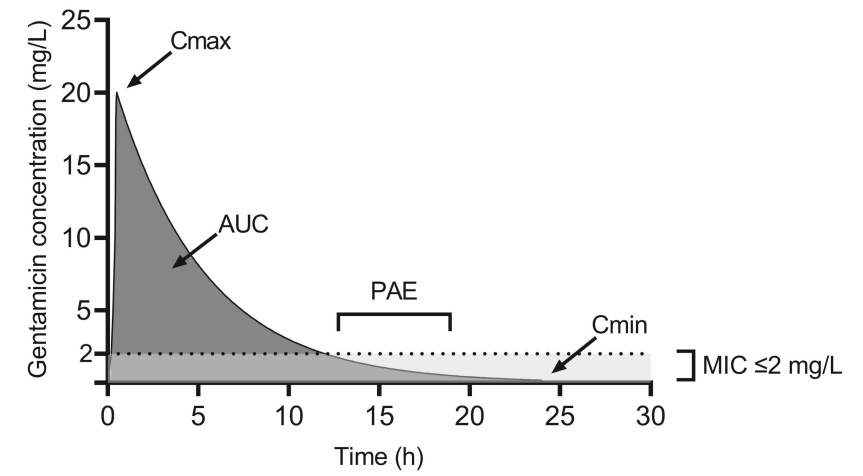

Fig. 1
Illustration of the pharmacokinetic/pharmacodynamic parameters associated with efficacy and toxicity. AUC = area under the concentration–time curve, Cmax = peak concentration, Cmin = trough concentration, MIC = minimal inhibitory concentration, PAE = post-antibiotic effect, persistent suppression of bacterial growth that occurs after the gentamicin concentration drops below the MIC [2]. A Cmax/MIC ratio ≥8–10 and a AUC/MIC ratio ≥70–100 are used as targets for efficacy when treating Gram-negative infections, Cmin <2 mg/L is associated with reduced risk of nephrotoxicity.

Alternatively, the ratio of area under the concentration–time curve to minimal inhibitory concentration (AUC/MIC) has been proposed as the primary PK/PD index for aminoglycosides (Fig. 1), mostly based on animal studies [21]. Two small clinical studies found AUC_{0-24}/MIC to be the superior PK/PD index for clinical efficacy of aminoglycosides, but these only included patients on tobramycin [22, 23]; a prospective study including 13 cystic fibrosis (CF) patients with an exacerbation caused by *Pseudomonas aeruginosa*, treated with the combination of tobramycin and ticarcillin (but most strains were resistant to ticarcillin, and no correlation was found between clinical effect and ticarcillin MIC or T>MIC) [22], and an analysis of data from two earlier prospective studies including 23 patients receiving tobramycin monotherapy for intra-abdominal infection (combined with clindamycin) or Gram-negative bacterial pneumonia [23]. Definitive AUC/MIC efficacy targets have not been established and could depend on the circumstances: an AUC/MIC of 30–50 may provide good outcomes in non-critically ill patients with lower and uncomplicated upper urinary tract infections or in patients receiving combination therapy, but an AUC/MIC of 80–100 may be needed in critically ill patients with non-urinary tract infections or in patients receiving gentamicin monotherapy [4]. For simulated patients with normal renal function treated with 7 mg/kg once daily, the probability of reaching an AUC/MIC of 30.7 was 99.8% for an MIC of 1 mg/L and 89.5% for an MIC of 2 mg/L [21]. However, the probability of reaching an AUC/MIC of 84.3 was 58.8% for an MIC of 1 mg/L and only 2.1% for an MIC of 2 mg/L [21]. Starting in January 2020, based on these considerations, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has restricted the clinical breakpoints for gentamicin to infections with *Enterobacterales* originating from the urinary tract treated with a daily dose of 6–7 mg/kg of ideal body weight (IBW), with the clinical breakpoint set at 2 mg/L [24]. Gentamicin is no longer considered an adequate treatment option for *Pseudomonas aeruginosa*, since wild-type MICs of *P. aeruginosa* are so high that the PTA is negligible. For lower and uncomplicated upper urinary tract infections with *Enterobacterales*, EUCAST notes that doses lower than 6–7 mg/kg may be adequate [25, 26] because gentamicin is concentrated in urine and renal tissues. Yet, they also note that the appropriate dosing regimen is not certain since most PK/PD data have been based on mouse thigh and lung models [27]. For other systemic infections, EUCAST states that aminoglycosides should only be used in combination with another active therapy because of low PTA in these infections [27]. Of note, treatment for pneumonia with systemic aminoglycosides is particularly difficult. Since only 12–30% of aminoglycoside serum levels are achieved in epithelial lining fluid [28, 29], the PTA when using a starting dose of 7 mg/kg will be negligible. In clinical practice,

both Cmax/MIC and AUC/MIC may be used as target, since they are highly correlated when using ODD [30, 31]. Of note, if an AUC/MIC target is used instead of a Cmax target, patients with decreased CL would need a lower daily dose to reach the same $AUC_{0\text{-}24}$. Theoretically, these patients might therefore have less risk of nephrotoxicity when dosing based on an AUC/MIC target compared with dosing on a Cmax/MIC target. However, the AUC threshold for nephrotoxicity remains to be established [4] and studies are needed to ascertain if AUC-guided dosing decreases the risk of nephrotoxicity, especially in patients with decreased CL, who are at increased risk of nephrotoxicity.

Predictors of efficacy and toxicity

Despite all mentioned considerations with regard to PK/PD targets, the question is whether these targets indeed predict efficacy in clinical situations. A large review from 2017 of PPK studies on aminoglycosides described nine studies that have associated PK/PD indices with efficacy, of which only one study included only patients on gentamicin [3]. The PK/PD indices evaluated in these studies were Cmax/MIC or Cmax in two studies, AUC/MIC or AUC in two studies and both Cmax/MIC and AUC/MIC in five studies. The most common PK/PD targets in these studies were Cmax/MIC ≥7–10 or AUC/MIC ≥70–100. However, no studies were identified that showed a correlation between estimated or predicted PK/PD target attainment and clinical success [3].

A meta-analysis from 2021 of the optimal target gentamicin trough concentration (Cmin) for reducing the risk of nephrotoxicity found no randomised controlled trials (RCTs) but included five observational studies (615 patients) evaluating a Cmin of 2 mg/L and one observational study (187 patients) evaluating a Cmin of 1 mg/L [32]. Patients with Cmin <2 mg/L had significantly less risk of nephrotoxicity (odds ratio [OR] 0.22, 95% confidence interval [CI] 0.12–0.40) compared with patients with Cmin ≥2 mg/L (Fig. 1). One of these studies used logistic regression to define the best Cmin cut-off point to predict acute kidney injury (AKI) and found a Cmin of 2.0 mg/L [33]. The only study using a Cmin <1 mg/L target also showed significantly less risk of nephrotoxicity compared with patients with Cmin ≥1.1 mg/L (OR 0.07, 95% CI 0.02–0.24) [34]. Of note, using a Cmin target to reduce the risk of nephrotoxicity has been under debate for several decades, since a Cmin above the threshold may be the result and not the cause of renal damage [35]. However, the largest and most recent study (from 2015) included in the aforementioned meta-analysis only used Cmin levels collected prior to the diagnosis of AKI, suggesting that high Cmin levels are indeed a risk factor for nephrotoxicity [33]. Daily AUC is also a predictor for

aminoglycoside nephrotoxicity [36, 37], but the optimal daily AUC to reduce the risk of nephrotoxicity is currently unclear [4].

Gentamicin treatment is also associated with a risk of ototoxicity: cochleotoxicity (often permanent sensorineural hearing loss) and/or vestibulotoxicity (balance disorders). The number of doses, the duration of therapy and the cumulative dose are weak predictors of aminoglycoside ototoxicity [38]. ODD does not appear to significantly reduce the risk of ototoxicity compared with multiple day dosing (MDD) [2], possibly because clearance of aminoglycosides from the inner ear is very slow, resulting in a very long exposure time of the inner ear [39]. Of 35 PPK studies on gentamicin included in a large review from 2017, none have evaluated the association between PK/PD indices and ototoxicity [3]. In a PPK study to predict the risk of ototoxicity in CF patients treated with tobramycin using a two-compartment model, Cmax >2 mg/L in the peripheral compartment showed the highest correlation with hearing loss severity [38].

Interestingly, there appears to be a circadian variation of gentamicin toxicity [40]. A prospective study including 184 patients receiving 4 mg/kg gentamicin once daily reported increased risk of nephrotoxicity when gentamicin was administered during the night [41]. Although baseline renal function was not equally distributed between treatment groups, the results did not change when baseline clearance was added to the model in a multivariate analysis [41]. Increased risk of both ototoxicity and nephrotoxicity during the rest period was also found in animal studies [42, 43]. However, a more recent retrospective cohort study including 310 general ward patients and 411 ICU patients found no differences in pharmacokinetics or toxicity between patient groups that received aminoglycosides in the morning, afternoon or night and advised not to wait until the next morning but to start aminoglycosides as soon as possible [44].

Recommendations

For the general adult population, a starting dose of 7 mg/kg is recommended, followed by therapeutic drug monitoring (TDM) after the first administration for optimisation of the dosing interval, in order to reduce the risk of nephrotoxicity. This dose is expected to reach both the Cmax/MIC and AUC/MIC targets, although we found no studies that showed a correlation between PK/PD target attainment and clinical success. A Cmax >16 mg/L target (Cmax/MIC >8 for a maximal MIC of 2 mg/L) can be achieved in a large majority of adult patients using 7 mg/kg (e.g. 85% of patients with sepsis at the emergency department [45]). Using a starting dose of 7 mg/kg also results in a simulated 89.5% PTA

when aiming for an AUC/MIC target of 30.7 with a maximal MIC of 2 mg/L [21]. The starting dose recommendations for the general adult population and other subpopulations are reported in Table 2. We advise against the use of gentamicin monotherapy for infections caused by *Pseudomonas aeruginosa* and for pneumonia.

Table 2

General recommendations on starting doses for several subpopulations

Subpopulation	General recommendation on starting doses[a]
General adult population	7 mg/kg TBW
Obese patients	5-6 mg/kg ABW[b] or according to dosing nomogram from Smit et al. [46]
Critically ill patients	7 mg/kg TBW
Paediatric patients	7 mg/kg TBW
Neonates	4-5 mg/kg TBW
Elderly patients	7 mg/kg TBW
Patients on IHD	2-3 mg/kg loading dose after dialysis, followed by 1.5 mg/kg after each following session or 4-6 mg/kg before dialysis
Patients on PD	40 mg IP or 0.6 mg/kg IP once daily with 6-hour dwell time

ABW = adjusted body weight, AUC = area under the concentration–time curve, Cmax = peak concentration, IHD = intermittent hemodialysis, IP = intraperitoneal, MIC = minimal inhibitory concentration, PD = peritoneal dialysis, TBW = total body weight.

[a] Therapeutic Drug Monitoring (TDM) is always advised to optimise the dosing interval in order to reduce the risk of nephrotoxicity; TDM to optimise the probability of pharmacokinetic/pharmacodynamic target (Cmax/MIC or AUC/MIC) attainment is advised for patients with highly variable pharmacokinetics, including patients from all subpopulations that are critically ill (such as elderly, children and neonates) and patients on IHD.

[b] ABW = ideal body weight + (total body weight – ideal body weight) * 0.4

Pharmacokinetics in obese patients

Pharmacokinetic parameters

In several studies from the 1980s and 1990s, gentamicin CL was reported to be increased in obese patients compared with non-obese patients [46]. For example, Bauer et al. reported a CL of 8.46 L/h in obese versus 5.76 L/h in non-obese patients [47]. After standardising to a body surface area (BSA) of 1.73 m^2 or a TBW of 70 kg, mean CL was comparable in these studies, with 4.3–4.6 L/h/1.73 m^2 or L/h/70 kg in obese patients versus 4.0–5.5 L/h/1.73 m^2 or L/h/70 kg in non-obese patients, leading to higher CL in patients with larger BSA or higher TBW [47–49]. However, CL in these studies is difficult to extrapolate to the

current situation. The definition of obesity was different from today, with obese patients having an average TBW of 80–100 kg, which is significantly lower than the average TBW of obese patients in more recent studies. Moreover, dosing regimens were also different from today, with patients receiving MDD. A PPK study from 2019 including 20 richly sampled obese patients reported a CL of 5.4 L/h/70 kg, but excluded patients with glomerular filtration rate (GFR) <60 mL/min, so CL is expected to be lower than 5.4 L/h/70 kg in obese patients with renal impairment [46].

Gentamicin Vd is increased in obese patients compared with non-obese patients when not weight normalised, due to higher TBW and BSA, with mean Vd in seven studies ranging from 13.3 L to 26.8 L in obese patients versus 10.0 to 24.3 L in non-obese patients [46–52]. However, since the extracellular water (ECW) volume in adipose tissues is lower than in other tissues, Vd is decreased in obese patients when normalised to L/kg TBW, with mean Vd in five studies ranging from 0.15 to 0.29 L/kg in obese patients versus 0.19 to 0.35 L/kg in non-obese patients [11, 47, 49, 50, 52].

Variability and causes

In a PPK model including 20 morbidly obese patients and eight non-obese patients, TBW was the best predictor for both CL and V1 [46]. Addition of TBW as a covariate for V1 and CL led to a large reduction in unexplained IIV, from 49.6 to 18.5% for V1 and from 32.2 to 17.4% for CL. Addition of lean body weight (LBW) or adjusted body weight (ABW) as a covariate to V1 was inferior to TBW [46].

Interestingly, a retrospective study including 335 patients, of whom 223 were overweight or obese, showed that skeletal muscle area and volume extracted from computed tomography (CT) images as measures of body composition explained more of IIV in CL than TBW, an observation to be confirmed in further studies [53].

Dosing and PK/PD targets

Several weight-based dosing regimens have been proposed for obese patients. A large study including 2073 patients including underweight and obese patients advised the use of LBW for dosing, since LBW performed better in estimating gentamicin Vd across all weight strata than TBW and IBW [11]. However, most studies advise the use of ABW. ABW introduces a dosing weight correction factor (DWCF) for the excess body weight (TBW − IBW) to account for the limited gentamicin diffusion in adipose tissues [49]. The standard weight-based

dose is then performed on ABW = IBW + (TBW − IBW) * DWCF instead of on TBW, with DWCF ranging from 0.3 to 0.55 in seven studies [47–52, 54], with 0.4 being currently most commonly used [54]. The aforementioned PPK study recommends using a dose nomogram for patients with GFR >60 mL/min, based on a TBW derived 'dose weight': 70 * (TBW/70)$^{0.73}$ [46]. Based on simulations, dosing 5–6 mg/kg ABW (using a DWCF of 0.4) or 8 mg/kg LBW would lead to similar exposure in some obese patients and could be considered as alternatives [46]. However, calculated starting doses using ABW, 'dose weight' or the nomogram can differ substantially, particularly at the higher end of the weight range (see Table 3). Therefore, a conservative approach to dosing and prompt TDM are suggested to avoid toxicity. Several PK/PD targets have been used in studies on pharmacokinetics of obese patients. Several older studies used a Cmax of 5–8 mg/L as target [47, 49], studies from the last decade have used a Cmax of 16–20 mg/L [11], $AUC_{0\text{-}24}$ of 68.7 mg*h/L [46] or a serum concentration of 0.5–2.0 mg/L 16 hours after infusion, based on a nomogram [54].

Table 3

Comparison of gentamicin starting doses for obese patients when using adjusted body weight, 'dose weight' or a nomogram for determining dosing

TBW (kg)	Dose (mg) using 5 mg/kg ABW[a]	Dose (mg) using 6 mg/kg ABW[a]	Dose (mg) using 5 mg/kg 'dose weight'[b]	Dose (mg) using nomogram [46]
110	430	516	487	480
130	470	564	550	560
150	510	612	611	600
170	550	660	669	680
190	590	708	725	760
210	630	756	780	800

ABW = adjusted body weight, TBW = total body weight.

[a] ABW = ideal body weight + (total body weight – ideal body weight) * 0.4. For this comparison, a fixed ideal body weight of 70 kg was used

[b] 'Dose weight' = 70 * (TBW/70)$^{0.73}$ [46]

Predictors of efficacy and toxicity

We did not find any studies investigating the association between target attainment and clinical cure or toxicity specifically for obese patients.

Recommendations

Obese patients are at risk of overdosing when a starting dose of 7 mg/kg TBW is used. Instead, using the dosing nomogram based on a 'dosing weight'

calculated as 70 * (TBW/70)$^{0.73}$ or dosing 5–6 mg/kg ABW with a DWCF of 0.4 (ABW = IBW + 0.4 * [TBW – IBW]) is advised for obese patients with normal renal function, followed by TDM after the first administration for optimisation of the dosing interval in order to reduce the risk of nephrotoxicity [46]. Lower doses and extension of the dosing interval is recommended in obese patients with reduced renal function [55].

Pharmacokinetics in critically ill patients

Pharmacokinetic parameters

In critically ill patients, many pathophysiological changes affecting both Vd and CL can occur that complicate gentamicin dosing [56]. Based on 11 studies summarised in a review from 2021 of aminoglycosides PPK studies in critically ill patients, the median CL of gentamicin in these patients is 3.0 L/h (range 1.15–5.7 L/h) and the median Vd 29 L (range 19–53 L) [57]. Two other studies also reported CL and Vd within these ranges [58, 59]. Several studies including only critically ill patients using renal replacement therapy (i.e. continuous venovenous hemodiafiltration [CVVHDF], continuous venovenous hemofiltration [CVVH], intermittent hemodialysis [IHD], and extended daily diafiltration [EDD-f]) showed a Vd ranging from 14.1 L to 46.9 L [60–65].

Variability and causes

Even when using body weight standardised starting doses, large IIV in Vd (ranging from 10.9% to 64.4% [57, 59]) causes a wide range in Cmax, resulting in an increased risk of both supra- and subtherapeutic Cmax [58, 66, 67]. This variability in Vd can partially be explained by body weight (TBW [62, 67] or IBW [68]), disease severity [69], hypoalbuminemia [68], the use of total parenteral nutrition [70] and several other variables that are associated with the capillary leak syndrome that can occur during septic shock [56].

Additionally, CL also shows large IIV, ranging from 29.3% to 83.7% [57]. GFR, often CLCR estimated using CRGT, is the most common retained covariate for CL in gentamicin PPK models in critically ill patients [57]. GFR is often decreased due to an interplay of sepsis-related AKI, pre-existing comorbidities and nephrotoxic drugs [71], leading to lower CL and an increased risk of Cmin >2 mg/L. While such reductions in GFR and increases in exposure have been associated with toxicity [32], data establishing a causal link between gentamicin exposure and AKI in humans do not yet exist; however, animal models support that increasing gentamicin exposure (AUC) increases the risk of AKI and that vulnerability to

AKI may be greater in males [72]. Conversely, augmented renal clearance (ARC, defined as GFR >130 mL/min/1.73 m^2) can also occur, most often in relatively young trauma patients without pre-existential comorbidities, for whom higher gentamicin doses may be indicated [73]. Other determinants reported to explain variability in CL include usage of CVVH [68] or IHD [63] and several measures of body weight [62, 68, 74].

Obesity in critically ill patients is associated with both increased CL and Vd compared with non-obese critically ill patients, which can lead to both sub- or supra-therapeutic gentamicin concentrations; strict TDM after the first dose is therefore recommended in this subpopulation [75].

Dosing and PK/PD targets

The daily dosing regimens of gentamicin as reported in PPK studies in critically ill patients have ranged from 3 mg/kg to 8 mg/kg [57, 76–78]. The PK/PD target used varied between these studies; most have used a Cmax/MIC ≥8–10 as target [57], resulting in a Cmax target of ≥16–20 mg/L when targeting micro-organisms with a maximum MIC of 2 mg/L [24]. Studies dosing 8 mg/kg used a Cmax target of 30–40 mg/L, to also target microorganisms with an MIC of 4 mg/L [76–78]. Several recent studies have shown unsatisfactory Cmax target attainment in critically ill patients: 47% reached a target Cmax of ≥15 mg/L with 4 mg/kg [66], 59% reached a target Cmax of ≥16 mg/L with a median dose of 6.2 mg/kg [79] and only 0–6% achieved a target Cmax >30 mg/L when using 8 mg/kg [76–78]. Simulation studies showed that 11 mg/kg would be needed to achieve a Cmax >30 mg/L in more than half of the patients [80] and that even with the highest simulated dose of 12 mg/kg, <90% of patients in an ICU specialising in severe respiratory and infectious diseases would achieve Cmax >16 mg/L [59].

Predictors of efficacy and toxicity

In multiple studies evaluating aminoglycoside efficacy in critically ill patients, no significant correlation was found between PK/PD target attainment and clinical outcome [79, 81, 82]. The largest of these studies was a prospective observational cohort study in 59 intensive care units that included 931 patients on aminoglycosides, of which 303 received gentamicin. Of 90 patients with a measured gentamicin Cmax after the first dose, 59% attained the targeted Cmax of >20 mg/L. In multivariate analysis, there was no significant association between target attainment of aminoglycosides and clinical success (odds ratio 1.24, 95% confidence interval 0.79–1.94; P = 0.35).

To the best of our knowledge, there are no studies focusing specifically on the critically ill population that show an association between gentamicin Cmin and the risk of toxicity.

Recommendations
Especially in critically ill patients with increased Vd, a starting dose of 7 mg/kg is necessary to increase the PTA. Although using a starting dose of 8–10 mg/kg in this population would further increase the PTA, these higher doses can also result in an increased risk of nephrotoxicity as the Cmin will also increase, resulting in Cmin >2 mg/L in a proportion of patients if dosing intervals are not adjusted. In these patients, the risk of nephrotoxicity is already relatively high, since AKI can also develop because of the septic shock in itself, because of comorbidities like diabetes mellitus, pre-existent reduced renal function and dehydration and because of treatment with nephrotoxic co-medication like vancomycin, diuretics and contrast media [71]. In a propensity-based study including critically ill patients that had no AKI before day 3, no increased risk of nephrotoxicity was found in 39 patients receiving a short course of gentamicin 7 mg/kg for a mean of 2.6 days, compared with patients who did not receive gentamicin [83]. However, even a small decrease in renal function may negatively impact the clinical outcome in critically ill patients [84, 85]. Since targeting an adequate Cmax/MIC in all critically ill patients inevitably increases the risk of nephrotoxicity on a population level [86], one should carefully weigh the risks and benefits of gentamicin therapy in this patient population.

Although there is no evidence that attainment of the PK/PD target (with or without the use of TDM) is associated with clinical success, TDM is advised to optimise the PTA in critically ill patients.

Pharmacokinetics in paediatric patients

In the paediatric population, pharmacokinetics can vary between several subpopulations, each requiring a different dosing regimen. The pharmacokinetics in paediatric patients in general (infants aged >28 days to 12 months, children aged >12 months to 11 years and adolescents aged 12–18 years) will be reviewed separately from the pharmacokinetics in neonates (0–28 days).

Pharmacokinetics parameters
The Vd of gentamicin is greater for paediatric patients than for adult patients. This is the result of body compositional changes with increasing age: at birth,

ECW comprises 45% of TBW but rapidly declines to 27% of TBW at the age of 1 year, after which the ECW only slightly decreases to reach adult values of circa 20% [87, 88]. Although studies addressing the effect of age on pharmacokinetic parameters of gentamicin remain scarce, several studies have been published in the last 10 years that make it possible to define the actual pharmacokinetic differences more clearly [89]. In infants, Vd of gentamicin is estimated to be 0.35 L/kg [89], higher than reported in adults and lower compared with neonates [90]. Studies on pharmacokinetics of gentamicin in febrile neutropenic children aged 0–17 years showed a Vd ranging from 0.25 L/kg to 0.32 L/kg [91, 92].

Gentamicin CL is determined by the developmental stage of the renal function. The renal function is fully matured at the age of 1–2 years [88, 93]. CL is therefore expected to be lower during the first weeks of life, but higher in 2-to 5-year-old children, where the weight-corrected GFR is almost 70% higher compared with adults [94, 95]. Mean CL for infants is estimated to be 0.12 ± 0.01 L/h/kg [90]. In febrile neutropenic paediatric patients, CL was estimated to be 0.08–0.13 L/h/kg [91, 92].

Variability and causes

A large variability of pharmacokinetic parameters can be observed in the paediatric population, which is to be expected considering the relatively rapidly changing body composition. Age and weight (birth and/or current weight) are the most important covariates influencing gentamicin Vd and CL [3], with significantly higher Vd and CL values for febrile neutropenic children aged ≤10 years compared with children aged >10 years [91]. In contrast with the adult population, CLCR was often not found to influence CL, possibly because the linear equations often used for estimating GFR (such as CRGT) do not accurately predict GFR in young children [96, 97], since renal function develops non-linearly with increasing age [98]. The IIV ranges from 21.6% to 49% for Vd and from 16% to 39% for CL [3].

Critically ill paediatric patients are subject to even larger pharmacokinetic variability due to pathophysiological changes affecting Vd and CL, as described in a systematic review from 2020 [95]. In a review of the pharmacokinetic alterations of gentamicin in critically ill paediatric patients treated with extracorporeal membrane oxygenation (ECMO), Vd was found to be enlarged by 28.8% to 58.8% and CL to be decreased by 26.3% to 31.7% [99]. Conversely, CL can also be increased due to ARC, which occurs in up to 67% of critically ill paediatric patients [95, 100]. These findings underscore the importance of TDM.

Obese children are subject to additional body compositional changes. Adipose tissue has a smaller ECW volume than other tissues, decreasing Vd (if measured in L/kg TBW) of gentamicin in obesity [101–103]. A retrospective study compared Vd of gentamicin in 25 obese children (defined as a body mass index [BMI] ≥95th percentile for age and gender) with that of 25 healthy weight children (defined as a BMI ≥5th percentile and ≤85th percentile) and found a significantly lower Vd in obese children (0.20 ± 0.05 vs 0.28 ± 0.07 L/kg TBW, P <0.01) [101]. No changes in CL of gentamicin were observed in obese children compared with non-obese children [101, 103].

Dosing and PK/PD targets

Gentamicin dosing recommendations for the paediatric population are inconsistent [3, 104]. In general, based on PK/PD targets from the general adult population, a starting dose of 7 mg/kg/24 h is recommended for children aged 1 month to 18 years, followed by TDM performed before administration of the second dose [89, 90, 105]. Higher doses of 8 mg/kg/24h have been suggested for oncology patients based on a PPK study targeting Cmax/MIC >10 [106]. Several studies have proposed to use separate dosing regimens for several age categories, where infants and children aged 1 month to 8–12 years should receive at least 7 mg/kg/day and older children should receive 5–7 mg/kg/day [89–91, 107, 108]. The exact cut-off age is unclear, as different age categories have been proposed. It is currently unknown whether a weight index other than TBW should be used for obese paediatric patients and, if so, what index should be used. Studies have suggested the use of fat-free mass (amongst others) instead of TBW, but evidence is limited [89, 106, 109].

In three studies on gentamicin in a review from 2020 of pharmacokinetics and target attainment of antibiotics in critically ill children, dosing recommendations ranged from 6 mg/kg to 9 mg/kg per day [95]. Currently, the same dosing regimens used for the general paediatric population are applied to the critically ill paediatric patients, but TDM is of even more importance due to the additional IIV. Special attention should be given to patients with renal failure and ARC to avoid toxic or subtherapeutic gentamicin exposure.

Despite the increasing evidence favouring ODD over MDD [110], both dosing regimens are still being used [104]. Altogether, ODD is considered the preferred dosing regimen in paediatric patients, based on the similar effectivity and toxicity rates, the reduced costs and increased convenience of ODD [110].

Predictors of efficacy and toxicity
We did not find studies investigating the association between target attainment and clinical cure in the paediatric population. It is therefore currently unknown which PK/PD target predicts efficacy best. The same holds true for toxicity: Cmin ranging from 0.5 mg/L to 2 mg/L are referred to in the literature [107]. However, nephrotoxicity and ototoxicity also occur in paediatric patients when adequate trough concentrations are maintained and ODD is used [105]. To our knowledge, no recent studies specifically reported toxicity of gentamicin in the critically ill paediatric patient.

Recommendations
For children older than 1 month, a starting dose of 7 mg/kg is advised, followed by TDM after the first administration for optimisation of the dosing interval in order to reduce the risk of nephrotoxicity [89]. Simulations show that higher starting doses may be needed for optimal treatment of infections caused by micro-organisms with an MIC of 2 mg/L [107] and that younger children may need higher starting doses than older children (e.g. 10.8 mg/kg for children ≤10 years vs 6.4 mg/kg for children >10 years [91] or 9.5 mg/kg for children <2 years, 8.5 mg/kg for children 2–7 years and 7 mg/kg for children ≥8 years [108]). Clinical studies are needed to confirm these findings. In critically ill paediatric patients, TDM is also advised to optimise the PTA.

Pharmacokinetics in neonates

Pharmacokinetic parameters
The Vd of gentamicin in neonates ranges from 0.38 L/kg to 0.91 L/kg for both preterm and term neonates [89, 111–116, 117]. CL is largely linked to size and age and is estimated to range from 0.007 L/kg/h to 0.09 L/kg/h [89, 112, 114–116, 117]. Since nephrogenesis is not completed until 36 weeks of gestation, CL is lower for preterm neonates than for term neonates [112].

Variability and causes
Neonates are subject to considerable pharmacokinetic variability, due to body compositional changes that are most pronounced in the first weeks of life and the functional maturation of organs [112]. Two reviews from 2017 and 2019 have extensively described PPK models of neonates [3, 89]. Weight (birthweight, current weight) is the most important covariate influencing Vd and age (predominantly gestational age [GA] or GA and postnatal age combined) and weight (birthweight, current weight) are the most important covariates

influencing CL [3]. The IIV ranges from 10.3% to 35% for Vd and from 16.1% to 58.6% for CL. In neonates undergoing controlled hypothermia, there is no significant change in Vd but CL is 25–50% lower [117, 118].

Dosing and PK/PD targets
Several dosing regimens have been suggested for neonates depending on GA and weight [89]. ODD is preferred over MDD, as CL of gentamicin is decreased and gentamicin half-life is therefore prolonged [119]. Altogether, most studies recommend dosages of 4–5 mg/kg bodyweight and prolonged (36–48 h) dosing intervals for preterm patients (GA <37 weeks) and for patients with very low birthweight [89, 111–114, 117, 120–122]. Most studies in neonates use this dose of 4–5 mg/kg bodyweight, resulting in a mean Cmax value of 5.4–11.2 mg/L; a few studies aimed for a Cmax of 15–20 mg/L [89].

Predictors of efficacy and toxicity
For neonates, peak concentrations of 5–12 mg/L and trough concentration of <0.5–2 mg/L have been proposed based on adult data [19]. Yet, studies addressing target attainment and its association with clinical cure are lacking. With regard to toxicity, a retrospective study showed that patients weighing >1500 mg who had Cmax >10 mg/L had an increased risk of developing ototoxicity [111]. However, a review on aminoglycoside toxicity in neonates found no clear association between gentamicin use and ototoxicity and nephrotoxicity [123].

Recommendations
For neonates, most studies advise a starting dose of 4–5 mg/kg, with prolonged dosing intervals of 36–48 hours for preterm and very low birthweight neonates. TDM is advised after the first administration for optimisation of the dosing interval in order to reduce the risk of nephrotoxicity. In critically ill neonates, TDM is also recommended to optimise the PTA.

Pharmacokinetics in elderly patients

Pharmacokinetics parameters
Mean gentamicin CL is lower in elderly patients due to the decrease of mean GFR with advancing age, but age as an independent factor does not appear to be of influence [124]. Of note, a recent study in non-elderly adult CF patients (age range 19–50 years) did find age to be an independent modifier of aminoglycoside clearance [125]. Gentamicin Vd in the elderly is similar to Vd in the general patient population: in a review comparing pharmacokinetic parameters from

several studies across a range of ages, patients with mean ages of 39, 61 and 80 years all had a mean Vd of approximately 25 L/70 kg [124].

Variability and causes

A PPK study including 38 patients aged >65 years with a mean age of 80 years estimated IIV in CL to be 20.5% (after adding CLCR as a covariate) and IIV in Vd to be 10.5% (after adding LBW as a covariate) [126]. This study also found that gentamicin CL was reduced by 12% in frail elderly patients (scored using the Reported Edmonton Frailty Scale) compared with non-frail patients, even after adjustment for LBW and renal function [126].

Dosing and PK/PD targets

To the best of our knowledge, the only recent study focusing on target attainment in the elderly was a large, multicentre, retrospective observational study including 128 patients >75 years receiving gentamicin with a mean dose of 3.5 ± 1.2 mg/kg/day [127]. Cmax was measured in 27 patients (21%), with a mean Cmax of 9.4 mg/L and adequate Cmax/MIC >10 in only 6/22 (27%) patients for whom an MIC was available. Cmin was measured in 57 patients (44%), with adequate Cmin <0.5 mg/L in only 16 patients (28%) [127].

Predictors of efficacy and toxicity

We did not find any studies investigating the association between PK/PD target attainment and clinical cure or toxicity specifically for elderly patients.

Elderly patients are at increased risk of nephrotoxicity, and probably of ototoxicity [124]. Based on eight studies, a meta-analysis from 2021 found the overall absolute risks of AKI following aminoglycoside exposure (with 68.6%–100% of patients receiving gentamicin) to be 15.1% among patients aged >65 years, significantly higher than the average 10.5% risk of AKI among patients >18 years (P <0.00001) [128]. In the aforementioned retrospective study including patients >75 years, nephrotoxicity was associated with treatment length ≥3 days and concomitant use of nephrotoxic drugs [127].

Recommendations

Because of increased risk of toxicity in elderly patients, an individualised risk–benefit assessment should be performed in elderly patients for whom aminoglycoside therapy is indicated. If treatment with gentamicin is started, it is recommended to use a starting dose of 7 mg/kg, to limit treatment duration to <3 days, to perform TDM after the first administration for optimisation of the

dosing interval in order to reduce the risk of nephrotoxicity and to reduce use of other nephrotoxic drugs whenever possible [127]. In critically ill elderly, TDM is also recommended to optimise the PTA.

Pharmacokinetics in patients on intermittent hemodialysis

Pharmacokinetic parameters
During IHD sessions, mean gentamicin CL ranged from 4.68 L/h to 6.96 L/h, approximating normal renal function (but total daily CL is much lower in patients on IHD because of low CL between sessions) [63, 129–132]. Mean Vd ranges from 12.4 to 23.1 L or L/70 kg [63, 64, 129–132], which is also comparable to patients from the general population.

Variability and causes
A wide range of CL of 1.1–22.2 L/h is reported in patients during IHD [64, 129, 130, 132]. IHD effectively clears aminoglycosides, but CL is highly variable because of differences in dialyser types, length and frequency of dialysis sessions, blood flow rates, small solute clearance and patient characteristics such as residual renal function [130, 131, 133–136]. In a PPK study including six anuric patients, the addition of TBW as a covariate decreased IIV from 55.7% to 0.3% for non-IHD CL and from 90.7% to 50.7% for V1 [137]. In another PPK study including 46 patients with end-stage renal disease, CLCR explained 35% and 53% of IIV in non-IHD CL and Vd, respectively. Of note, here CLCR is likely to be a marker of LBW and non-renal CLCR [63].

Dosing and PK/PD targets
For patients on IHD, data are limited and optimal dosing remains controversial [138]. Traditionally, gentamicin is administered at the end of an IHD session using a loading dose of 2–3 mg/kg, followed by a maintenance dose of 1.5 mg/kg [138, 139]. Using a range of simulated dosing schemes, several studies have evaluated the possible effects of higher doses of gentamicin preceding IHD, resulting in a higher Cmax, an acceptable AUC and a lower Cmin, maximising efficacy while reducing the risk of toxicity, using Cmax/MIC >8–10 or Cmax >8 mg/L as PK/PD targets [64, 130, 137, 140]. One prospective observational study first performed simulations and subsequently treated ten critically ill patients using IHD with 6 mg/kg gentamicin just before dialysis, resulting in a mean Cmax of 31.8 mg/L, a mean Cmin (after 24 h) of 4.1 mg/L and a mean AUC of 190 mg*h/L [64]. This dosing schedule was subsequently validated in another prospective observational study [65]. A prospective PPK study including 23

patients on IHD concluded that predialysis doses of 2 mg/kg (for an MIC of 1 mg/L), 4 mg/kg (for an MIC of 2 mg/L) or 8 mg/kg (for an MIC of 4 mg/L) were associated with the best efficacy/toxicity ratio [140].

Predictors of efficacy and toxicity
Nephrotoxicity concerns do not play a significant role in deciding on the optimal dose and time of aminoglycoside administration for patients with end-stage renal disease. For critically ill patients on IHD, a strategy with dosing of gentamicin preceding IHD may result in more potential for efficacy and less potential for toxicity [64]. However, we found no studies on the association between PK/PD target attainment and efficacy or toxicity in patients on IHD.

Recommendations
When gentamicin is administered after the IHD session, a loading dose of 2–3 mg/kg is currently recommended, followed by a maintenance dose of 1.5 mg/kg after each following session [139] and TDM for optimisation of both the dosing interval (in order to reduce the risk of nephrotoxicity) and the probability of PK/PD target attainment. When gentamicin is administered before the IHD session, allowing a high Cmax and low Cmin, a first dose of 4–6 mg/kg is recommended, followed by TDM [64, 139]. A first dose of 6 mg/kg before the IHD session may be the optimal approach for critically ill patients [64, 65].

Pharmacokinetics in patients on peritoneal dialysis

Pharmacokinetic parameters
Gentamicin can be administered intraperitoneally (IP) to achieve higher local concentrations for treatment of peritoneal dialysis (PD)-related peritonitis. The pharmacokinetic parameters of gentamicin IP are not well described, particularly during inflammation and infection. The largest prospective pharmacokinetics study to date, including 24 patients with peritonitis treated with gentamicin IP, reported systemic CL of 0.25 L/h and Vd of 21.0 L/70 kg [141]. Median bioavailability of IP gentamicin was reported to be 76% (interquartile range 69–82%) [141].

Variability and causes
Apart from residual renal function, peritonitis is an important determinant for gentamicin CL in PD patients. After IP gentamicin is absorbed into the circulation, CL takes place by glomerular filtration and through PD in anuric patients. Mean systemic half-life was 28.7 hours in peritonitis patients compared with 36 hours

in volunteer PD patients without peritonitis [142, 143], which can be explained by increased membrane permeability in peritonitis patients, resulting in increased clearance from the plasma into the peritoneal cavity during the 18 hours that no IP gentamicin is administered [141].

Dosing and PK/PD targets

The currently used gentamicin IP dose is 40 mg or 0.6 mg/kg TBW once daily with 6 hours dwell time [141, 144–146]. Using 0.6 mg/kg and a PK/PD target of Cmax/MIC >8 in peritoneal dialysate, median intraperitoneal Cmax and Cmin were 23.8 mg/L and 1.5 mg/L and median Cmax and Cmin in plasma were 3.1 mg/L and 1.9 mg/L, respectively [141]. In a prospective cohort study using a plasma Cmin of 0.5–2.0 mg/L at day 2 as PK/PD target, mean Cmin in plasma was 1.8 mg/L but 43% had Cmin >2 mg/L [146]. However, even in patients with a Cmin in plasma <2 mg/L, the high systemic absorption of 76% in patients with peritonitis and the prolonged plasma elimination half-life of 28.7 hours may lead to drug accumulation in the systemic circulation, increasing the risk of toxicity [141]. A lower dose would decrease plasma Cmin but also intraperitoneal Cmax, which may negatively impact efficacy. A shorter dwell time would decrease systemic absorption and result in lower plasma Cmin, while the intraperitoneal Cmax would not change. A recent PPK study including 24 patients evaluated the PTA for treatment success (defined as IP Cmax/MIC >10) and toxicity (defined as plasma AUC <120 mg*h/L) for a 2-week course using several dosing schemes with dwell times ranging from 2 to 6 hours using Monte Carlo simulations. They reported that a dose of 0.6 mg/kg with a dwell time of 5 hours or a dose of 0.7 mg/kg with a dwell time of 3 hours is sufficient (PTA >80% and >90%, respectively) to treat organisms with an MIC of ≤2 mg/L without the risk of significant systemic exposure (PTA >90%) [147]. However, to the best of our knowledge, there are no clinical studies that evaluate the efficacy and toxicity of dosing regimens with a shorter dwell time.

Predictors of efficacy and toxicity

There are no data on the association between drug levels, PK/PD target attainment and peritonitis outcomes or toxicity. In a prospective cohort study including 51 patients, gentamicin serum levels at day 2 did not predict gentamicin-related efficacy or toxicity during short-course gentamicin therapy for Gram-negative PD-related peritonitis, except in cases of polymicrobial peritonitis, where higher day 2 serum levels were associated with cure (2.06 ± 0.41 in cured patients vs 1.29 ± 0.71 in patients with treatment failure; P = 0.01) [146].

Recommendations
For patients on continuous ambulatory peritoneal dialysis (CAPD), the current recommended gentamicin IP dose is 40 mg or 0.6 mg/kg once daily with 6 hours' dwell time [141, 146], although regimens with shorter dwell time should be evaluated in future clinical studies.

Discussion

We aimed to review the clinical pharmacokinetics and consequences for optimal dosing of gentamicin for infections caused by Gram-negative bacteria in various patient populations, focusing on new insights from the past decade. Several new PPK studies have focused on specific subpopulations including obese patients [46], critically ill patients [66, 68, 148], paediatric patients [90, 92, 106, 149], neonates [112, 115–118, 122], elderly patients [126] and patients on IHD [64, 137], providing insights into the typical values of CL and Vd in these patient groups, the variability of these parameters and possible explanations for this variability. But despite inclusion of covariates in many of these PPK models, unexplained IIV in CL and Vd often remained high, especially in critically ill patients, resulting in wide ranges of Cmax, Cmin and AUC. Because of this high variability, it is difficult to give unambiguous advice on optimal dosing, which is also illustrated by the wide range of dosing schemes used in the literature. Moreover, dosing advice from the literature is often based on simulations using PPK models that have not been externally validated and may therefore not be generalisable [3, 57, 89]. In addition, very limited new PPK data have been published in the last 10 years from healthy volunteers or the general adult patient population, which is quite remarkable since the general adult population may be the largest population in which gentamicin is used.

As described earlier, the PK/PD targets used in the literature vary widely and definitive clinical evidence on the optimal PK/PD target for gentamicin is still lacking, despite 50 years of clinical use. Both Cmax/MIC and AUC/MIC targets are advocated, and in clinical practice both may be used, since they show high collinearity when using ODD [30, 31]. The starting dose recommendations presented in Table 2 are expected to result in a high PTA after the first administration for both the Cmax/MIC and AUC/MIC targets associated with clinical efficacy.

However, a higher PTA does not automatically result in higher efficacy. Strikingly, a large review from 2017 of PPK studies on aminoglycosides identified no

studies that showed a correlation between estimated or predicted PK/PD target attainment and clinical success [3]. Two more recent studies specifically focusing on ICU patients also failed to find this correlation; both studies also included patients treated with amikacin or tobramycin and used aminoglycosides as part of combination therapy [79, 82]. The failure to identify an association between target attainment and clinical efficacy may be due to the fact that gentamicin is often used as part of short courses of empirical combination therapy and rarely as targeted monotherapy. This complicates clinical evaluation of optimal dosing since co-administered antibiotics may be responsible for clinical success. Furthermore, the location of the infection could be a determinant of the optimal PK/PD target. Moreover, other factors such as severity of illness and comorbid conditions are probably stronger predictors of clinical outcome than PK/PD target attainment, especially in critically ill patients [81]. Consequently, before optimal dosing regimens can be defined, more research is needed on the targets for efficacy in the clinical situations in which gentamicin is currently used, that is, monotherapy for urinary tract infections or as part of combination therapy, with a focus on the validity of the AUC/MIC and Cmax/MIC targets.

Likewise, using a Cmin target to reduce the risk of nephrotoxicity has been under debate for several decades, but the best available evidence suggests that high Cmin levels are indeed a risk factor for nephrotoxicity [33]. Additionally, the usefulness of daily AUC for predicting nephrotoxicity should be further investigated [3, 4].

Several studies have evaluated if patients receiving short empirical courses of gentamicin (mostly 1–2 days, sometimes 3–5 days) are at increased risk of nephrotoxicity, with conflicting results. Two studies found an increased risk of nephrotoxicity: one study in critically ill patients reported an adjusted odds ratio of 1.39 for renal failure in patients receiving empirical gentamicin add-on therapy for a median duration of 2 days compared with patients who did not receive gentamicin [150] and one study in cardiac surgery patients reported an adjusted odds ratio of 1.38 for AKI in patients receiving a single prophylactic dose of gentamicin compared with patients who received non-aminoglycoside prophylaxis [151]. In contrast, three studies in patients with bacteremia [152–154], one in septic patients at the emergency department [155] and one in critically ill patients [83] did not find an increased risk of nephrotoxicity after short empirical courses of gentamicin.

Performing TDM to optimise dosing intervals has been proven effective in reducing nephrotoxicity in non-critically ill patients, whether using only Cmin monitoring, both Cmin and Cmax monitoring or more complex Bayesian models [71]. An RCT has shown that TDM, using Cmax and a random concentration or Cmin measurement after the first administration of gentamicin in a Bayesian model, reduced nephrotoxicity and duration of hospital stay in non-critically ill patients who were treated for >48 hours [156]. In critically ill patients, where increasing the dosing interval is often necessary to reach a Cmin ≤0.5–1 mg/L, the interval recommended by the Hartford nomogram was correct in only 62% of all cases when compared with Bayesian TDM based on a Cmax measurement and a measurement after 6 hours [58]. Although, to the best of our knowledge, there is no evidence that TDM reduces the risk of gentamicin nephrotoxicity in critically ill patients, we consider it prudent to perform TDM for optimisation of the dosing interval in both critically and non-critically ill patients who receive more than one administration of gentamicin.

TDM using Cmax monitoring, with or without the use of Bayesian models, can also be used to increase the PTA in patients who show large variability in Cmax and AUC, particularly in critically ill patients (regardless of whether they are adult, child or neonate) and patients on IHD, as some of these patients are still at risk for underexposure despite a starting dose of 7 mg/kg. However, several studies evaluating TDM have shown an improvement of the PTA but no increase in clinical success [71]. As mentioned earlier, studies evaluating efficacy in critically ill patients have found no significant correlation between PK/PD target attainment and clinical outcome. Moreover, there is often high variability in Vd within the same patient over time, at least in the critically ill population, limiting the predictive value of one Cmax or AUC estimation for the next [66]. It is therefore unclear if performing TDM for optimisation of Cmax and/or AUC is of clinical value in critically ill patients. But despite a lack of evidence, we think that performing TDM for optimisation of the PK/PD target would be sensible in populations with large variability in Vd and CL.

Meanwhile, there is ongoing debate on the value of gentamicin as part of empirical combination therapy, usually combined with a broad-spectrum β-lactam antibiotic, especially for critically ill patients. Some observational studies found added clinical benefit of gentamicin for specific subpopulations [157–159] while others did not [150,160,161], and meta-analyses have shown conflicting conclusions [162, 163]. An RCT is needed to evaluate the clinical value of gentamicin in empirical combination therapy [164], which is currently being

performed [165]. If used, gentamicin should be dosed once daily and empirical treatment duration should be restricted to 2–5 days [31, 166, 167].

Conclusion

A standard gentamicin starting dose of 7 mg/kg based on TBW (or on ABW in obese patients) appears to be the optimal strategy for increasing the PTA after the first administration in both adults and children older than 1 month, including critically ill patients, although we found no studies that showed a correlation between PK/PD target attainment and clinical success. Higher starting doses may further increase the PTA but evidence for improved clinical efficacy is lacking while the risk of nephrotoxicity is likely to increase. To reduce the risk of nephrotoxicity, the optimal dosing interval for each patient should be established using TDM, targeting a Cmin of at least <2 mg/L but preferably <0.5–1 mg/L. TDM to optimise the probability of PK/PD target attainment is advised for patients with highly variable pharmacokinetics, including patients from all subpopulations that are critically ill (such as elderly, children and neonates) and patients on IHD. Despite numerous recent PPK studies in specific subpopulations, the optimal PK/PD target for efficacy is still unclear for the clinical setting in which gentamicin is currently mostly used, that is, as part of short-term empirical combination therapy.

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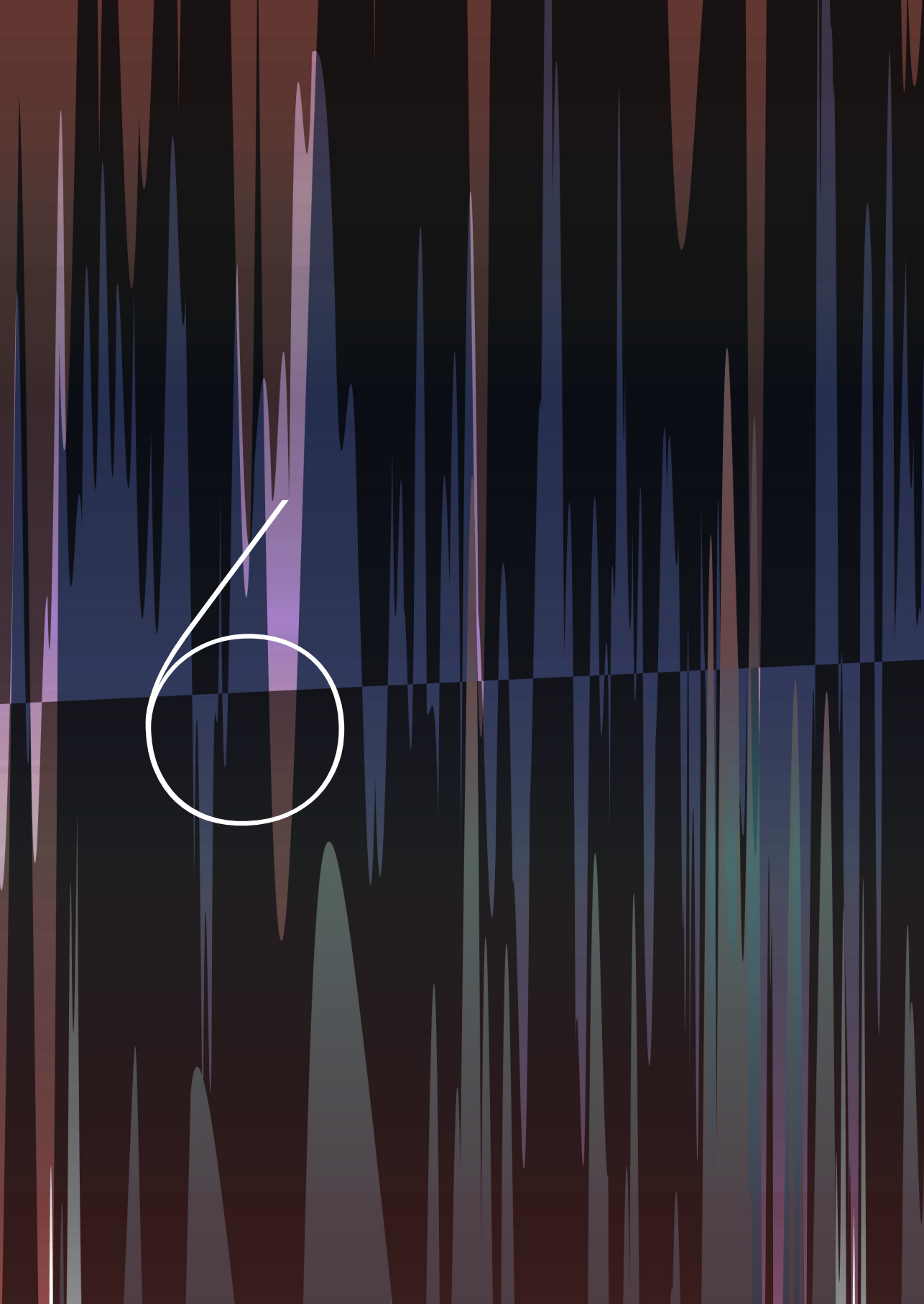

Impact of a vancomycin loading dose on the achievement of target vancomycin exposure in the first 24 h and on the accompanying risk of nephrotoxicity in critically ill patients

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J Antimicrob Chemother. 2021;76(11):2941-2949. DOI: 10.1093/jac/dkab278.

Abstract

Background: The advocated pharmacokinetic/pharmacodynamic (PK/PD) target for vancomycin, AUC/MIC ≥400 mg*h/L, may not be reached with a conventional fixed starting dose of 1000 mg in critically ill patients, but increasing the dose may cause nephrotoxicity.

Objectives: To evaluate the effect of a weight-based loading dose of 25 mg/kg vancomycin on PK/PD target attainment in the first 24 h (AUC_{0-24}) in critically ill patients and to evaluate whether this increases the risk of acute kidney injury (AKI).

Patients and methods: A prospective observational before/after study was performed in ICU patients, comparing the percentage of vancomycin courses with AUC_{0-24} ≥400 mg*h/L and the incidence of AKI, defined as worsening of the risk, injury, failure, loss of kidney function and end-stage kidney disease (RIFLE) score. The conventional dose group received 1000 mg of vancomycin as initial dose; the loading dose group received a weight-based loading dose of 25 mg/kg. A population PK model developed using non-linear mixed-effects modelling was used to estimate AUC_{0-24} in all patients.

Results: One hundred and four courses from 82 patients were included. With a loading dose, the percentage of courses achieving AUC_{0-24} ≥400 mg*h/L increased significantly from 53.8% to 88.0% (P = 0.0006). The percentage of patients with new-onset AKI was not significantly higher when receiving a 25 mg/kg loading dose (28.6% versus 37.8%; P = 0.48). However, the risk of AKI was significantly higher in patients achieving AUC_{0-24} >400 mg*h/L compared with patients achieving AUC <400 mg*h/L (39.0% versus 14.8%; P = 0.031).

Conclusions: A weight-based loading dose of 25 mg/kg vancomycin led to significantly more patients achieving AUC_{0-24} ≥400 mg*h/L without increased risk of AKI. However, some harm cannot be ruled out since higher exposure was associated with increased risk of AKI.

Introduction

Vancomycin is a glycopeptide antibiotic used in the treatment of infections caused by Gram-positive bacteria, including MRSA, methicillin-resistant CoNS and *Enterococcus faecium* [1], which occur in particular in the critically ill.

In patients treated with vancomycin for MRSA bloodstream infections, achievement of an adequate AUC/MIC ratio in the first 24 h is associated with a significant decrease in treatment failure and 30 day mortality [2]. Recently revised guidelines on vancomycin dosing are aimed at achieving an AUC/MIC between 400 and 600 mg*h/L for MRSA infections [3]. There is some evidence that the same target could be used for enterococcal infections [4]. Critically ill patients are at risk of undertreatment in the first 24 h, because of an increased volume of distribution and augmented renal clearance [5]. In the Netherlands, the conventional vancomycin starting dose is 1000 mg [6], which was also used at the ICU at our hospital, followed by therapeutic drug monitoring (TDM) within the first 48 h. However, guidelines suggest using a vancomycin loading dose of 25–35 mg/kg (based on total body weight) in critically ill patients, since this has been found to decrease the risk of subtherapeutic serum concentrations in the first 24–72 h [3, 7–12]. But increasing the dosage can come at a price, since daily AUC values >600–800 mg*h/L are associated with increased risk of vancomycin-associated nephrotoxicity [13].

The aims of this study were to evaluate the effect of the introduction of a weight-based loading dose of 25 mg/kg on vancomycin AUC target attainment in the first 24 h (AUC_{0-24}) in critically ill patients and to evaluate whether this loading dose significantly increased the risk and/or severity of new-onset nephrotoxicity or contributed to prolonged duration of acute kidney injury (AKI) or mortality during ICU stay.

Patients and methods

Patients and data

A prospective observational before/after study was performed in all adult patients in whom treatment with vancomycin was started at the ICU of Amsterdam UMC, location Academic Medical Center, between December 2013 and April 2014 and between October 2014 and December 2014 and from whom blood samples were available. Patients were eligible for multiple inclusions, but only if at least 72 h existed between the last dose of the first treatment course

and the first dose of the second course. The Human Research Ethics Committee of the Amsterdam UMC had taken notice of the study protocol and decided that no ethical approval was required, given that anonymous data from routine diagnostic databases were used.

A new vancomycin loading dose protocol was initiated in January 2014. Included treatment courses were divided into three groups (Figure 1). Courses included in the study before introduction of the loading dose started with a fixed first vancomycin dose of 1000 mg (December 2013 to January 2014). These patients were included in the conventional dose (CD) group. After introduction, patients received a weight-based loading dose of 25 mg/kg with a maximum of 2500 mg (after January 2014). These courses were included in the loading dose (LD) group. However, some patients were accidentally not given a loading dose but a fixed first vancomycin dose despite the introduction of a new protocol (so following the old protocol). These courses were considered to be in the CD group. The third group consisted of courses that accidentally received a loading dose <25 mg/kg or >25 mg/kg.

After the first dose, patients were treated with 1000 mg vancomycin twice a day followed by TDM. A trough serum concentration was measured within 48 h, or before the first maintenance dose in patients with impaired renal function (estimated glomerular filtration rate <60 mL/min).

Blood samples were collected both routinely for TDM and from waste material used for blood gas analyses. The exact time of vancomycin administration and of sample collection was recorded. Samples were collected from an arterial catheter and stored at room temperature for a maximum of 3 days, until samples were processed [14]. The samples were centrifuged (2750 g for 10 min at 20° C) and plasma was frozen at -80° C until samples were analysed. The blood sample collection and processing was standardised in accordance with the quality standards of the Dutch accreditation body CCKL (which transferred to ISO 15189 in 2019). Vancomycin plasma concentrations were measured by auto-immunoassay using COBAS INTEGRA 400 plus (Roche Diagnostics, Basel, Switzerland) [15]. The limit of quantification was 0.74 mg/L and the assay showed linearity from 3 to 80 mg/L.

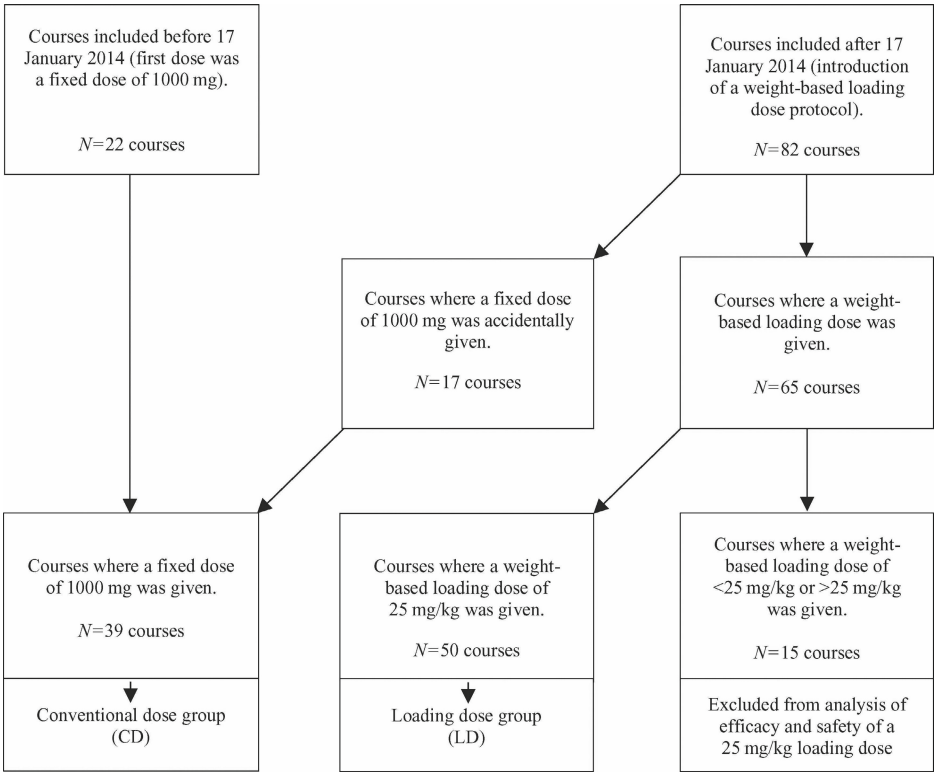

Fig. 1
Group allocations.

The following patient-related parameters were collected from the electronic patient data monitoring system or calculated from these parameters: age, sex, height and total bodyweight (TBW). At the start of therapy, baseline serum creatinine (SCr), the presence of severe neutropenia (defined as an absolute neutrophil count <0.5 * 10^9 cells/L) and severity of disease as assessed by the APACHE II score were noted [16]. During therapy, daily SCr and daily diuresis were noted. CLCR was calculated using the Cockcroft and Gault formula (CRGT) [17]. Patients with continuous venovenous hemofiltration (CVVH), were noted on/off for each event. The use of other nephrotoxic medication [aminoglycosides, piperacillin/tazobactam, trimethoprim/sulfamethoxazole, (val)aciclovir, (val)ganciclovir, liposomal amphotericin B, voriconazole, angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors] was noted. Additionally, the source of infection, use of concomitant antibiotics and the pathogens that were isolated, including their antimicrobial susceptibility testing results, were collected.

The outcome of first interest was the percentage of vancomycin courses with AUC ≥400 mg*h/L in the first 24 h of therapy (assuming MIC = 1 mg/L). Other endpoints of interest were incidence of new-onset AKI during treatment with vancomycin, duration of AKI during ICU stay, maximum risk, injury, failure, loss of kidney function and end-stage kidney disease (RIFLE) score during ICU stay, use of CVVH at ICU discharge, AKI at ICU discharge and mortality during ICU stay.

Pharmacokinetic (PK) analysis
Vancomycin concentration–time data were analysed using non-linear mixed-effects modeling (NONMEM 7.3; Icon Development Solutions, Ellicott City, MD, USA) [18]. Pirana 2.9.4 (Pirana Software & Consulting BV, The Netherlands) was used as the modelling environment [19].

Firstly, a population PK model of vancomycin in critically ill patients was developed. The first-order conditional estimate method with interaction (FOCE + I) was used. One-, two- and three-compartment PK models were fitted on log-transformed data. Additive, proportional and combined error models were tested to describe the residual variability. Interindividual variability (IIV) and interoccasion variability (IOV) were separately tested for all PK parameters, with each new dose being defined as a new occasion. PK parameters were normalised by allometric scaling [20].

In the population model, several measures for renal function (CRGT, RIFLE score, RIFLE score based only on SCr), the use of CVVH, age and sex were tested as covariates, explaining interpatient variability. These covariates were added in a stepwise manner to evaluate whether addition led to a statistically significant improvement of the model (forward inclusion). An intermediate covariate model with all statistically significant covariates was constructed, after which a backward elimination procedure was performed. Covariate data were considered missing if they were not available from the day that the sample was drawn for vancomycin concentration measurement. Concentration–time data from patients for whom covariate data were missing were ignored in estimating the correlation between the PK parameter and the covariate, as described earlier [21].

A decrease in the objective function value (OFV) of ≥3.84, corresponding to $P < 0.05$ in a χ^2 distribution with one degree of freedom, was considered a statistically significant improvement of the model. For the backward elimination procedure, covariates were only retained in the final model if elimination of the covariate led to a rise in OFV of ≥10.8, corresponding to $P < 0.001$. Additionally,

the precision of PK parameter estimation and goodness-of-fit plots were evaluated. Goodness-of-fit plots were generated using Xpose 4.5.3 (Uppsala, Sweden) [22] and R 3.4.1.

A bootstrap analysis with replacement (1000 samples) was used for determination of 95% CI of the parameters. Prediction-corrected visual predictive checks (VPCs) were performed to assess the predictive performance of the final model by simulating 1000 patients. VPCs and bootstrap analyses were performed using Perl-speaks-NONMEM 4.6.0 [23].

Assessment of vancomycin AUC_{0-24}

The AUC_{0-24} was estimated in all courses using the empirical Bayes parameter estimates from the final population PK model.

Analysis of other endpoints

New-onset AKI was defined as worsening of the RIFLE score during a course with vancomycin, or achieving a RIFLE score of ≥1 during a course with vancomycin if patients did not meet the criteria for a RIFLE score at the start of vancomycin therapy [24]. A 50% increase of SCr from baseline or urinary output <0.5 mL/kg/h during >6 h were classified as RIFLE score 1, a 100% increase of SCr or urinary output <0.5 mL/kg/h during >12 h were classified as RIFLE score 2 and a 200% increase of SCr or urinary output <0.3 mL/kg/h during >24 h or a SCr ≥350 μmol/L in the setting of an acute rise of SCr ≥44 μmol/L were classified as RIFLE score 3. Patients starting CVVH were also considered to have RIFLE score 3.

Duration of AKI was defined as the number of hours between the first laboratory result showing ≥50% increase of SCr from baseline and the first laboratory result showing return of SCr below 1.5% baseline. If AKI was still present at ICU discharge or death, patients were excluded from analysis of duration of AKI. For patients on CVVH or other renal replacement therapy (RRT), return of SCr below 1.5% baseline was not considered to end the duration of AKI. If patients recovered from AKI but subsequently developed a second episode of AKI (during the same ICU admission or during a second ICU admission), this was considered a separate event.

In addition to the analysis of new-onset AKI during vancomycin treatment (using the maximum RIFLE score during the vancomycin course), the same analysis was performed using the maximum RIFLE score during the complete ICU stay, including both the period during vancomycin treatment and the period after vancomycin treatment had been ended.

Statistical analysis

Descriptive statistics were used to present the data. Data were presented as mean ± SD, unless stated otherwise. Unpaired t-test (for normally distributed continuous variables in two groups), Mann–Whitney U-test (for non-normally distributed continuous variables in two groups), Fisher's exact test (for binary categorical variables in two groups) and χ^2 test (for nominal categorical variables in two groups) were used to evaluate differences in baseline characteristics of patients without versus with loading dose. Unpaired t-test, χ^2 test, Fisher's exact test and one-way ANOVA test (for normally distributed continuous variables in more than two groups) were used to evaluate differences between treatment groups in endpoints. A P-value of <0.05 was considered to be statistically significant.

Results

A total of 104 vancomycin courses from 82 patients receiving a total of 544 doses of vancomycin (median 4 doses per course, IQR 2–8) were included, yielding 609 vancomycin concentrations (median 4.5 concentrations per course, IQR 2–8), of which 178 were taken in the first 24 h (median 2 concentrations per course, IQR 1–3).

Baseline characteristics are reported in Table 1 and group allocations are illustrated in Figure 1. The CD group consisted of 39 courses of 35 patients; the LD group, receiving a loading dose of 25 mg/kg with a maximum of 2500 mg, consisted of 50 courses of 45 patients. Two patients had courses in all three treatment groups, 9 patients had courses in two of the three treatment groups and 71 patients had one or more courses in only one of the treatment groups. There were 15 courses of 15 patients where a loading dose of <25 mg/kg (N = 12) or >25 mg/kg (N = 3) was accidently given. PK data from all three groups were included in the population PK analysis and for the analysis of the association between AUC_{0-24} and the incidence of AKI. Data from the CD and LD groups were used for the analysis of the effect of a loading dose on vancomycin AUC target attainment.

The median vancomycin starting dose was 25.0 mg/kg (IQR 23.2–25.3) in the LD group versus 13.3 mg/kg (IQR 11.8–15.9) in the CD group (P <0.0001). There were no statistically significant differences between groups in baseline characteristics, including renal function at the start of vancomycin therapy (see Table 1).

Table 1

Baseline characteristics

	All episodes included for model building (N = 104)	Episodes without loading dose (CD group) (N = 39)	Episodes with loading dose 25mg/kg (LD group) (N = 50)	P-value
Male (%)	56.7	66.7	50.0	0.13
Age (years)	58.8 ± 14.0	60.1 ± 14.8	59.4 ± 13.0	0.82
Height (cm)	172.3 ± 12.0	172.1 ± 12.6	172.2 ± 12.0	0.96
TBW (kg)	76.2 ± 16.6	73.8 ± 13.4	78.1 ± 19.4	0.60
Obesity (BMI >30 kg/m^2) (%)	10.6	7.7	14.0	0.50
Starting dose (mg)	1477 ± 538	1000 ± 0	1889 ± 398	<0.0001
Starting dose (mg/kg)	19.8 ± 6.1	14.0 ± 2.8	24.4 ± 1.8	<0.0001
Treatment duration (h)	89.8 ± 58.5	86.6 ± 51.1	92.3 ± 64.5	0.89
Cumulative AUC (mg*h/L)	1937 ± 1448	1849 ± 1359	2027 ± 1543	0.60
APACHE II score	18.7 ± 7.0	19.0 ± 7.3	19.5 ± 6.7	0.70
Severe neutropenia (%)	6.7	2.6	10.0	0.22
SCr at study entry (µmol/L)	138 ± 120	167 ± 163	132 ± 80	0.78
CLCR at study entry (mL/min)	87.6 ± 65.7	80.0 ± 62.4	81.0 ± 60.4	0.81
Median number (range) of nephrotoxic drugs concomitantly administered	0 (0-3)	0 (0-2)	0 (0-3)	0.10
Courses with concomitant administration of nephrotoxic drugs (%)	50.0	43.6	58.0	0.20
Courses with concomitant administration of gentamicin (%)	35.6	35.9	42.0	0.66
CVVH at any time during vancomycin treatment (%)	33.7	35.9	36.0	>0.99

Reported as mean ± SD, unless stated otherwise. Patients with more than one course are included multiple times. P-value reflects differences between all episodes without versus with 25 mg/kg loading dose. P-value was calculated using unpaired t-test for age, height and APACHE II score, using Fisher's exact test for sex, obesity (yes/no), severe neutropenia (absolute neutrophil count <0.5 * 10^9 cells/L) (yes/no), percentage of courses with concomitant administration of nephrotoxic drugs (and specifically gentamicin) and CVVH (yes/no), using Mann–Whitney U-test for TBW, starting dose (mg), starting dose (mg/kg), SCr at study entry, CLCR at study entry, treatment duration and cumulative AUC and using χ^2 test for the number of concomitant nephrotoxic drugs, including aminoglycosides, piperacillin/tazobactam, trimethoprim/sulfamethoxazole, (val)aciclovir, (val)ganciclovir, liposomal amphotericin B, voriconazole, angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors. Nephrotoxic drugs that were given as co-medication in at least 5% of all courses were also included separately in the table.

Only six courses consisted of vancomycin monotherapy. Most patients were treated with a combination of antibiotics (on average 2.8 antibiotics including vancomycin), where vancomycin was added to also empirically treat infections with CoNS, enterococci and sporadically MRSA (in the Netherlands, approximately 99% of Staphylococcus aureus isolates are MSSA, so patients suspected of *S. aureus* infection are only treated with vancomycin if they have risk factors for MRSA carriage).

The sources of infection in the 104 courses were predominantly abdominal infection and catheter-related bloodstream infection (43 and 27 courses, respectively, of which 3 cases had both). Other sources were meningitis (17 courses), neutropenic sepsis (5 courses), sepsis of unknown origin (5 courses), severe skin and soft tissue infections (4 courses), post-operative mediastinitis after cardiac surgery (4 courses) and prosthetic vascular graft infection (2 courses)

In 41 of 104 courses, a pathogen was cultured that was treated with vancomycin either empirically or as directed therapy and was not covered with any other antibiotics that the patient received. In 6 of these courses, two pathogens were isolated; the remaining 35 showed one pathogen. There were 22 blood culture isolates: 8 enterococci (4 *E. faecium*, 3 *Enterococcus faecalis*, 1 *Enterococcus gallinarum*) and 14 staphylococci [8 *Staphylococcus epidermidis*, 3 *Staphylococcus hominis*, 2 *S. aureus* (MSSA) and 1 *Staphylococcus capitis*]. Additionally, there were 25 isolates from other, normally sterile body sites that were deemed clinically relevant: 15 enterococci (12 *E. faecium*, 3 *E. faecalis*), 9 staphylococci (7 *S. epidermidis*, 1 *S. aureus*, 1 *Staphylococcus haemolyticus*) and 1 *Rothia mucilaginosa* isolate from CSF samples of a neutropenic patient with meningitis. No cases of MRSA or VRE infection were found.

Model

The data were best described with a two-compartment model with first-order elimination. IIV for CL, V1 and V2 and estimation of IOV for V1 could be estimated. An additional error model best described the residual variability. Allometric scaling of all PK parameters to 70 kg TBW significantly improved the fit of the model to the data (OFV decrease of 95 units). Furthermore, renal function (both RIFLE score and CRGT) was statistically significantly associated with vancomycin clearance, since addition of RIFLE score or CRGT as a covariate for vancomycin clearance led to a significant improvement in fit of the model to the data. CRGT (OFV decrease of 92 units; $P < 0.001$) performed statistically better than the RIFLE score (OFV decrease of 16 units; $P < 0.001$). The addition of age, sex and the use of CVVH as covariates did not improve the model.

Parameter estimates are reported in Table 2 and goodness-of-fit plots in Figure 2. Of the 609 concentration–time data, 15 (2.5%) had missing data for CLCR, but this had no effect on parameter estimates, given that the correction parameter when CRGT is missing was 0.99, so very close to 1. VPC of the final model showed that the model could adequately predict the vancomycin concentrations in the first 24 h, although there was a slight underestimation of vancomycin concentrations at the end of the dosing interval (Figure 3).

Table 2

Parameter estimates

Parameter	Final model			Bootstrap of final model	
	Estimate	RSE (%)	Shrinkage (%)	Median	95% CI
CL (L/h)[a]	1.86	6		1.83	1.65 – 2.08
V1 (L)[b]	13.4	14		13.1	9.6 – 21.9
Q (L/h)[c]	7.57	7		7.56	5.78 – 10.03
V2 (L)[d]	36.9	7		35.7	30.5 – 42.7
IIV					
CL (CV%)[e]	49.2	12	14	50.8	40.0 – 59.0
V1 (CV%)[e]	128.9	13	23	135.7	75.5 – 192.0
V2 (CV%)[e]	68.3	11	24	68.2	43.2 – 86.8
IOV					
V1 (CV%)[e]	58.2	17	64	58.1	42.6 – 77.2
Residual variability					
Additive error	0.209	2		0.207	0.166 – 0.256
Covariate effects					
CRGT on CL	0.65	8		0.63	0.46 – 0.84
Correction parameter when CRGT is missing	0.99	33		0.98	0.62 – 1.28

RSE = relative standard error, CL = vancomycin clearance, V1 = vancomycin central volume of distribution, Q = vancomycin intercompartmental clearance, V2 = vancomycin peripheral volume of distribution.

[a]$CL = 1.86 * (TBW/70)^{0.75} * (CRGT/83)^{0.65*FLG} * 0.99^{(1-FLG)} * e^{\eta IIVCL}$, where FLG=1 when CRGT data are available and 0 when CRGT data are missing and where ηIIVCL represents the random-effect parameter for IIV in CL.

[b]$V1 = 13.4 * (TBW/70) * e^{\eta IIVV1 + \eta IOVV1}$, where ηIIVV1 represents the random-effect parameter for IIV in V1 and ηIOVV1 represents the random-effect parameters for IOV in V1.

[c]$Q = 7.57 * (TBW/70)^{0.75}$.

[d]$V2 = 36.9 * (TBW/70) * e^{\eta IIVV2}$ where ηIIVV2 represents the random-effect parameter for IIV in V2.

[e]CV% calculated as the square root of $(e^{\omega}-1) * 100\%$.

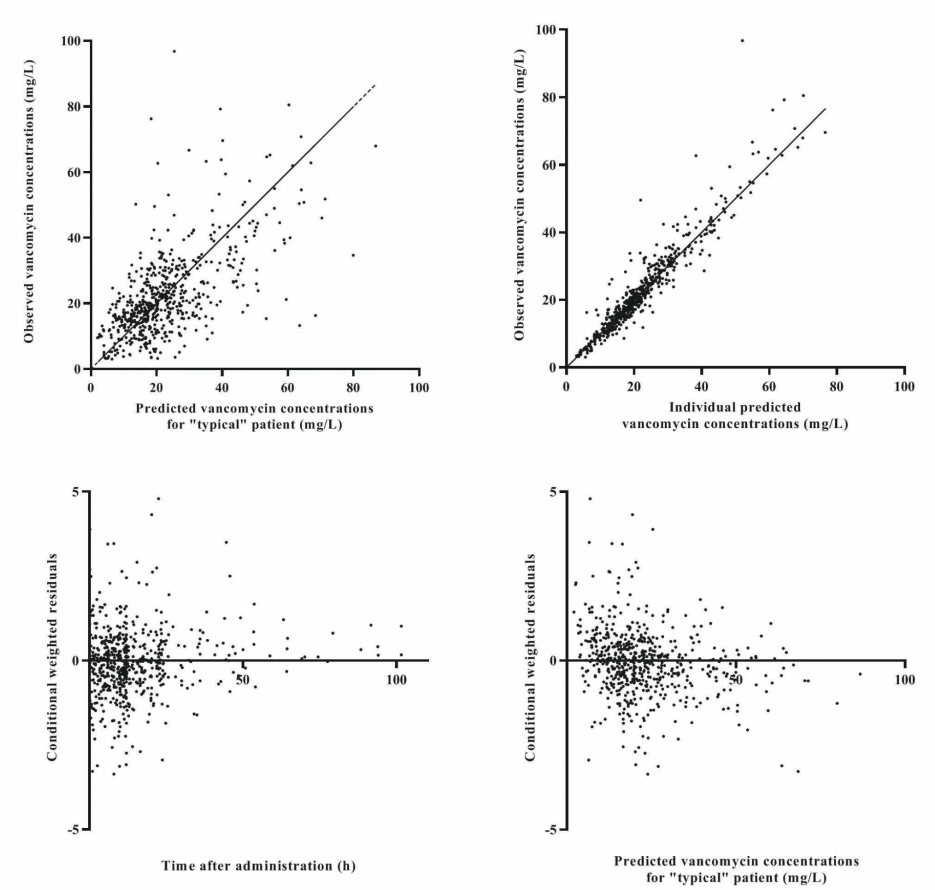

Fig. 2
Goodness-of-fit plots of the final population PK model.

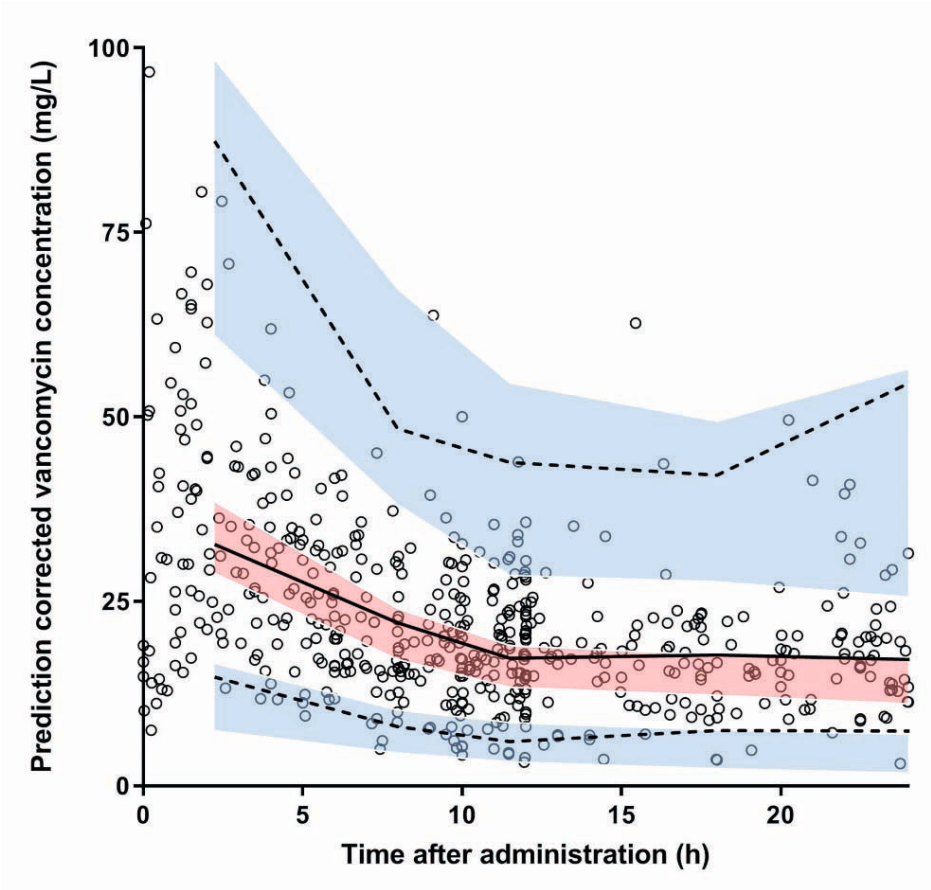

Fig. 3
Prediction-corrected VPC of the first 24 h using the final model. The circles represent the observed data. The solid line represents the median and the dotted lines represent 5th and 95th percentiles of the observed data. The shaded regions summarise the predicted 95% CIs of the median/percentile in that bin.

The results of the bootstrap of the final model matched the results of the final model well (Table 2).

Analysis of vancomycin $AUC_{0\text{-}24}$

The empirical Bayes estimates resulting from the final population PK model were used to estimate AUC_{0-24} for the individual patients. Use of a loading dose resulted in a higher percentage of courses achieving AUC_{0-24} ≥400 mg*h/L compared with the group receiving standard care (88.0% versus 53.8%; P = 0.0006 using Fisher's exact test). Also, use of a loading dose resulted in a median AUC_{0-24} of 602 mg*h/L (range 306–1212), which was higher than in the

group receiving standard care [401 mg*h/L (range 200–683); P <0.0001 using Mann–Whitney U-test] (see Figure 4).

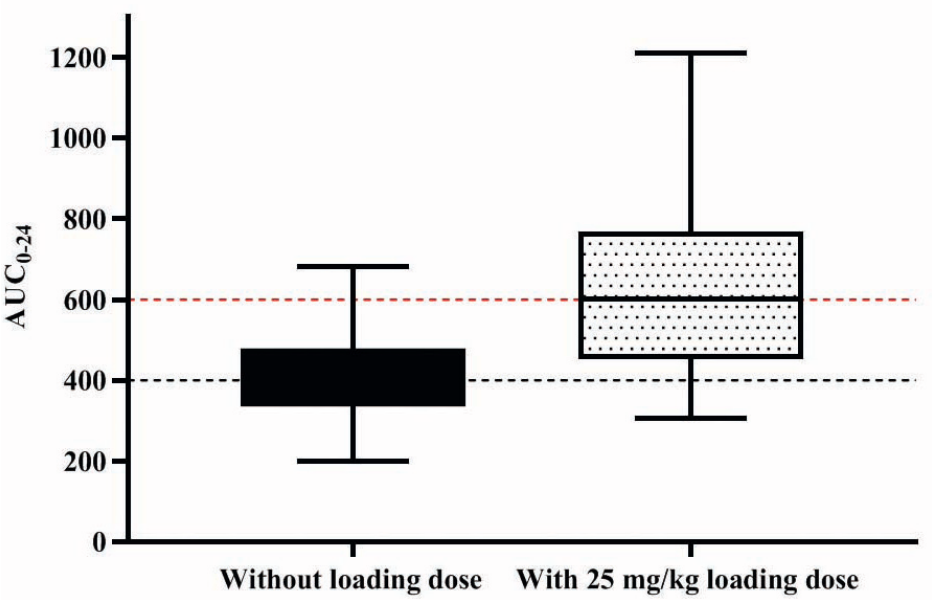

Fig. 4
AUC_{0-24} without (N = 39) versus with (N = 50) 25 mg/kg loading dose. Whiskers represent minimum to maximum AUC_{0-24}. The dotted lines represent the lower and upper boundaries of the therapeutic window.

Analysis of new-onset AKI

Although the percentage of patients with new-onset AKI was numerically higher in the group of patients who received a loading dose, this difference was not statistically significant [10/35 (28.6%) in the CD group versus 17/45 (37.8%) in the LD group; P = 0.48 using Fisher's exact test]. However, when analysing the association between AUC_{0-24} and new-onset AKI, achieving an AUC_{0-24} ≥400 mg*h/L was associated with a significantly higher incidence of new-onset AKI: 30/77 (39.0%) versus 4/27 (14.8%) compared with patients with an AUC_{0-24} <400 mg*h/L (P = 0.031 using Fisher's exact test), resulting in a relative risk of 2.6 (95% CI 1.02–6.78; number needed to harm = 4.1). The same was true for achieving an AUC_{0-24} ≥600 mg*h/L, which is the upper limit of the therapeutic window: 17/35 (48.6%) versus 17/69 (24.6%); P = 0.017 using Fisher's exact test.

Analysis of other endpoints

There was no statistically significant difference in mean AKI duration (75.2 h in the CD group versus 37.2 h in the LD group; P = 0.71 using Mann–Whitney U-test), in percentage of patients with AKI using the maximum RIFLE score during the complete ICU stay (59.4% in the CD group versus 57.5% in the LD group; P >0.99 using Fisher's exact test), in percentage of patients still on CVVH or other RRT at ICU discharge (21.2% in the CD group versus 31.7% in the LD group; P = 0.43 using Fisher's exact test), in percentage of patients with AKI at ICU discharge (30.3% in the CD group versus 34.1% in the LD group; P = 0.81 using Fisher's exact test) or in mortality during ICU stay (33.3% in the CD group versus 26.8% in the LD group; P = 0.61 using Fisher's exact test).

Discussion

We evaluated the effect of a loading dose on vancomycin PK/pharmacodynamics (PK/PD) target attainment in the first 24 h in critically ill patients admitted to the ICU, where AUC_{0-24} for calculation of PK/PD target attainment was estimated using a NONMEM population PK model, which was developed specifically for the purpose of this study. Our results show improved target attainment in the first 24 h of vancomycin treatment when a weight-based loading dose was used, confirming the results of previous studies [7–12]. To the best of our knowledge, our study is currently the largest study on the effect of a loading dose on vancomycin AUC target attainment, including approximately twice the number of patients and four times the number of samples than in other studies [11, 12]. Most previous studies on the effect of a loading dose used vancomycin trough concentrations as target [7–10]. However, trough concentrations underestimate the AUC_{0-24} [25] and AUC-guided vancomycin dosing has been shown to decrease nephrotoxicity without reducing efficacy [26, 27]. Therefore the recently updated IDSA/ASHP guideline does not recommend target trough concentrations, but AUC_{0-24} [3]. Two smaller studies including 41 patients (of which 23 were treated with a loading dose) and 45 patients (of which 8 were treated with a loading dose) showed a significant increase in AUC_{0-24}/MIC target attainment when using a loading dose [11, 12]. Both studies used predominantly trough levels and an external population PK model for maximum a posteriori Bayesian estimation of AUC_{0-24}. However, they did not report whether this model was valid for their investigated population. We used Bayesian analysis based on a population PK model that was specifically developed for the purpose of this study (leading to more reliable estimation of AUC_{0-24}) and was based on vancomycin concentrations covering the whole dosing interval (Figure 3) [3].

We also evaluated the impact of a vancomycin loading dose on the incidence of nephrotoxicity. No statistically significant difference in incidence of AKI was found between the patient groups with and without a loading dose, nor in mean AKI duration or in other clinically relevant outcomes like mortality during ICU stay. This is in concordance with other studies. A systematic review and meta-analysis of nine studies including 2816 patients found a significantly higher rate of vancomycin trough concentrations of 15–20 mg/L after a loading dose, without an increased risk of nephrotoxicity or other adverse effects [28]. A multicentre, retrospective, cohort study including 316 patients with MRSA bacteraemia found that receipt of vancomycin loading doses >1750 mg was protective against treatment failure, without increasing nephrotoxicity [29]. Of note though, the risk of AKI was significantly higher in patients who achieved an AUC_{0-24} >400 mg*h/L compared with patients who achieved an AUC <400 mg*h/L and in patients who achieved an AUC_{0-24} >600 mg*h/L compared with patients who achieved an AUC <600 mg*h/L. These findings do suggest a positive association between vancomycin exposure and risk of new-onset AKI and therefore an increased risk of nephrotoxicity for each increase in AUC. This was also found in earlier observational studies [30, 31]. Both studies showed an incidence of nephrotoxicity comparable to the current study (39% in patients with vancomycin AUC >400 mg*h/L versus 14.8% in patients with AUC <400 mg*h/L). So while it is clear that higher vancomycin exposure is associated with an increased risk of AKI, it is uncertain whether use of a loading dose poses an additional risk. The additional risk may be limited if the loading dose does not lead to an AUC_{0-24} >600 mg*h/L [13]. However, in our study, 26/50 (52%) of courses with a loading dose led to an AUC_{0-24} >600 mg*h/L (Figure 4). Using TDM to measure the AUC_{0-24} within 48 h after start of vancomycin therapy (within 24 h when renal function is impaired) is therefore essential to identify patients with an AUC_{0-24} >600 mg*h/L and to adjust the maintenance dose accordingly.

Our study shows some limitations. Firstly, CLCR was calculated using CRGT, since more accurate ways were not available. CRGT is known to overestimate the clearance in patients with AKI [32]. Indeed, our model underestimated the vancomycin concentrations at the end of the dosing interval, which is also reflected in the VPC (Figure 3). However, the model described the observed data reasonably well for the first 24 h, which was relevant for calculating AUC_{0-24}. Moreover, CRGT performed statistically better than the RIFLE score, which was also tested as a covariate for vancomycin clearance, leading to a larger decrease in OFV and better goodness-of-fit plots. Since addition of CLCR using CRGT led to a better model fit and hence to better AUC_{0-24} estimations, it was included in

the final model. Secondly, for a profound analysis of the association between vancomycin AUC_{0-24} and new-onset AKI, a multivariate regression analysis would be needed since many comorbidities, co-administered drugs and events during ICU admittance can have a significant impact on the renal function. Unfortunately, our data were insufficiently complete to reliably perform such an analysis. In addition, our main goal was to evaluate the efficacy and safety of a loading dose by comparing the CD group with the LD group. We did not see significantly more AKI after a loading dose, but there are clues using a limited univariate analysis that a higher AUC_{0-24} could form an increased risk of AKI. Thirdly, we used intermittent vancomycin dosing in both treatment groups, but continuous infusion of vancomycin is also increasingly being used as it may be associated with less nephrotoxicity [33]. Our data cannot be extrapolated to continuous infusion, where loading doses are generally lower. Fourthly, this study was carried out at one centre, so the results may not be applicable to other institutions. Fifthly, the sample size of our study was small, also precluding a reliable analysis of the association between AUC_{0-24} and new-onset AKI, and there were no MRSA patients included, which may have limited the ability to identify significant predictors for mortality.

In conclusion, a weight-based loading dose of 25 mg/kg vancomycin led to significantly more patients achieving AUC_{0-24} ≥400 mg*h/L and did not lead to a significantly increased risk of AKI, but some harm cannot be ruled out since higher exposure was associated with increased risk of AKI.

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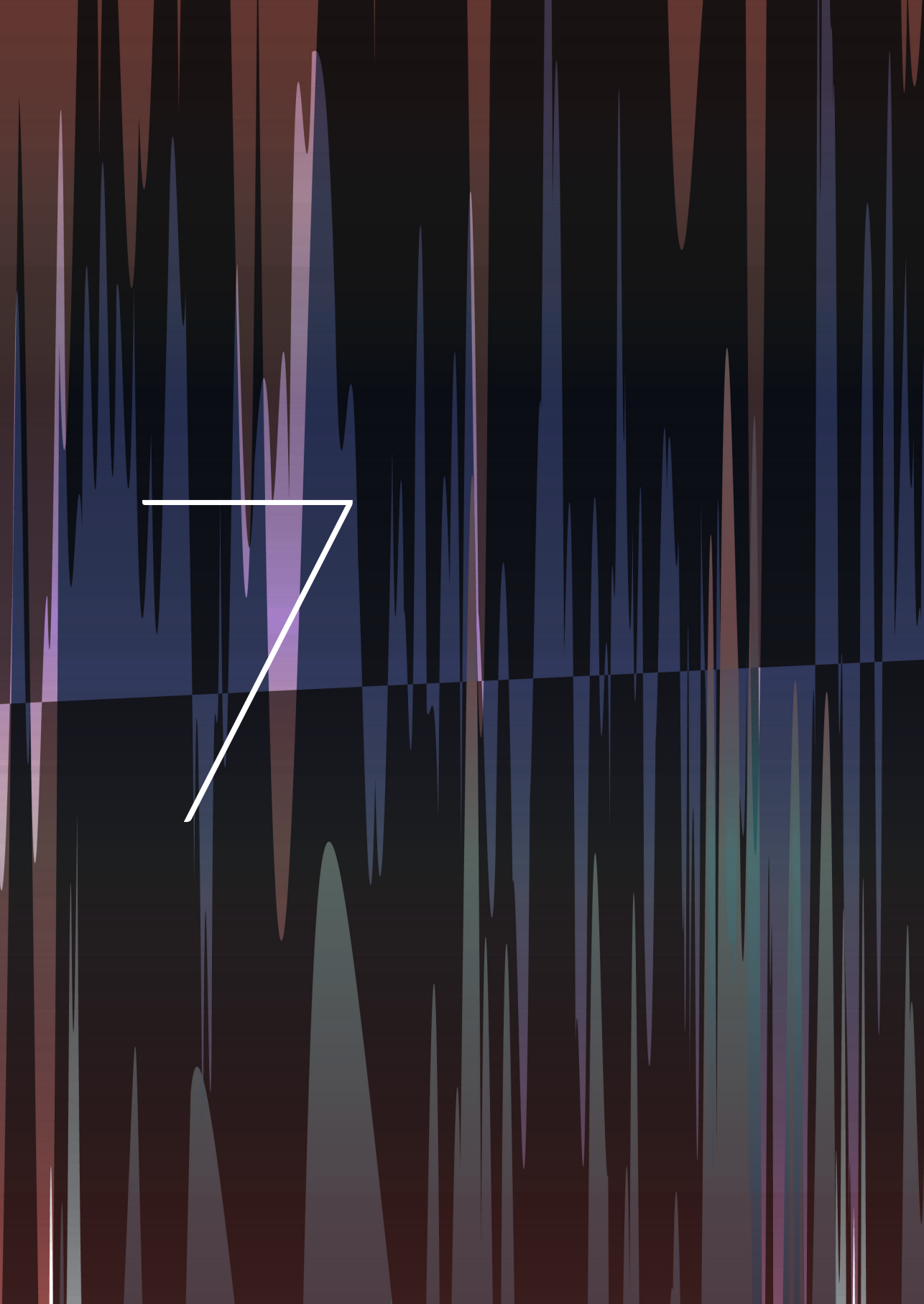

Population pharmacokinetics and probability of target attainment of different dosing regimens of ceftazidime in critically ill patients with a proven or suspected *Pseudomonas aeruginosa* infection

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Antibiotics (Basel). 2021;10(6):612. DOI: 10.3390/antibiotics10060612.

Abstract

Altered pharmacokinetics (PK) of hydrophilic antibiotics in critically ill patients is common, with possible consequences for efficacy and resistance. We aimed to describe ceftazidime population PK in critically ill patients with a proven or suspected *Pseudomonas aeruginosa* infection and to establish optimal dosing. Blood samples were collected for ceftazidime concentration measurement. A population PK model was constructed, and probability of target attainment (PTA) was assessed for targets 100%T>MIC and 100%T>4xMIC in the first 24 h. Ninety-six patients yielded 368 ceftazidime concentrations. In a one-compartment model, variability in ceftazidime clearance (CL) showed association with CVVH. For patients not receiving CVVH, variability in ceftazidime CL was 103.4% and showed positive associations with creatinine clearance and with the comorbidities hematologic malignancy, trauma or head injury, explaining 65.2% of variability. For patients treated for at least 24 h and assuming a worst-case MIC of 8 mg/L, PTA was 77% for 100%T>MIC and 14% for 100%T>4xMIC. Patients receiving loading doses before continuous infusion demonstrated higher PTA than patients who did not (100%T>MIC: 95% (N = 65) vs. 13% (N = 15); P <0.001 and 100%T>4xMIC: 20% vs. 0%; P = 0.058). The considerable IIV in ceftazidime PK in ICU patients could largely be explained by renal function, CVVH use and several comorbidities. Critically ill patients are at risk for underexposure to ceftazidime when empirically aiming for the breakpoint MIC for *P. aeruginosa*. A loading dose is recommended.

Introduction

Ceftazidime, a third-generation cephalosporin, is a first line treatment option for critically ill patients with *Pseudomonas aeruginosa* infections. *P. aeruginosa* infections occur in critically ill patients with a reported 30-day mortality ranging between 20.9% to 49% in previous studies. These infections are typically nosocomial (ventilator associated) pneumonia, (catheter-associated) urinary tract infections or sepsis [1–4].

Early and adequate treatment of sepsis with antimicrobial therapy improves morbidity and mortality outcomes in critically ill patients with an infection [5]. Pharmacokinetics of hydrophilic antibiotics that are renally cleared, such as ceftazidime, are susceptible to variations in renal function, oedema, and to the impact of resuscitation therapy during sepsis, which could lead to alterations in clearance as well as volume of distribution. In addition, the presence of co-morbidity may also influence the pharmacokinetics of these drugs [6]. These pharmacokinetic changes may cause low drug concentrations, with a risk for not achieving the pharmacokinetic/pharmacodynamic (PK/PD) target [7–17]. For ceftazidime, the PK/PD target in critically ill patients is reached when the free (f) drug plasma concentration is maintained above the minimum inhibitory concentration (MIC) for 100% of a dosing interval [8]. There is debate as to whether the PK/PD target should be 100% f T>MIC or whether a higher PK/PD target of 100% f T>4xMIC should be aimed for in critically ill patients [10].

Studies comparing different ceftazidime dosing regimens in large populations are generally lacking. Moreover, existing ceftazidime PK models are based on small study populations and these models mostly do not describe ceftazidime PK in ICU patients [9–21].

In this study, a population pharmacokinetic (POP/PK) analysis of ceftazidime is performed in critically ill patients with a proven or suspected *P. aeruginosa* infection. The objective is to describe the population PK of ceftazidime, quantify variability in PK between patients and to identify factors associated with this variability. Additionally, we aimed to identify the dosing regimen with optimal PK/PD target attainment. Finally, development of antimicrobial resistance was analysed, and exploratory analyses were carried out to test whether PK/PD target attainment could be associated with microbiological and clinical cure.

Results

Patients and ceftazidime concentrations

A total of 394 blood samples were collected from 96 ICU patients. Fifteen percent of these samples were taken within the first 24 h of treatment with ceftazidime and for 46% of patients a sample was drawn within the first 24 h. The median number of samples per patient was 3 (interquartile range: 1–5). The majority of patients (83%) had a continuous intravenous dosing regimen. Only ten percent of patients were treated with an intermittent dosing regimen. The remainder switched between dosing regimens during the first 24 h of treatment. A total of 2.5% of the samples were taken during intermittent infusion. Patient characteristics are presented in Table 1. Twenty-eight (7.1%) of 394 ceftazidime samples contained a concentration below LLQ.

Table 1

Baseline characteristics of critically ill patients at ceftazidime therapy initiation (N = 96).

Characteristic	Median [range]
Female [N (%)]	38 (40%)
Age (years)	59 [20-84]
Body weight (kg)	79 [44-237]
Body mass index (kg/m^2)	25 [16-66]
Ceftazidime dose prescribed in the first 24 hours [N (%)]	
1 g tid	7 (7%)
2 g tis	3 (3%)
<3 g continuous infusion	1 (1%)
3 g continuous infusion	34 (35%)
3-5 g continuous infusion	11 (11%)
5 g continuous infusion	25 (25%)
6 g continuous infusion	9 (9%)
Other	6 (6%)
Loading dose [N (% of patients with continuous infusion)]	65 (81%)
SOFA score at start of ceftazidime therapy (N = 64)[c]	10 [4-16]
30-day mortality [N (%)]	37 (39%)
Primary infection site [N (%)]	
Pneumonia	37 (39%)
Bloodstream	17 (18%)
Abdominal infection	13 (14%)
Meningitis	22 (23%)

Baseline characteristics of critically ill patients at ceftazidime therapy initiation (N = 96). Continued

Characteristic	Median [range]
Other	7 (7%)
Admission Category [N (%)]	
Medical	54 (56%)
Surgical	42 (44%)
Comorbidity [N (%)]	
Hematologic malignancy	14 (15%)
Oncologic malignancy	12 (13%)
Trauma or head injury	27 (28%)
Other	43 (45%)
Vasopression [N (%)]	66 (69%)
Ventilation [N (%)]	74 (77%)
Creatinine (mg/dL)	0.98 [0.19-7.49]
eGFR[a] (mL/min/m^2)	73 [6-153]
CVVH [N (%)][b]	20 (21%)
RIFLE score [N (%)]	
No AKI	62 (65%)
Stage 1	4 (4%)
Stage 2	1 (1%)
Stage 3	29 (30%)
Mean Inhibitory concentration (mg/L) *P. aeruginosa* at start therapy [N (%)]	
1	6 (19%)
2	13 (40%)
4	8 (25%)
8	3 (9%)
16	2 (6%)

[a] The estimated glomerular filtration rate is calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

[b] Patients with application of CVVH during (a part of) their treatment with ceftazidime.

[c] SOFA, Sequential Organ Failure Assessment. The SOFA score could be assessed for only 64 patients because of missing data in, for example, the Glasgow coma scale.

Population pharmacokinetic analysis

The ceftazidime data best fitted a one-compartmental model with first-order elimination (Table 2). The variability between patients, or the interindividual variability (IIV), could be estimated for CL and V. Residual variability was best described by a proportional error model. Introduction of CVVH improved the model fit as evidenced by the drop in objective function of 60.6 points (P <0.001)

and improvement of the goodness-of-fit plots. Further covariate analysis resulted in a model with a positive significant association between ceftazidime CL and CLCKD-EPI and associations between CL and comorbidities, indicating higher CL in the presence of the comorbidities hematologic malignancy and trauma or head injury (factor 1.57 and 1.99, respectively). The comorbidities trauma and head injury were merged into one group, due to having the same underlying mechanism for increasing drug clearance, being the hyperdynamic state with glomerular hyperfiltration. With the inclusion of these associations, the estimate for IIV CL for patients not receiving CVVH, IIV dropped from 103.4% to 36% (Table 2).

Table 2

Parameter estimates of the structural and final model.

	Structural model		Final model		Bootstrap[#]	
	Estimation	**RSE (%)**	**Estimation**	**RSE (%)**	**Estimation**	**95% CI**
CL_{CVVH} (L/h)	2.82	11	2.9	11	2.88	2.18-3.47
$CL_{nonCVVH}$ (L/h)	4.56	9	3.42	9	3.46	2.88-4.04
V (L)	47.6	13	46.8	12	46.7	37.5-59.5
Proportional error	0.288	12	0.281	12	0.277	0.216-0.352
IIV						
$CL_{nonCVVH}$ (CV%)	103.4	11	36.0	14	35.3	24.7-46.8
V (CV%)	84.7	15	102.8	18	100.1	59.8-160.0
Covariate effects						
CKD-EPI	-	-	0.772[a]	11	0.788	0.655-1.022
Comorbidity hematologic malignancy	-	-	1.57	17	1.54	1.07-2.15
Comorbidity trauma and head injury	-	-	1.99	13	1.96	1.51-2.55

Abbreviations: CI = confidence interval, CL = clearance, CV% = variation coefficient in %, IIV = interindividual variability, RSE = relative standard error, V = volume of distribution. The shrinkage was 29% for both IIV on CL and V.

[a] $CL_{nonCVVH}$ = 3.42 * (CKD-EPI individual/median CKD-EPI population)$^{0.772}$ * 1.57(hemat) * 1.99(trauma/head injury), hemat = 1 if comorbidity was hematologic malignancy, zero if otherwise. Trauma/head injury = 1 if comorbidity was trauma or head injury, zero if otherwise.

[#] 98.2% of bootstrap runs were successful. The condition number for the final model was 19.81, indicating that the model was stable.

At four time points of ceftazidime sampling, CKD-EPI data were missing. Because of the small fraction of missing data, the 'last observation carried forward' principle was applied to handle these data. There were no missing data

for the other covariates, comorbidities and CVVH. The associations between the covariates and CL are shown in Figure 1.

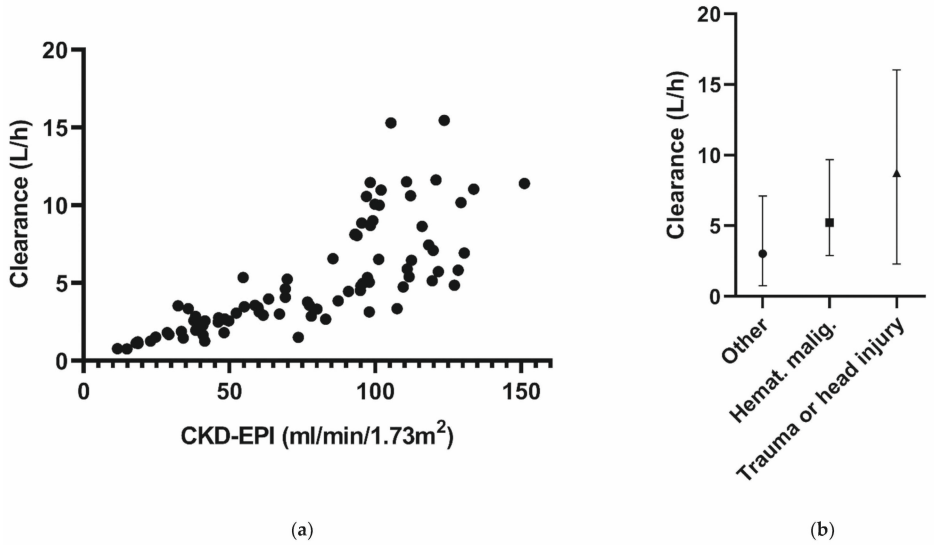

Fig. 1
Ceftazidime clearance in relation to (a) CKD-EPI and (b) the different comorbidities in the final model.

The final model had an adequate fit, as shown by the VPCs stratified for CVVH and non CVVH (Figure 2). Goodness-of-fit plots and the NONMEM control stream of the final model are shown in appendices B and C, respectively.

PK/PD target attainment

For the assessment of PK/PD target attainment, 32 MIC values of isolated *P. aeruginosa* bacteria were available for 31 patients during 32 ICU stays. The distributions of the measured MICs are shown in Appendix A. All patients achieved the PK/PD target attainment for 100%T>MIC within the first 24 h. Of these patients, 66% (21/32) also achieved the higher target of 100%T>4xMIC.

Patients receiving loading doses before continuous infusion demonstrated higher target attainment rates in the first 24 h of treatment compared to patients not receiving a loading dose for the higher target (100%T>4xMIC: 72% (N = 25) vs. 0% (N = 4); P = 0.006).

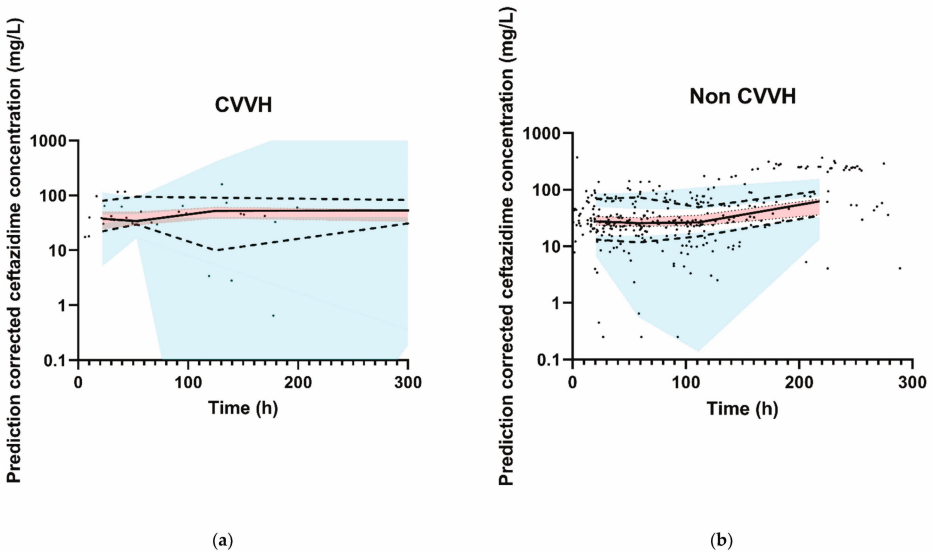

Fig. 2
Observed ceftazidime concentration–time data and prediction-corrected VPC of the final model. The black dots represent the observed ceftazidime concentrations. The thick red line is the observed median, and the small blue lines are the 5th and 95th percentiles of the observed data. The red shaded area represents 95% CI of the model-predicted median and the blue-shaded areas are the 95% CIs of the model-predicted 5th and 95th percentiles. (a) CVVH patients, and (b) non-CVVH patients. For the X-axis, the VPC was zoomed in on the first 300 h in order to properly assess the fit. For both groups (non CVVH and CVVH), 12 data points were collected after 300 h and are therefore not in the figures. The thick red line and small blue lines run within their shaded areas, demonstrating an adequate fit of the model.

PK/PD target attainment was also calculated for all patients treated with ceftazidime ≥1 day, using the worst case (breakpoint) MIC of 8 mg/L, which is a realistic scenario, as ceftazidime is used as empirical therapy in the treatment of suspected *P. aeruginosa* infections when no MIC is available yet. This could be estimated for 94 patients with 96 treatment periods longer than 24 h. PK/PD target was achieved in 77% of the patients for the target of 100%T>MIC, and 14% achieved the target of 100%T>4xMIC. Administration of a loading dose before continuous infusion resulted in higher PK/PD target attainment for both PK/PD targets within the first 24 h of treatment [100%T>MIC: 95% (N = 65) vs. 13% (N = 15); P <0.001 and 100%T>4xMIC: 20% vs. 0%; P = 0.058].

Monte Carlo dosing simulations
The association between ceftazidime clearance and CLCKD-EPI is illustrated in the simulated concentration–time profiles for the dosing regimen 3 g continuous infusion and 2 g loading dose with 5 g continuous infusion. For

this, the median CLCKD-EPI and both the 10th and 90th percentile of the study population was used. Figure 3a,b show that patients with higher CLCKD-EPI had lower ceftazidime concentrations. For *P. aeruginosa* infections with an MIC of 8 mg/L and patients with a CLCKD-EPI of 122 mL/min, simulations with a 3 g continuous infusion and a 2 g loading dose followed by 5 g continuous infusion regimen showed that 10.8% and 97.9%, respectively, achieved the 100%T>MIC target. In Figure 3c,d, the concentration–time profile with the same two dosing regimens is shown for the different comorbidities. For *P. aeruginosa* infections with an MIC of 8 mg/L, and patients with the comorbidity 'trauma or head injury', 100%T>MIC was achieved in 9.1% and 97.9%, respectively, for the 3 g continuous infusion and the 2 g loading dose followed by 5 g continuous infusion.

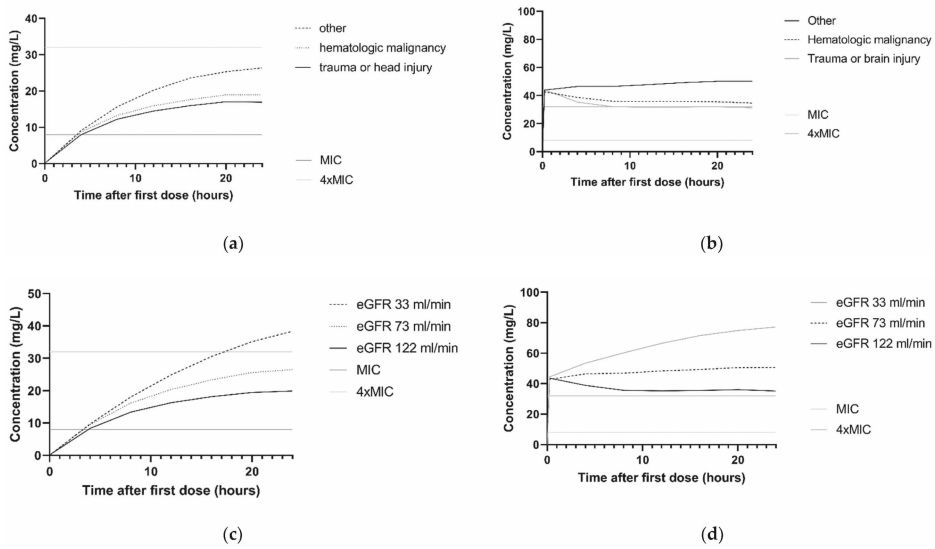

Fig. 3

Simulations of ceftazidime concentration–time profiles in the first 24 h. The median of N = 1000 virtual patients is shown. The MIC and 4 × MIC lines are displayed for a worst-case MIC of 8 mg/L. (a) Simulation of 3 g continuous infusion dosing regimen for patients with a CLCKD-EPI of 33 mL/min/m^2 (10th percentile), 73 mL/min/m^2 (median) and 122 mL/min/m^2 (90th percentile). All patients were simulated with the comorbidity 'other'. (b) Simulation of 2 g loading dose followed by 5 g continuous infusion for patients with the a CLCKD-EPI of 33 mL/min/m^2 (10th percentile), 73 mL/min/m^2 (median) and 122 mL/min/m^2 (90th percentile). All patients were simulated with the comorbidity 'other'. (c) Simulation of 3 g continuous infusion dosing regimen for patients with different comorbidities: other, hematologic malignancy and trauma or head injury. All patients were simulated with a median CLCKD-EPI. (d) Simulation of 2 g loading dose with 5 g continuous infusion for patients with different comorbidities: other, hematologic malignancy and trauma or head injury. All patients were simulated with a median CLCKD-EPI.

Furthermore, PTA was calculated for frequently applied dosing regimens and different MICs (Figure 4). For *P. aeruginosa* infections with an MIC of 8 mg/L, simulations showed that the PTA of 2 g loading dose and 5 g continuous infusion regimen was 98.4% for 100%T>MIC and 65.6% for 100%T>4xMIC. For a continuous dosing regimen without a loading dose, PTA did not exceed 40% of the simulated patients with a *P. aeruginosa* infection with an MIC of 8 mg/L for both 100%T>MIC and 100%T>4xMIC.

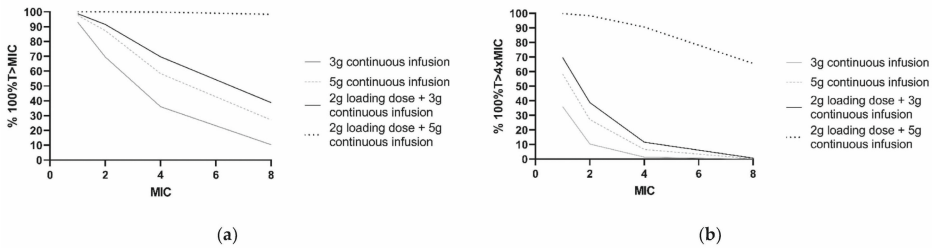

Fig. 4
PK/PD target attainment in the first 24 h with four different ceftazidime dosing regimens. Percentages of 1000 patients simulated with a median CLCKD-EPI of 73 mL/min/m^2 and 'other' comorbidity. (a) For achievement of 100%T>MIC and (b) 100%T>4×MIC for a range of MIC values. The clinical susceptibility breakpoint for *P. aeruginosa*, according to the European Committee on Antimicrobial Susceptibility Testing, is 8 mg/L.

Clinical outcome measures: microbiological and clinical cure
For 17 patients, the endpoint microbiological cure could be assessed. Of these, 9 (53%) patients had isolates which became resistant (category C in Table 3) during therapy. In this study, only one negative follow-up isolate (category A in Table 3) was identified.

For 21 patients, the endpoint clinical cure could be assessed. Ten (48%) patients achieved clinical cure during treatment with ceftazidime. Eleven patients failed on treatment with ceftazidime, meaning they were escalated to other anti-*P. aeruginosa* therapy. Among the patients with clinical failure and of whom a microbiological outcome was known (N = 10), 80% developed decreased susceptibility (category C).

No association could be found between PK/PD target attainment and the clinical outcome measures.

Table 3

Definitions of the secondary endpoints.

Secondary endpoints	Definition
100%T>MIC	Ceftazidime concentration maintained above MIC of the pathogen throughout ≥95% of the first 24 h of treatment.
100%T>4xMIC	Ceftazidime concentration maintained above a concentration 4-fold higher than the MIC of the pathogen throughout ≥95% of the first 24 h of treatment.
Microbiological response: assessed between 48 h after start of therapy until 48 h after stop of therapy	
Patients with microbiological cure.	*P. aeruginosa* cultures become negative during or after ceftazidime treatment.
Patients with microbiological failure without decreased susceptibility for ceftazidime.	*P. aeruginosa* cultures (from the same or relevant location) remain positive during ceftazidime treatment, MIC remains equal.
Patients with microbiological failure with decreased susceptibility (resistance) for ceftazidime.	*P. aeruginosa* cultures (from the same or relevant location) remain positive during ceftazidime treatment, MIC increases with at least factor 4.
Clinical response	
Clinical cure	Completion of full treatment course without change or addition of antibiotic therapy, and no additional antibiotics commenced within 48 h of cessation.
Clinical failure	Any clinical outcome other than clinical cure.

Discussion

In the present study, a population PK model of ceftazidime in adult ICU patients with a suspected or proven *P. aeruginosa* infection was developed. The study population was generally severely ill, as illustrated by the median SOFA score of 10. A one-compartment model best described the ceftazidime PK. The $CL_{nonCVVH}$ was comparable to the values found in previous studies [16, 18]. However, V was nearly two-fold higher than found in previous studies [10, 12]. A possible explanation could be that patients in the current study where more severely ill, as indicated by the SOFA score. Additionally, in the previous studies, V was estimated for patients receiving intermittent dosing, whereas in our study, continuous dosing was mostly used.

The interpatient variability of ceftazidime PK was high, for example, it was 103.4% in $CL_{nonCVVH}$ in the structural model. This variability could largely be explained when creatinine clearance (CLCKD-EPI) was taken into account. Since

ceftazidime is a hydrophilic drug with low protein binding and with predominant renal clearance, this is an expected finding. Furthermore, the comorbidities hematologic malignancy, trauma or head injury explained variability on $CL_{nonCVVH}$. These comorbidities have been shown to cause augmented clearance of other hydrophilic antibiotics in previous studies [22–24].

Although there was a large drop in IIV CL in the final model relative to the structural model upon inclusion of the covariates (from 103.6% to 36.0%), there was a simultaneous increase in IIV V (from 84.7% to 102.8%). An explanation might be that the vast majority of patients received continuous infusion, making it more difficult to separate the IIV that belongs to CL from the IIV that belongs to V than in situations where greater data availability from intermittent infusion. Importantly, overall variability decreased with the addition of the covariates.

This study showed that critically ill patients with *P. aeruginosa* infections are at considerable risk for underexposure to empirical therapy with ceftazidime in the first 24 h of treatment, when a worst-case MIC for *P. aeruginosa* of 8 mg/L needs to be covered (77% and 14% achieved the targets of 100%T>MIC and 100%T>4xMIC, respectively). This is reason for concern. The risk of not attaining the target was especially high when a loading dose was omitted. In addition, there is a high risk of not attaining the target when the higher target of 100%T>4xMIC was aimed for (66% of included patients in whom a baseline MIC was available (N = 32) achieved this target). On the other hand, these patients all achieved the target 100%T>MIC.

Monte Carlo simulations gave further insight into the influence of different dosing regimens and the identified covariates on PTA. The probability of PK/PD target attainment was lower with higher CLCKD-EPI and in the presence of the defined comorbidities when a 3 g continuous infusion dosing regimen was applied and when 100%T>4xMIC was aimed for with worst-case MIC (Figure 2a,c). When 5 g per 24 h continuous infusion with a 2 g loading dose was simulated, the PTA was barely affected by changes in CLCKD-EPI or the presence of comorbidities (Figure 2b,d). Furthermore, simulations of different dosing regimens showed that less than 50% of patients treated with a continuous dosing regimen without loading doses achieve the PK/PD targets when treating *P. aeruginosa* infections with MICs of 4 mg/L and above. Since our PK model is based for the most part on concentration–time data from patients receiving continuous infusion, the model was used to simulate continuous dosing regimens only.

In this study, the relationship between ceftazidime concentrations and toxicity was not investigated. In general, ceftazidime is a drug with relatively low toxicity. However, neurotoxicity has been reported in patients with renal failure, elderly, and patients with neurological disorders [25]. Although a concentration cut-off for toxicity is not known, therapeutic drug monitoring could be used in patients with high risk for developing this adverse event. The dose should be adjusted when the ceftazidime concentration is far above the target needed for effect against *P. aeruginosa*. The adaptive target of C <10xMIC (<80 mg/L in empiric therapy) could be used as proposed by Gatti et al. [25].

To our knowledge, this is the first study to investigate the association between ceftazidime target attainment and microbiological and clinical cure. In 53% of the patients in which follow-up isolates were available, *P. aeruginosa* developed resistance for ceftazidime during therapy. Only one of these patients was classified as achieving microbiological cure. This observation is prone to selection bias, as follow-up isolates are more likely to be collected in patients who are not recovering. However, even in comparison with the total population studied (N = 96, i.e., best case scenario), the incidence of development of resistance is high (almost 10%), confirming the findings of earlier studies [26, 27]. No statistically significant difference was observed in ceftazidime target attainment between patients with and without development of microbiological resistance, yet the numbers per group were small (N = 9 and 8, respectively). There was also no observed statistically significant association between ceftazidime target attainment and clinical cure, and again likely due to small patient numbers (N = 10 and 11, respectively).

This study has several limitations. Firstly, our results could be influenced by selection bias. Cultures were only taken on clinical indication and the follow-up of patients varied as a result of the observational design of our study. Consequently, the patients with more cultures available could be more severely ill. Therefore, the percentage of patients with microbiological failure was probably overestimated since patients with no follow-up isolates were excluded from that part of the analysis.

Secondly, although our study included a high number of patients and ceftazidime samples for the primary aim of the study, being the assessment of the population PK of ceftazidime in ICU patients, the sample size for the secondary aims, being exploration of associations with clinical outcomes, was limited.

Thirdly, we used the CKD-EPI formula for the estimation of renal clearance, which has limited predictive value in critically ill patients [28]. However, use of the CKD-EPI resulted in a better fit of the model compared to the use of the AKIN score.

Fourthly, since molecular analysis of resistant *P. aeruginosa* strains was not performed, there was no further insight into the underlying mechanisms of the resistance pattern.

Fifthly, only 15% of the collected blood samples were obtained within the first 24 h of treatment. Therefore, one could argue that the developed model might not be suitable to calculate the target attainment within the first 24 h. However, during the development of the model, interoccasion variability for both V and CL was tested and found not to improve the fit of the model. Therefore, no significant difference in PK between different days, other than that accounted for by CLCKD-EPI and CVVH, could be identified.

Finally, this study was carried out in a single centre. Therefore, the results that were found might not be representative for other hospitals.

Materials and methods

Study design and setting
The current study was an observational population pharmacokinetic study of ceftazidime at the ICU of Amsterdam University Medical Center, location AMC, a tertiary referral centre in Amsterdam, The Netherlands. The institutional review board of the Amsterdam University Medical Center considered the study as not requiring WMO approval. Patients and relatives were given the opportunity for an opt-out consent method.

Study population
ICU Patients aged ≥18 years treated with IV ceftazidime for a proven or suspected clinically relevant *P. aeruginosa* infection, and with at least one detectable ceftazidime serum concentration available during the course of therapy, were included. Cystic fibrosis patients were excluded. If patients received ceftazidime therapy after discontinuation for more than 28 days, this was assessed as a new treatment period.

For the secondary objective, PTA, the inclusion criterion was one positive *Pseudomonas aeruginosa* culture with a successful MIC measurement for calculation of PK/PD target attainment and treatment for at least 24 h.

Microbiological and clinical cure were evaluated for patients in whom PK/PD target attainment could be calculated. For the assessment of microbiological cure, the availability of at least one follow-up culture from a relevant location was needed with successful MIC measurement >48 h while the patient was receiving ceftazidime treatment. Additionally, the treatment period with ceftazidime had to be longer than 48 h for inclusion. For both microbiological and clinical cure, patients receiving anti-pseudomonal agents for treatment of a different suspected or proven infection than for which the ceftazidime course was prescribed were excluded.

Outcome measures

In this study, several outcome measures were evaluated. The primary objective of this study was to develop a ceftazidime population pharmacokinetic (POP/PK) model in critically ill patients using nonlinear mixed effect modeling (NONMEM) and to quantify and explain the interpatient variability in ceftazidime exposure. As such, primary outcome measures are the population PK parameters and the variability in these parameters.

Secondary outcome measures were (i) PK/PD target attainment, (ii) microbiological cure, and (iii) clinical cure. The definitions of these endpoints are displayed in Table 3.

Sample and data collection

Ceftazidime samples were obtained prospectively, as part of routine clinical care, from both waste materials of arterial blood gas samples, assuring random sampling and from routine therapeutic drug monitoring (TDM), for which samples were collected at standard rounds in the early morning on every Monday, Wednesday and Friday. PK data were collected from ICU patients admitted between November 2013 and March 2018.

Baseline patient characteristics and ceftazidime treatment data were retrieved retrospectively from the Patient Data Monitoring System (PDMS) Metavison (iMDsoft, Tel Aviv, Israel) and EPIC (EPIC Systems Corporation, Verona, WI, USA). Over the years of the study, different ceftazidime dosing regimens have been applied on the ICU for the treatment of proven or suspected infections with *P.*

aeruginosa. These dosing regimens ranged from intermittent dosing of 1 g tid or 2 g tid, to 3 g or 6 g over 24 h via continuous infusion, with and without loading doses. A loading dose was defined as a bolus administered in several minutes immediately before initiation of continuous infusion.

The following data were collected: admission type, time, dose and administration mode (intermittent or continuous) of ceftazidime administration, time of sample collection, sex, age, bodyweight, BMI, height, Sepsis-related Organ Failure Assessment (SOFA) score at the start of ceftazidime treatment, Acute Kidney Injury Network (AKIN) score, and comorbidities including hematologic malignancy, oncologic malignancy, acute trauma, and head injury. During treatment, the serum creatinine, estimated glomerular filtration rate (eGFR, calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation 2009), serum albumin, serum sodium and use of continuous veno-venous hemofiltration (CVVH) and mechanical ventilation, were obtained.

Furthermore, information on norepinephrine use and furosemide use during ceftazidime therapy was collected. Missing data in these patients were replaced with the closest value in time, or when absent, the median population value.

Measured MIC values from the positive *Pseudomonas aeruginosa* cultures were used for the assessment of attaining the PK/PD target. In addition, PK/PD target attainment was calculated by using a surrogate worst case MIC of 8 mg/L for *Pseudomonas aeruginosa*, being both the highest MIC within the wild-type distribution and the breakpoint, since measured MIC data were not available for all patients. This MIC was extracted from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) database [29].

Drug assay and isolates

Serum blood samples were centrifuged and stored at -80°C, in the pharmacy's research laboratory. Since protein binding for ceftazidime is low (approximately 10%), total serum concentrations were measured. These concentrations were measured using a validated high-performance liquid chromatography tandem mass spectrometry (LCMS/MS) method (LC:LC30 Shimadzu, Kyoto, Japan; MS QTRAP 5500 system, Sciex, Framington, MA, USA). The lower limit of quantification (LLQ) was 0.5 mg/L and the higher limit of quantification (HLQ) was 40 mg/L. Concentrations higher than the HLQ were reanalysed after dilution. Accuracy at concentrations of 0.5, 10 and 40 mg/L was 106.2%, 102.2% and

102.2%, respectively. Precision at concentrations of 0.5, 10 and 40 mg/L was 109.8%, 92.4% and 102.4%, respectively.

In this study, all *Pseudomonas aeruginosa* isolates from samples taken for clinical purpose were collected. Identification was performed by MALDI-TOF MS (Bruker Daltonics, Billerica, MA, USA). The MICs of ceftazidime for the *P. aeruginosa* isolates were determined semi-automatically using the VITEK 2 system (BioMerieux, Marcy-l'Étoile, France) or manually by E-test (BioMerieux), carried out by the department of Medical Microbiology at the AMC.

Population pharmacokinetic analysis
POP/PK analysis was performed using nonlinear mixed-effects modeling software (NONMEM 7.1.2; Icon Development Solutions, Ellicott City, MD, USA). Detailed methodologic information on model development and validation is available in Appendix D.

Monte Carlo simulations
The final POP/PK model was used to simulate ceftazidime concentration–time curves for the dosing regimens 3 g continuous infusion and 2 g loading dose with 5 g continuous infusion, to generate insight in the magnitude of the effect of the identified covariates on ceftazidime exposure. The concentration–time curves following these dosing regimens were simulated for the first 24 h of treatment for 1000 virtual patients with all median characteristics of the population but with the 10^{th}, 50^{th} and 90^{th} percentile values of the statistically significantly associated covariates from the final model.

To generate insight into PTA, the percentage of patients expected to attain 100%T>MIC and 100%T>4xMIC in the first 24 h of treatment was calculated for different dosing regimens: 3 g via continuous infusion with or without a loading dose and 5 g via continuous infusion with or without a loading dose, which are the most frequently applied dosing regimens at our ICU. Simulations of these dosing regimens were performed for patients with all median characteristics of the population. One thousand virtual patients were simulated for each dosing regimen, and target attainment was calculated for different MICs, ranging from 1 to 8.

Statistical analysis
Data are presented as percentages for categorical values and median values and ranges for continuous variables. Differences in PTA between patients with different dosing regimens were compared using the Pearson chi square test. A

two-sided P-value of <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics v25 (IBM corporation, Armonk, NY, USA).

Conclusions

In conclusion, the population PK of ceftazidime in critically ill patients with a suspected or proven *P. aeruginosa* infection demonstrated a high interindividual variability, which could to a large extent be explained by CLCKD-EPI, CVVH and the comorbidities hematologic malignancy and trauma or head injury.

Critically ill patients are at risk of underexposure to ceftazidime, in particular, in the case of infections with an increased MIC. A loading dose prior to continuous infusion dosing regimens improved PTA. These results are in line with the performed simulations, suggesting that a dosing regimen of a 2 g loading dose followed by 5 g via continuous infusion can be recommended for optimal target attainment. Development of resistance of *P. aeruginosa* against ceftazidime seems common during therapy with ceftazidime.

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Appendix A. Results: MIC distribution

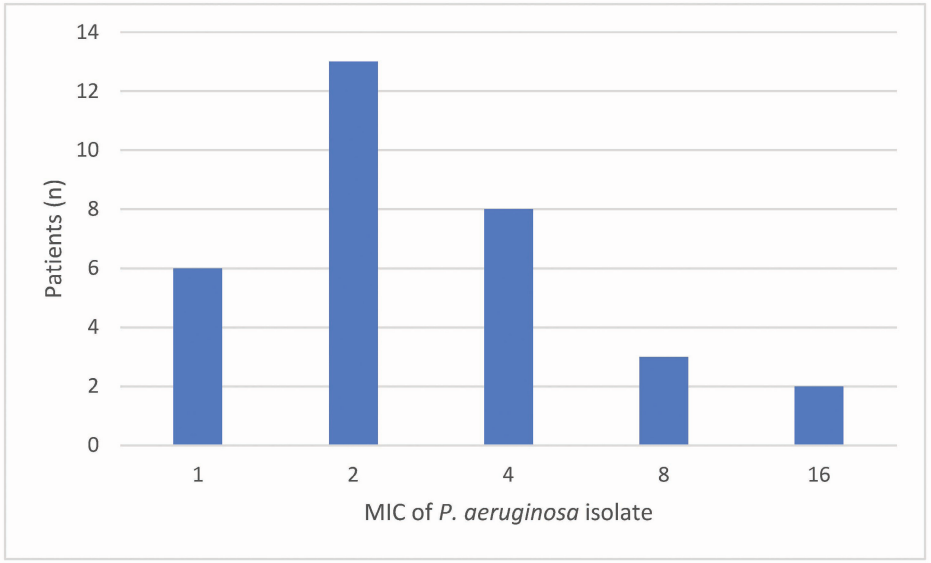


Fig. A1
The measured mean inhibitory concentrations (MIC) of *P. aeruginosa* at baseline.

Appendix B. Results: Goodness-of-Fit plots

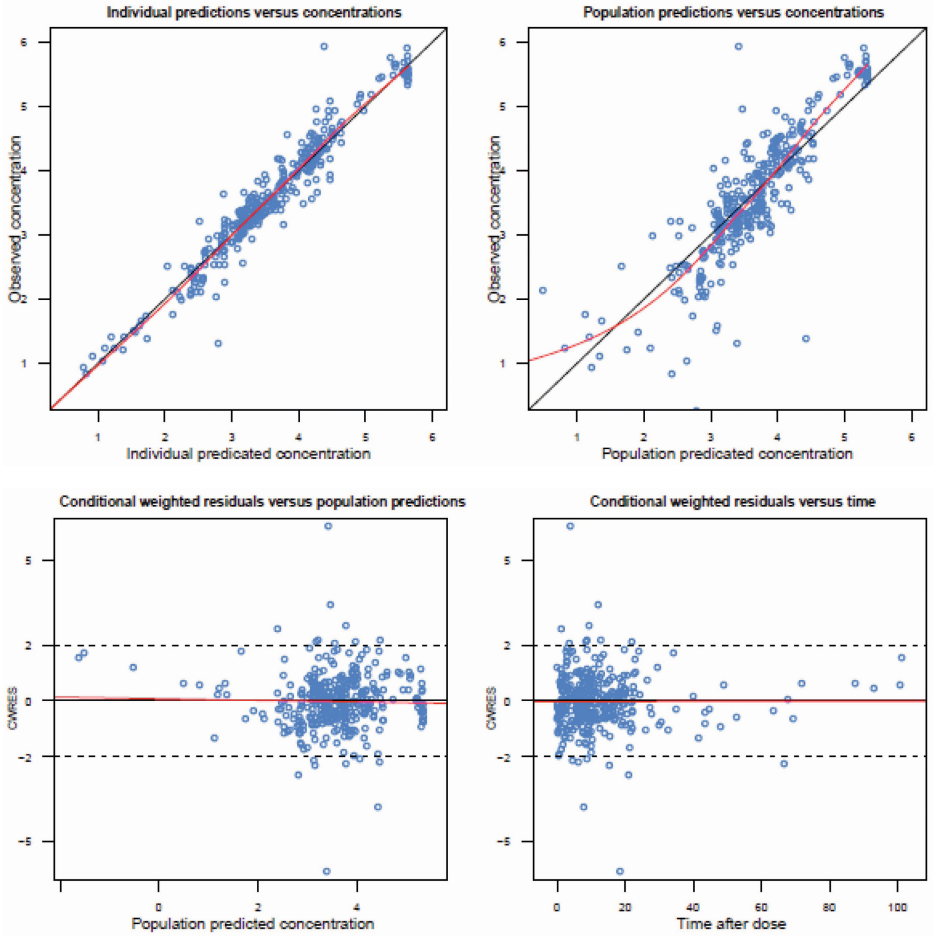


Fig. A2
Basic goodness-of-fit plots of the final model. Population predicted concentrations are logarithmically transformed.

Appendix C. Results: NONMEM control stream

```
$PROBLEM PK model
$INPUT AORTA ID DROP DROP TIME TAD AMT RATE DROP DV MDV EVID OCC DROP
DROP DROP DROP DROP DROP CVVH DROP DROP DROP DROP COMO DROP DROP
DROP DROP CKD
$DATA 28.csv IGNORE = #;
$SUBROUTINES ADVAN1 TRANS2
$PK
FLAT1 = 0
FLAT2 = 0
IF(COMO.EQ.1) FLAT1 = 1
IF(COMO.EQ.3) FLAT2 = 1
IF(COMO.EQ.4) FLAT2 = 1
IF(CVVH.EQ.0) THEN
CL = THETA(2)*(CKD/73)**THETA(5)*THETA(6)**(FLAT1)*THETA(7)**(FLAT2)*EXP(ETA(1))
ELSE
CL = THETA(4)
ENDIF
V = THETA(3) * EXP(ETA(2))
S1 = V
$THETA
0.281 ;1 proportional error
3.42 ;2 CL non CVVH
46.8 ;3 V
2.9 ;4 CL CVVH
0.772 ;5 CKD on CL nonCVVH
1.57 ;6 factor COMO CAT1 (hematologic malignancy) on Cl
1.99 ;7 factor COMO CAT3 (trauma) + CAT4 (brain injury) on Cl
$OMEGA
0.122 ;1 IIV CL NON CVVH
0.721 ;2 IIV V
$SIGMA
1 FIX ;residual variability
$ERROR
ERR1 = SQRT(THETA(1)**2)
IPRED = -3
IF(F.GT.0) IPRED = LOG(F)
Y = IPRED + ERR1*EPS(1)
```

```
IRES = DV-IPRED
IWRES = IRES/ERR1
$EST METHOD = 1 INTERACTION MAXEVAL = 9999 SIG = 3 PRINT = 5 NOABORT POSTHOC
$COV PRINT = E UNCONDITIONAL
$TABLE ID TIME DV MDV EVID IPRED IWRES TAD AMT CWRES CL V ETA1 ETA2 OCC
CVVH CKD COMO NOPRINT ONEHEADER FILE = sdtab83a
```

Appendix D. Methods: Population pharmacokinetic analysis

Firstly, a structural POP/PK model was developed based on logarithmically transformed concentration–time data that described the PK of ceftazidime, including quantification of the volume of distribution (V) and clearance (CL). One- and two-compartmental models were tested, and interpatient variability (IIV) and interoccasion variability (IOV) was tested for the PK parameters in an exponential way, e.g., for ceftazidime CL according to Equation (A1):

Eq. (A1) $$CL_i = CL_{pop} * e^{\eta CL + \eta IOV}$$

where CL_i denotes the ceftazidime CL of individual *i*, CL_{pop} is the median CL of ceftazidime in the population, ηCL represents the random-effect parameter for IIV in ceftazidime CL and ηIOV represents the random-effect parameter for IOV in ceftazidime CL. Estimation of residual variability occurred through testing additive, proportional and combined error models. Goodness of fit was assessed with goodness-of-fit plots, magnitude of residual variability, precision of parameter estimates and a decrease of the objective function value, where a decrease of 3.8 units relative to the reference model was considered statistically significant ($P < 0.05$) as determined with the Likelihood Ratio Test (LRT) with one degree of freedom.

Secondly, patient demographics and physiological factors (covariates) were tested for associations with the PK parameters through a univariate analysis. The following covariates were tested initially for their association with CL and V: age, sex, weight, BMI, serum sodium, norepinephrine use (yes/no), furosemide use (yes/no), CVVH (yes/no), CLCKD-EPI, RIFLE score, serum albumin, mechanical ventilation (yes/no), $CL_{\text{cockcroft and gault}}$, serum creatinine, site of infection and the comorbidity categories 'hematologic malignancy', 'oncologic malignancy', 'trauma' and 'head injury'. Categorical covariates were tested by calculation of a separate parameter for each covariate category. Continuous covariates were examined with a power function:

Eq. (A2) $$CL_i = CL_{pop} * (COV_i/COV_{median})^X$$

COV_i represents the covariate value of the concerning individual, COV_{median} represents the median value of the covariate of the population, and X is an exponent representing the magnitude of the association of the covariate and the

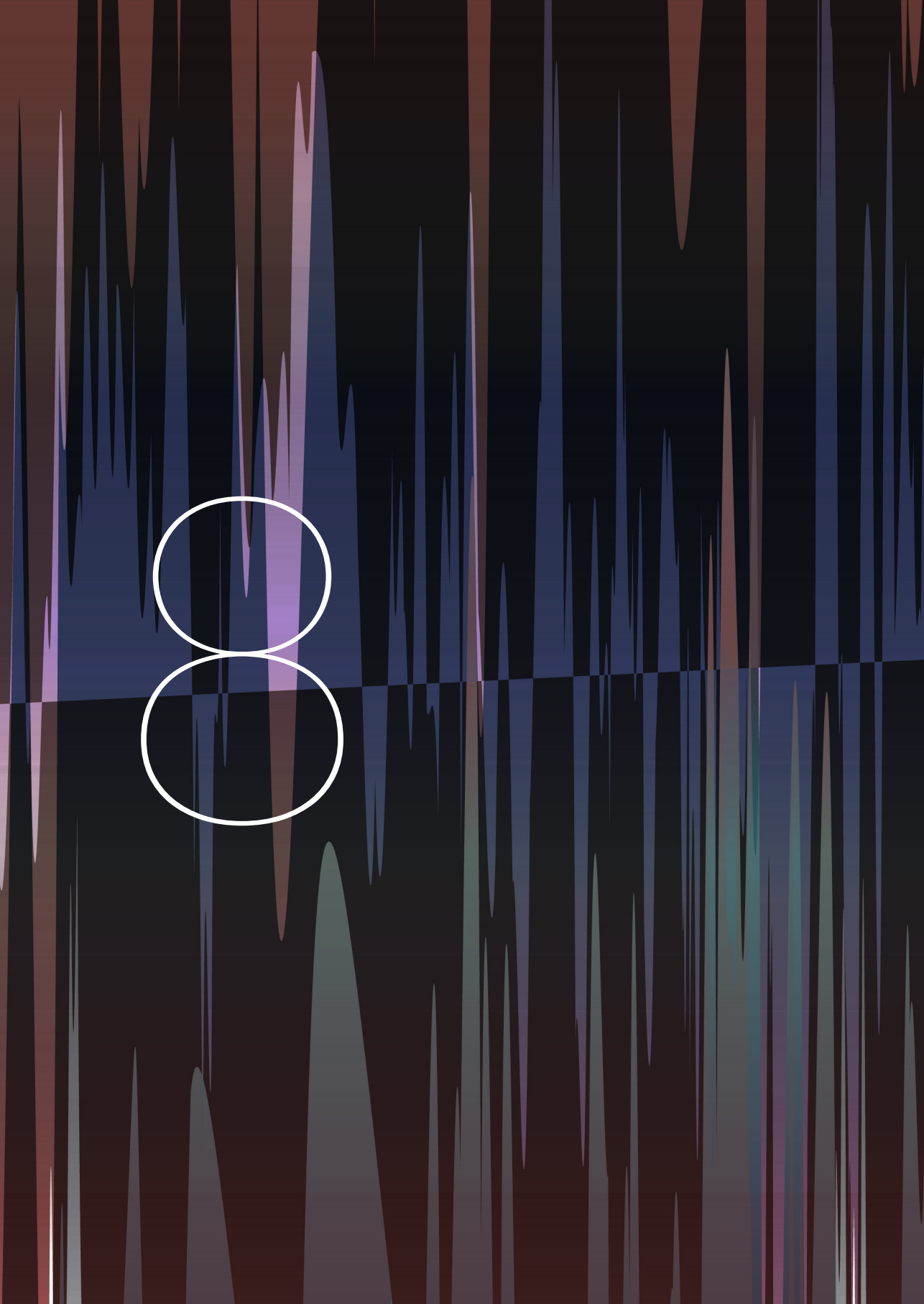
PK parameter. Univariate associations were considered statistically significant at P <0.05 following LRT.

Subsequently, a multivariate analysis was done with all statistically significant covariates from the univariate analysis, through a forward addition procedure, yielding the final model. For this multivariate analysis, the cut-off value was P <0.001, following the LRT.

LLQ data were analysed as follows. In case >10% of samples contained concentrations below LLQ, the M3 method for handling LLQ data was used. Otherwise, the M5 method was used [30].

Internal validation of the final model was performed using a visual predictive check (VPC), N = 1000 simulations. In addition, robustness of the model was tested using a bootstrap analysis (N = 1000). Both bootstrap and VPC analyses were executed using Perl-speaks-NONMEM version 3.5.3 software (PsN, Uppsala, Sweden). To evaluate the stability of the model, a condition number was calculated. A condition number above 1000 is an indication of the instability of the model.

Finally, T>MIC and T>4xMIC were calculated for every patient using the empirical Bayesian estimates from the final model.



General discussion

Although adequate antibiotic therapy is of paramount importance for treatment of critically ill patients suffering from severe bacterial infections, these patients are at increased risk of not reaching the pharmacokinetic/pharmacodynamic (PK/PD) targets that are associated with efficacy, safety and suppression of resistance development compared to non-critically ill patients [1]. In this thesis, we investigated three PK approaches to increase the probability of PK/PD target attainment in critically ill patients treated with gentamicin, vancomycin or ceftazidime: (1) *a priori* optimization of the initial dosing scheme for the critically ill patient population as a whole by introducing a loading dose and/or continuous infusion, (2) *a priori* optimization of the initial dosing scheme based on specific patient characteristics that are associated with decreased probability of target attainment, with the use of a population PK model, and (3) *a posteriori* optimization of the maintenance doses using TDM by Bayesian forecasting.

Gentamicin

When treating patients with gentamicin, the PK/PD target associated with maximal efficacy is a ratio of the peak concentration to the minimal inhibitory concentration (Cmax/MIC) of ≥10 [2, 3]. Additionally, a trough concentration (Cmin) ≤0.5–2 mg/L is associated with a lower risk of nephrotoxicity [4]. In **chapter 2**, we described a population PK model that was used to quantify the impact of several patient parameters on gentamicin peak concentrations [5]. We showed that albumin concentrations <15 g/L in serum were strongly associated with an increased risk of achieving subtherapeutic gentamicin Cmax: 100% of gentamicin peak concentrations in patients with an albumin concentration <15 g/L were inadequate compared to 44% of gentamicin peak concentrations in patients with an albumin concentration >15 g/L ($p<0.0001$). This association was also found in an earlier study [6]. We therefore recommend that, especially for critically ill patients with hypoalbuminemia, Cmax should be measured immediately after the first dose to facilitate adequate dosing of the second gentamicin administration. At least a 150% higher starting dose may be necessary to achieve a therapeutic Cmax in patients with albumin concentrations <15 g/L. However, because of the narrow therapeutic index of gentamicin, this should be confirmed in a prospective setting before higher starting doses can be unequivocally recommended.

Since gentamicin is mainly cleared through the kidneys by glomerular filtration, the glomerular filtration rate is the most important determinant of gentamicin clearance. Estimated individual gentamicin clearance and volume of distribution

can be used in TDM to calculate half-life and subsequently predict gentamicin Cmin and to calculate appropriate dosing intervals for the concerning critically ill patient in which Cmin <2 mg/L is reached. In clinical practice, several measures of renal function have been used to estimate gentamicin clearance for TDM. Multiple studies have evaluated the association between gentamicin clearance and several equations that estimate the glomerular filtration rate based on creatinine levels in serum. In studies focusing on non-critically ill patients, the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) performed better than the Cockcroft-Gault equation or the Modification of Diet in Renal Disease equation (MDRD) [7-9]. However, studies focusing on critically ill patients found that equations based on creatinine levels in serum (including the Cockcroft-Gault equation, MDRD (both the short and long version) and CKD-EPI) do not accurately represent renal function in these patients, showing much bias and poor precision and accuracy compared to the measured glomerular filtration rate [10-12]. In **chapter 2**, we showed that serum creatinine or the Cockcroft-Gault equation overestimated gentamicin clearance and that urinary creatinine clearance calculated from the creatinine concentration in a 6-hour urine portion is a better predictor of gentamicin Cmin in critically ill patients. Since overestimation of clearance may lead to application of inappropriately short dosing intervals with resulting increased risks of toxicity, the use of serum creatinine or creatinine based equations for clearance are not recommended for guidance of the gentamicin dosing interval in critically ill patients. If feasible, we recommend to use a measured glomerular filtration rate for estimating gentamicin clearance when performing TDM.

A population PK model, like the model described in chapter 2, can aid in selecting adequate starting doses and optimizing individual dosing regimens by Bayesian forecasting in the patient cohort whose data the model was based on. However, external validation of the model is necessary to evaluate whether it can be used reliably for this purpose in other patient cohorts [13, 14]. External validation determines the bias, accuracy and reproducibility of a PK model by applying a new dataset within the PK model [14]. In **chapter 3**, we reported the predictive performance of the gentamicin population PK model described in chapter 2 in two independent populations of critically ill patients, to evaluate if this model could be used for dosage prediction in other Western Intensive Care Unit (ICU) populations. Validation data were collected from a new patient cohort at the ICU where the model was originally developed (Academic Medical Centre (AMC), Amsterdam) and from a patient cohort at another Western ICU (Centre Hospitalier Universitaire (CHU) de Nîmes). The PK model proved valid for

use in the ICU population at the AMC, with a non-significant mean bias and an acceptable mean inaccuracy of 2.5 mg/L, based on all concentrations. However, it was not valid for use in the CHU Nîmes ICU population, showing a significant mean bias of 4.8 mg/L (95%CI: 4.0–5.6) and an inadequate mean inaccuracy of 5.5 mg/L. This inaccuracy is often seen in critically ill patient populations [14]. In fact, a study from 2022 externally validated four population PK models of gentamicin in critically ill patients (including the two models described in chapter 2 and chapter 4 in this thesis), using data from two Quebec hospitals, and found that none of these presented acceptable values for bias and inaccuracy [15]. This illustrates that caution is needed when using a population PK model for dosage prediction in an external population. Nevertheless, external validation of a published PK model is uncommon: of eleven population PK models of gentamicin in critically ill patients included in a large review from 2021, only two performed an external validation (of which our study was one) [14]. This may be due to the fact that it is difficult to collect data from enough patients with similar characteristics from another ICU to build an adequate validation dataset [14]. When one intends to use a published population PK model for Bayesian TDM, we strongly recommend to validate the model with data from the population it will be used in, especially when it has not been externally validated by the developers of the model.

When patients are treated with gentamicin in the Netherlands, performing TDM for optimization of the gentamicin dose and dosing interval is standard of care [16]. Additionally, performing TDM to increase the probability of target attainment for efficacy is also recommended in the Dutch guidelines for the treatment of sepsis [17]. A randomized controlled trial from 1999 has shown that TDM of gentamicin, using Cmax and a random concentration or Cmin measurement after the first administration in a Bayesian model, increased clinical efficacy and reduced nephrotoxicity in non-critically ill patients [18]. In **chapter 4**, we evaluated whether routine TDM of gentamicin Cmax increases the probability of PK/PD target attainment for efficacy in a population of critically ill patients. We found that, following a median weight-based gentamicin starting dose of 5 mg/kg, subsequent dosing based on Cmax measurements modestly increased the percentage of patients with a therapeutic Cmax (defined as a Cmax of 15-20 mg/L) from 40% before TDM to 50% after TDM. In addition, it decreased the percentage of patients with subtherapeutic Cmax (<15 mg/L) from 47% before TDM to 30% after TDM. Therefore, although less patients reached subtherapeutic Cmax after model-based TDM based on actual measurement of the Cmax, half of the patients still did not reach a therapeutic Cmax. Monte

Carlo simulations were performed to study the effect of a higher starting dose on the probability of PK/PD target attainment before and after TDM. Increasing the simulated starting dose from 5 mg/kg to 6 mg/kg slightly increased the percentage of patients with a therapeutic Cmax after the first dose from 28% to 34% and substantially decreased the percentage of patients with subtherapeutic Cmax from 59% to 36%. However, after this first dose of 6 mg/kg, TDM had no substantial beneficial effect on these percentages after the second dose. We concluded that TDM of Cmax corrected for the relatively low starting dose of 5 mg/kg by increasing the median follow-up dose, but did not decrease the variability of Cmax found in critically ill patients. The most likely explanation is the high inter-occasion variability (i.e. pharmacokinetic variability within a patient from one dose to the next) of the volume of distribution, estimated to be 25%, which limits the predictive value of a Cmax for the next Cmax. This high inter-occasion variability of the volume of distribution in critically ill patients is in concordance with previous data: an even higher inter-occasion variability of 40.9% was reported in an earlier population PK study of gentamicin and tobramycin in ICU patients [19]. It therefore remains unclear if performing TDM for optimization of Cmax is useful in critically ill patients, especially if a higher starting dose is used than 5 mg/kg. Since the currently recommended standard weight-based starting dose for gentamicin for ICU patients is 6-7 mg/kg [17], the risk of subtherapeutic Cmax is reduced when compared to the study period. However, we believe that performing TDM of gentamicin Cmax is sensible in this population with large interindividual variability (i.e. pharmacokinetic variability between patients) in volume of distribution. TDM of gentamicin Cmax could be useful to detect extremely high Cmax values, which are to be expected more frequently with a higher starting dose, as well as in detecting extreme low Cmax values, which may still occur despite a higher starting dose. A randomized controlled trial to evaluate the clinical benefit of TDM of gentamicin Cmax is urgently needed.

As noted, TDM is also used to optimize the dosing interval, maximizing the probability that patients reach a Cmin ≤0.5–2 mg/L, associated with a lower risk of nephrotoxicity in non-critically ill patients [4]. In critically ill patients, prolonging the dosing interval is often necessary to reach an adequate Cmin. Although, to the best of our knowledge, there is no clinical evidence that gentamicin TDM also reduces the risk of nephrotoxicity in critically ill patients, we consider it prudent to also perform TDM for optimization of the dosing interval in all patients who receive more than one administration of gentamicin.

In **chapter 5**, the clinical PK and optimal dosing of gentamicin in several patient populations were reviewed. Based on the available literature on optimal dosing for critically ill patients, we recommend a relatively high starting dose of 7 mg/kg to decrease the risk of subtherapeutic Cmax, since critically ill patients often have a large volume of distribution and are therefore at increased risk of underdosing. We do not recommend using an even higher starting dose of 8–10 mg/kg to further increase the probability of PK/PD target attainment, since this may result in an increased risk of nephrotoxicity in a population where the risk of nephrotoxicity is already relatively high: the Cmin will also increase, resulting in Cmin >2 mg/L in a proportion of patients if dosing intervals are not adjusted.

Moreover, a higher probability of PK/PD target attainment does not automatically result in higher clinical efficacy: a review on aminoglycosides from 2017 identified no correlation between the probability of PK/PD target attainment and clinical success [13]. Two recent studies focusing on critically ill patients also failed to find this correlation [20, 21]. Especially in critically ill patients, other factors such as comorbidity and severity of illness may be stronger predictors of clinical outcome than PK/PD target attainment [22]. Additionally, gentamicin is often used as part of short courses of empirical combination therapy and only rarely as targeted monotherapy. This complicates clinical evaluation of optimal dosing since co-administered antibiotics may be responsible for clinical success. More research is needed on the optimal PK/PD target for efficacy of gentamicin as part of short-term empirical combination therapy.

Since targeting a high probability of PK/PD target attainment in critically ill patients inevitably increases the risk of nephrotoxicity on a population level, one should carefully weigh the risks and benefits of gentamicin therapy in this patient population. Hence, there is ongoing debate on the value of gentamicin as part of empirical combination therapy. The most recent Dutch guidelines on the treatment of sepsis have expressed concern about the efficacy and toxicity of gentamicin, but have found insufficient evidence to discourage its use in patients with sepsis [17]. Amid these concerns, the use of gentamicin has steadily decreased in the Netherlands in the last few years, after many years of stable use [23, 24]. However, because resistance to 3rd generation cephalosporins and fluoroquinolones is increasing and piperacillin-tazobactam and carbapenems are considered “reserve” antibiotics, gentamicin may remain an attractive option if proven safe and effective, due to the low levels of antimicrobial resistance. A randomized controlled trial is needed to evaluate the safety and clinical value of gentamicin in empirical combination therapy. This trial is currently being

performed in the Netherlands [25]. If gentamicin is used as part of empirical treatment, we recommend that treatment duration should be restricted to 2–3 days.

Vancomycin

When treating patients with vancomycin, the PK/PD target associated with maximal efficacy is a ratio of the area under the drug concentration-time curve to the minimal inhibitory concentration (AUC/MIC) of ≥400 [26]. In the past, Cmin was routinely used as surrogate PK/PD target, but Cmin has been proven to underestimate the AUC [27]. As a result, AUC-guided dosing is now increasingly used. A retrospective analysis of routine vancomycin concentration measurements in critically ill patients admitted to the ICU of the AMC, revealed that 85% of patients did not reach the (former) target Cmin with a conventional starting dose of 1000 mg (unpublished data). In several studies, a loading dose of 25–35 mg/kg total body weight has been found to decrease the risk of subtherapeutic serum concentrations , defined as AUC values <400 mg*h/L or steady-state concentrations during continuous infusion <20 mg/L, in the first 24–72h of treatment [28]. However, increasing the starting dose can lead to more adverse events, since daily AUC values >600 mg*h/L are associated with higher risks of vancomycin-associated nephrotoxicity [29]. In **chapter 6**, we reported a prospective observational study to evaluate whether the introduction of a weight-based vancomycin loading dose of 25 mg/kg leads to more critically ill patients attaining the PK/PD target for efficacy in the first 24h, compared to a fixed starting dose of 1000 mg. This target was defined as an area under the drug concentration-time curve in the first 24h (AUC_{0-24}) ≥400 mg*h/L, assuming an MIC of 1 mg/L. Additionally, we evaluated whether the resulting increase in vancomycin starting doses results in a higher risk of acute kidney injury (AKI). We found that the loading dose increased the probability of PK/PD target attainment significantly from 54% to 88% (p<0.001). Earlier studies also found an increased probability of PK/PD target attainment after a loading dose, but these studies predominantly used vancomycin Cmin as target or used an external population PK model for AUC estimation, mostly from Cmin measurements from a limited number of patients. We used a population PK model that was specifically developed for the purpose of this study, leading to more reliable estimation of AUC_{0-24}, based on vancomycin concentrations obtained during the whole dosing interval. Our study was not powered to assess whether an increased probability of PK/PD target attainment after a loading dose improves clinical outcome.

In our study, the percentage of patients with new onset AKI was not significantly higher when receiving a 25 mg/kg loading dose compared to a fixed 1000mg starting dose (37.8% versus 28.6%; p=0.48). However, for a thorough analysis of the association between vancomycin AUC_{0-24} and new-onset AKI, a multivariate regression analysis would be needed, since many co-administered drugs and events during ICU admittance can cause AKI. Our data were too limited to reliably perform this analysis. Nevertheless, our findings are in concordance with earlier studies: a meta-analysis from 2022 which included 17 studies on vancomycin loading doses (of which our study was one) even found that the use of a loading dose lowered the risk of nephrotoxicity, possibly through more effective treatment of infections that can contribute to AKI [30]. Of note, this finding was largely based on observational studies, with only 2 small randomized controlled trials included. Therefore, the authors of the review concluded that there was not enough evidence to endorse the safety and efficacy of a loading dose. Importantly, the risk of new onset AKI in our study was significantly higher in patients achieving AUC_{0-24} >400mg*h/L compared with patients not achieving this target (39.0% versus 14.8%; p=0.031). This was also found in other studies, with comparable percentages of patients developing AKI [31, 32]. Although higher vancomycin exposure thus is associated with an increased risk of AKI, it remains controversial whether use of a loading dose poses an additional risk. A large randomized controlled trial is still necessary to evaluate the clinical efficacy and safety of vancomycin loading doses [30]. This trial is preferably performed using continuous infusion of vancomycin after the loading dose, since continuous infusion may be associated with a reduced risk of AKI compared to intermittent infusions [33].

Meanwhile, more than half of the patients receiving a loading dose in our study achieved an AUC_{0-24} >600mg*h/L, which is associated with increased risk of nephrotoxicity based on classification and regression tree (CART) analysis in several studies [29, 32]. Although we had insufficient data to perform a formal CART analysis, we could perform a receiver operating characteristic (ROC) analysis [34] to try and define a potential AUC_{0-24} breakpoint for AKI in our study. The optimal AUC_{0-24} breakpoint using ROC analysis was 602 mg*h/L, showing 80.0% sensitivity (i.e. 80.0% of patients without nephrotoxicity had an AUC_{0-24} <602 mg*h/L) and 55.6% specificity (i.e. 55.6% of patients with nephrotoxicity had an AUC_{0-24} >602 mg*h/L) (data not published). We strongly recommend using a loading dose followed by TDM to measure the AUC_{0-24} within 48h after start of vancomycin therapy (or within 24h if renal function is impaired), to

identify patients with an AUC_{0-24} >600 mg*h/L. In this way, the maintenance dose can be adjusted in a timely fashion.

Ceftazidime

When treating critically ill patients with ceftazidime, the PK/PD target for efficacy is reached when the ceftazidime plasma concentration is maintained above the MIC for 100% of a dosing interval (100%T>MIC) [37, 38]. However, especially for treatment of infections caused by *P. aeruginosa*, a higher target of a 100%T>4xMIC may be needed for prevention of mutations that can lead to antimicrobial resistance during therapy [39]. The standard dosing regimen for ceftazidime is 1g 3x/day, which has a high probability of PK/PD target attainment for treatment of infections caused by susceptible *Enterobacterales*, such as *E. coli*, with a maximal MIC of 1 mg/L [40]. In contrast, for treatment of infections caused by wild-type *P. aeruginosa* (i.e. without acquired resistance mechanisms, with a maximal MIC of 8 mg/L), the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has defined clinical breakpoints for high dosage ceftazidime therapy only: either 2g 3x/day or 1g 6x/day [41]. The rationale for these high dosage breakpoints is that the probability of PK/PD target attainment is too low when using a standard dosing regimen of 1g 3x/day for treatment of an infection with a micro-organism with an MIC of 8 mg/L [40]. For the same reason, the Dutch sepsis guidelines advice to use high dose ceftazidime for critically ill patients, with an option to lower the dose to 1g 3x/day only if *P. aeruginosa* is proven not to be involved in the infection [17].

In addition to increasing the dose, using prolonged or continuous infusion can further increase the T>MIC of antipseudomonal beta-lactam antibiotics. The use of prolonged or continuous infusion of beta-lactam antibiotics has proven to significantly lower mortality of patients suffering from sepsis [42].

For these reasons, in 2014, the ICU of the AMC increased the routine empirical dose of ceftazidime from 1g 3x/day to 5g/24h continuous infusion in combination with a 1 to 2 gram loading dose. In the following years, as part of the routine treatment protocol, blood samples were taken for ceftazidime concentration measurements to evaluate the resulting exposure. In addition, residual material from blood gas analyses was collected for ceftazidime concentration measurements, ensuring random sampling. In **chapter 7**, we describe a population PK model for ceftazidime based on these measurements in critically ill patients with a proven or suspected *P. aeruginosa* infection. This

model was used to identify dosing regimens that maximize the probability of PK/PD target attainment for efficacy in the first 24h. In routine practice, circa 10% of the patients still started treatment with intermittent dosing, despite the new protocol. The continuous infusion doses that were used ranged from 3g/24h to 6g/24h and the majority of these patients (>80%) also received a loading dose. As a result, a range of ceftazidime dosing regimens was available for evaluation.

Our study showed that critically ill patients are at considerable risk for underexposure to empirical therapy with ceftazidime in the first 24h of treatment when assuming an MIC of 8 mg/L: the probability of PK/PD target attainment was 77% for 100%T>MIC and only 14% for 100%T>4xMIC. Patients receiving a loading dose before continuous infusion demonstrated a higher probability of PK/PD target attainment in the first 24h than patients who did not (95% versus 13% for 100%T>MIC ($p<0.001$) and 20% versus 0% for 100%T>4xMIC ($p=0.058$)). This was confirmed in Monte Carlo simulations of a 2g loading dose followed by 5g continuous infusion, which is the dosing regimen currently used at the ICU of the AMC. This probability was barely affected by changes in renal function, in contrast to a simulated dosing regimen of 3g continuous infusion without a loading dose, where patients with a simulated glomerular filtration rate of 122 ml/min had a significantly lower probability of PK/PD target attainment than patients with median or lower simulated glomerular filtration rate of 73 and 33 ml/min, respectively. For a simulated 5g continuous dosing regimen without a loading dose, the probability of PK/PD target attainment did not exceed 40% for 100%T>MIC and was close to 0% for 100%T>4×MIC. We therefore strongly recommend the use of a loading dose and high-dose continuous infusion of ceftazidime in critically ill patients when treating *P. aeruginosa* infection.

Antimicrobial resistance commonly develops during antibiotic therapy for *P. aeruginosa* infections in critically ill patients [43, 44] and may result in future difficulties in selecting appropriate empirical therapy when a new infection occurs, potentially reducing clinical cure and increasing mortality. In **chapter 7**, we also aimed to evaluate if PK/PD target attainment was correlated with a reduced risk of antimicrobial resistance development. There were 16 patients of whom both ceftazidime concentrations and follow-up *P. aeruginosa* isolates from the same type of patient sample (e.g. sputum) were available. In 9/16 patients (56%), *P. aeruginosa* became resistant to ceftazidime during therapy. However, as follow-up isolates are more likely to be collected from patients who are not recovering, there is a high probability of selection bias for this analysis and hence an overestimation of the resistance rate. But even when assuming

that all *P. aeruginosa* isolates of patients that had no follow-up cultures remained susceptible, *P. aeruginosa* developed ceftazidime resistance during therapy in almost 10% of patients, which is comparable to the rate in several earlier studies [45, 46]. No statistically significant difference in target attainment was found in patients with versus without development of resistance, but the numbers per group were too small for a reliable analysis. Analyses in larger numbers of patients are needed and currently ongoing. Moreover, a prospective trial evaluating the association between ceftazidime exposure and the risk of resistance development under therapy is urgently needed. This trial should use maximal ceftazidime exposure (i.e. high dose continuous infusion after a loading dose) and should include routinely taken follow-up cultures from the infection site at predefined time points. If this trial would result in considerable resistance development under therapy despite high dose continuous infusion, a trial evaluating the effect of definite combination therapy on the risk of resistance development under therapy may be considered.

Improving antibiotic dosing in critically ill patients

Our studies are part of a growing body of research on optimal antibiotic dosing in critically ill patients. We know progressively better how to increase the probability of PK/PD target attainment for critically ill patients, but it remains unclear whether this approach improves clinical outcome. The single centre studies reported in this thesis illustrate that the probability of achieving the PK/PD target for vancomycin, gentamicin and ceftazidime can be increased by the three investigated PK approaches for dose optimization, i.e. by optimizing the initial dosing scheme for the entire critically ill patient population by introducing a loading dose and/or continuous infusion, by optimizing the initial dosing scheme to specific patient characteristics or by adjusting the maintenance doses using TDM. However, our studies are insufficiently powered to allow for reliable inferences on improved clinical outcome, reduced toxicity or decreased risk of resistance development. Definitive evidence requires large multi-centre clinical trials and/or meta-analyses, which are currently lacking for many antibiotics.

For gentamicin, pharmacokinetic dose optimization has been proven to increase clinical efficacy and to reduce nephrotoxicity in non-critically ill patients [18], but several studies in critically ill patients have shown no convincing evidence that improving the probability of PK/PD target attainment results in reduced mortality [13]. For vancomycin, a correlation has been found between attainment of the PK/PD target and clinical efficacy, mainly in retrospective, single-centre,

observational studies of patients with MRSA bloodstream infections. But although pharmacokinetic dose optimization has been proven to increase the probability of PK/PD target attainment and decrease the risk of nephrotoxicity, data on clinical outcome of dose optimization are scarce, do not include critically ill patients and have shown no significant benefit [47]. More research is needed to evaluate whether vancomycin dose optimization is clinically relevant for critically ill patients. In contrast, there is increasing evidence for the clinical impact of dose optimization by prolonged or continuous infusion of beta-lactams in critically ill patients, although this is mainly restricted to treatment with piperacillin-tazobactam or meropenem [42]. Pending the results of multi-centre clinical trials and meta-analyses, it appears valid to try and maximize the probability of PK/PD target attainment for antibiotic treatment of severe infections in critically ill patients.

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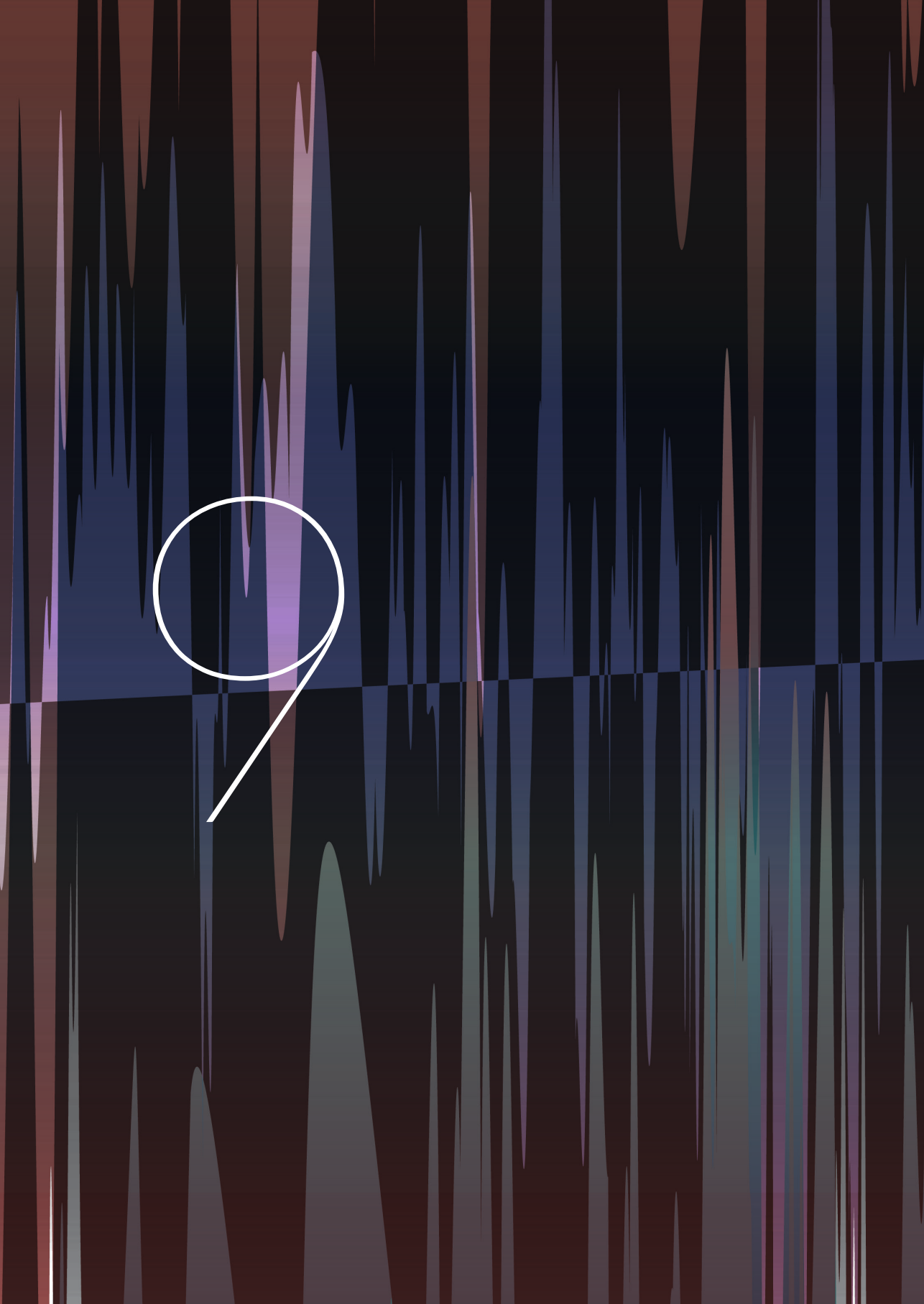

Summary

Each year, thousands of critically ill patients admitted to Dutch intensive care units (ICUs) suffer from severe bacterial infections. Early and adequate antibiotic treatment significantly lowers the mortality of these infections. Therefore, treatment is started as soon as possible using empirical antibiotic therapy aimed at the potential causative agents, although in these early stages it is often unclear which bacteria cause the infection. Examples of antibiotics that are used for treatment of bacterial infections in the Netherlands are gentamicin, vancomycin and ceftazidime.

The efficacy of these antibiotics depends on the concentrations that are achieved in serum and in infected body tissues. If concentrations are too low, there is an increased risk of treatment failure and development of antimicrobial resistance. If concentrations are too high, the risk of toxicity increases. However, it is particularly difficult to achieve adequate antibiotic concentrations in critically ill patients. On the one hand, the immune response to infection can lead to changes in volume of distribution and to accelerated metabolism or excretion of the antibiotic. On the other hand, the organ damage that can be caused by the immune response can lead to delayed metabolism or excretion of the antibiotic. Absorption, distribution, metabolism and excretion of antibiotics are examples of pharmacokinetic processes. These processes determine the rate at which an administered dose of a drug is absorbed and distributed throughout the body and subsequently excreted. Consequently, they determine the time course of the concentrations of that drug achieved in serum and body tissues after administration.

Use of the standard starting dose (i.e. the recommended dose for non-critically ill patients) can lead to antibiotic concentrations in critically ill patients that are too high or too low because the pharmacokinetic processes may vary widely. Large differences in pharmacokinetic processes are seen both between individual critically ill patients, as well as within an individual patient during different stages of the infection and the resulting immune response. There are several strategies to increase the probability that adequate antibiotic concentrations will be achieved timely in critically ill patients.

A first strategy is to adjust the standard starting dose in all critically ill patients, in order to counteract the consequences of the altered pharmacokinetic processes. For this strategy, it is important to know the average antibiotic concentration that results from administration of a standard starting dose in this patient group.

E.g., if the average concentration is lower compared to non-critically ill patients, it may be sensible to routinely start treatment with a higher dose.

A second strategy is to adjust the starting dose only in patients with certain characteristics that predict a lower probability of achieving adequate antibiotic concentrations. These predictive patient characteristics are called covariates. Examples of possible covariates are age, sex, body weight, history of chronic diseases, disease severity and renal function. Relevant covariates can be assessed using population pharmacokinetic analysis, which uses complex statistical and mathematical models to describe pharmacokinetic processes based on measured drug concentrations in a specific group of patients, in this case antibiotic concentrations in critically ill patients. The resulting model is called a population pharmacokinetic (PopPK) model. This model describes the average time course of antibiotic concentrations for this patient group after administration of certain doses of the antibiotic. In addition, the variation in concentrations between patients receiving the same doses is quantified and important covariates can be identified that explain why an individual patient has higher or lower concentrations than the average patient. These analyses can be performed using non-linear mixed-effects modelling (NONMEM) software.

A third strategy is to adjust the doses following the (un)adjusted starting dose using therapeutic drug monitoring (TDM) for each individual patient. When using TDM, the concentration of the administered antibiotic is measured in the patient's blood. Based on this measurement, one can evaluate whether the concentration is adequate, too low or too high in relation to a predetermined target concentration, and whether the dose should therefore be maintained, increased or reduced, respectively. The most precise estimate of the required dose can be obtained using maximum *a posteriori* (MAP) Bayesian forecasting, based on a combination of TDM and a PopPK model, i.e. by combining measured serum concentrations, individual patient characteristics and information on mean concentrations and the variability of these concentrations in the patient group of interest.

The antibiotic target concentrations that are considered "adequate" differ from antibiotic to antibiotic. As a result, the best strategy to quickly achieve adequate antibiotic concentrations may also vary. In this thesis we investigate several dosing strategies to increase the likelihood of achieving adequate antibiotic concentrations in critically ill patients treated with gentamicin, vancomycin or ceftazidime. For effective treatment with gentamicin, it is particularly

important that the maximum concentration reached in the individual patient immediately after intravenous administration, i.e. the peak level, is high enough. In order to prevent side effects, mainly nephrotoxicity, it is also important that the gentamicin trough level, i.e. the concentration just before the next administration, is low enough. For treatment with vancomycin, it is not the maximal or lowest concentration, but the average concentration of the antibiotic over time (expressed as the area under the plasma concentration-time curve) that determines both the efficacy and the risk of side effects. For effective treatment with ceftazidime, it is important that the concentration remains above a certain minimal value long enough.

In **chapter 2**, we investigated whether certain patient characteristics can predict a lower probability of achieving adequate gentamicin peak levels. After developing a PopPK model for gentamicin in critically ill patients, we investigated which covariates influence peak levels and could thus be used to adjust the starting dose of gentamicin, instead of using the same starting dose for every ICU patient. Albumin concentrations <15 g/L in serum were strongly associated with increased risk of an inadequate gentamicin peak level of <15 mg/L after a starting dose of 4 mg/kg total bodyweight: 100% of 11 peak levels in patients with an albumin concentration <15 g/L were inadequate compared to 44% of 163 peak levels in patients with an albumin concentration >15 g/L ($p<0.0001$). A higher gentamicin starting dose is probably needed in patients with severe hypoalbuminaemia.

We also used the PopPK model to evaluate which measure of renal function (which is the most important covariate for gentamicin clearance) best predicts the trough level in critically ill patients, which is important to reduce the risk of nephrotoxicity. Estimates of renal function based on creatinine serum concentrations proved to overestimate gentamicin clearance, which could lead to premature administration of the next dose of gentamicin and therefore an increased risk of side effects. Estimates of renal function based on urinary creatinine measurements were found to be a better predictor of gentamicin trough levels and would therefore be preferable to blood creatinine measurements to determine the optimal dosing interval.

In **chapter 3**, we investigated whether the PopPK model for gentamicin that is described in chapter 2 can also be used for dose adjustment in intensive care patients other than the group of patients with whose data the model was developed. The model proved adequate for a new patient cohort from the ICU

of the Academic Medical Center, showing a non-significant bias of 0.35 mg/L (95%CI: -0.11–0.81) and sufficient accuracy of 2.5 mg/L (95%CI: 2.3–2.8). But the model proved inadequate for a patient cohort from the ICU of the University Hospital in Nîmes, France, because it overestimated the concentrations after administration of gentamicin in this group, showing a significant bias of 4.8 mg/L (95%CI: 4.0–5.6) and inadequate inaccuracy of 5.5 mg/L (95%CI: 4.7–6.2). This illustrates that caution should be exercised when using PopPK models for dose adjustment in other patient groups admitted to the ICU. Prior validation of the model is recommended with data from the population in which the model is intended to be used.

In **chapter 4**, we investigated whether routine measurement of peak gentamicin levels in the context of TDM after the first administration increases the likelihood that critically ill patients have adequate gentamicin peak levels after the next administration, defined as a peak level between 15 and 20 mg/L. Using a PopPK model for gentamicin in critically ill patients, we estimated peak levels after the first administration with a dose of 5 mg/kg total bodyweight (i.e. before TDM) and after subsequent doses based on TDM in 30 critically ill patients. TDM of peak levels slightly increased the probability of adequate gentamicin peak levels from 40% after the first dose to 50% after the second dose, but even after TDM, 20% of the patients had peak levels that were too high and 30% had peak levels that were too low, probably due to the high variability of the pharmacokinetic processes in individual patients during the different stages of infection and the resulting immune response. In addition, we used Monte Carlo simulations to evaluate the effect of a higher starting dose of 6 mg/kg total bodyweight for all ICU patients on the peak level after the first gentamicin administration. After this simulated higher starting dose, the percentage of patients with low gentamicin peak levels decreased from 59% to 36%. Subsequent TDM did not result in a further decrease in the percentage of patients with low peak levels. We therefore recommend using a higher starting dose of 6-7 mg/kg (which is also the recommended starting dose in the most recent Dutch guidelines on the management of sepsis), but we think that performing TDM of gentamicin peak levels may still be prudent to detect extremely high or low peak levels.

In **chapter 5**, we review the pharmacokinetics of gentamicin in the general adult patient population and in other patient populations with different pharmacokinetics, such as obese patients, critically ill patients, paediatric patients, neonates, the elderly and patients with impaired renal function receiving renal replacement therapy. We also describe the consequences of

these different pharmacokinetics for optimal dosing and provide starting dose recommendations for each patient group.

In **chapter 6**, we investigated whether routine administration of a vancomycin loading dose increases the probability that critically ill patients admitted to the ICU have adequate vancomycin concentrations in the first 24 hours of treatment. Using a PopPK model for vancomycin in critically ill patients, we compared the average concentration in the first 24 hours, expressed as the area under the concentration-time curve (AUC_{0-24}), in 39 patients before introduction of a loading dose and 50 patients after the introduction of a loading dose of 25 mg/kg total bodyweight (with a maximum of 2500 mg). A loading dose proved to significantly increase the probability of adequate vancomycin concentrations in the first 24 hours, defined as an AUC_{0-24} ≥400 mg*h/L, from 54% to 88% (p=0.0006). In addition, we evaluated whether the increased concentrations after a loading dose would lead to more acute kidney injury (AKI), as this is a possible side effect of vancomycin. We did not find a significantly increased risk of AKI after a loading dose, but we did find a significantly increased risk for patients with adequate vancomycin concentrations: 39% of patients with vancomycin AUC_{0-24} ≥400 mg*h/L developed AKI, compared to 15% of patients with an AUC_{0-24} <400 mg*h/L (p=0.031). So while higher vancomycin concentrations increase the risk of AKI, it remains unclear whether administration of a loading dose poses an additional risk. Our study included an insufficient number of patients to completely rule out an increased risk of AKI after a loading dose. We recommend using a loading dose of vancomycin of 25 mg/kg total bodyweight in critically ill patients and then performing TDM to adjust the following dose in case of excessively high concentrations, i.e. an AUC_{0-24} >600 mg*h/L.

In **chapter 7**, we investigated which dosing regimen offers the highest probability of adequate ceftazidime concentrations in the first 24 hours in critically ill patients admitted to the ICU with a (possible) infection caused by *Pseudomonas aeruginosa*, a pathogen that is only treatable with ceftazidime when using high dose therapy and that can develop resistance to ceftazidime during treatment. After development of a PopPK model for ceftazidime in critically ill patients, we estimated the probability of adequate ceftazidime concentrations in the first 24 hours, defined as a plasma concentration maintained above the minimum inhibitory concentration (MIC) for 100% of a dosing interval (100% T>MIC). The 96 included patients were treated with different dosing schedules: 1 g or 2 g three times daily (n=10), ≤3 g/24h continuous infusion (n=35), 3-5 g/24h continuous infusion (n=11), 5 g/24h continuous infusion (n=25), 6 g/24h

continuous infusion (n=9) or other schedules (n=6). Of the 80 patients that were treated with continuous infusion, 65 (81%) received a 1 g or 2 g loading dose. Assuming an MIC of 8 mg/L, adequate ceftazidime concentrations in the first 24 hours were achieved in 77% of the patients. Administration of a loading dose before continuous infusion resulted in a higher probability of adequate ceftazidime concentrations in the first 24h of treatment: 95% with a loading dose (n=65) compared to 13% without a loading dose (n=15) ($p<0.001$). In Monte Carlo simulations, both use of a 2 g loading dose and use of high-dose (5 g/24h) continuous intravenous infusion proved to strongly increase the probability of adequate ceftazidime concentrations in the first 24 hours: using the standard dose of 3 g/24h continuous intravenous administration without a loading dose, the probability of adequate concentrations in patients with normal renal function was only 11%, while using a high dose of continuous intravenous administration after a loading dose this probability was 98%. We therefore recommend using a loading dose of 2 g followed by high-dose (5-6 g/24h) continuous intravenous administration of ceftazidime. In addition, we investigated whether adequate ceftazidime concentrations reduce the risk of *P. aeruginosa* becoming resistant during treatment. Although development of resistance occurred in 9 patients during treatment, the number of patients in this study in whom development of resistance could be evaluated (n=17) was too small to make a reliable statement on this subject.

In **chapter 8,** we discuss the findings of our studies, the possible applications in clinical practice and the missing information that may be the subject of future studies for further improvement of antibiotic therapy in critically ill patients by pharmacokinetic optimization.


10

Nederlandse samenvatting

Jaarlijks krijgen duizenden kritisch zieke patiënten op Nederlandse Intensive Care (IC) afdelingen ernstige infecties, veroorzaakt door bacteriën. Bij deze infecties is de kans op overlijden beduidend lager als er snel en adequaat behandeld wordt met antibiotica. Daarom wordt er zo snel mogelijk behandeling gestart met antibiotica die de mogelijke verwekkers bestrijden, ook al is op dat moment vaak nog onduidelijk welke bacteriën de infectie veroorzaken. Voorbeelden van antibiotica die in Nederland gebruikt worden bij ernstige infecties zijn gentamicine, vancomycine en ceftazidim.

De effectiviteit van deze antibiotica is afhankelijk van de concentratie die wordt bereikt in de bloedbaan en in de geïnfecteerde lichaamsweefsels. Bij een te lage concentratie is de effectiviteit van het antibioticum verminderd en bestaat bovendien het risico dat de bacterie ongevoelig wordt voor het antibioticum. Bij een te hoge concentratie neemt het risico op bijwerkingen toe. Maar juist bij kritisch zieke IC-patiënten is het moeilijker om een adequate antibioticum concentratie te bereiken. Enerzijds kan de afweerreactie van het lichaam bij ernstige infecties leiden tot een andere verdeling van het antibioticum over het lichaam en tot een versnelde afbraak of uitscheiding van het antibioticum door het lichaam. Anderzijds kan orgaanschade veroorzaakt door de afweerreactie leiden tot vertraagde afbraak of uitscheiding van het antibioticum door het lichaam. Absorptie, verdeling, afbraak en uitscheiding van antibiotica zijn voorbeelden van farmacokinetische processen. Deze processen bepalen hoe snel een geneesmiddel na toediening over het lichaam wordt verdeeld en weer wordt uitgescheiden. Zodoende bepalen ze het tijdsbeloop van de concentratie van het geneesmiddel die na toediening worden behaald in het bloed en de lichaamsweefsels.

Gebruik van de “normale” dosering, d.w.z. de aanbevolen dosering bij patiënten die niet kritisch ziek zijn, kan dus leiden tot te hoge of te lage antibiotica concentraties bij kritisch zieke patiënten omdat de farmacokinetische processen bij de laatste groep verschillend kunnen zijn. Ook tussen verschillende kritisch zieke patiënten worden grote verschillen gezien in farmacokinetische processen, evenals binnen één en dezelfde patiënt tijdens verschillende stadia van de infectie en de daarop volgende afweerreactie.

Er bestaan verschillende strategieën om de kans te vergroten dat snel een adequate antibioticum concentratie wordt bereikt bij kritisch zieke patiënten.

Een eerste strategie is om de standaard startdosering aan te passen bij alle kritisch zieke patiënten, om zo de gevolgen van de veranderde farmacokinetische processen tegen te gaan. Hiervoor is het belangrijk om te weten wat de gemiddelde antibioticaconcentratie in deze patiëntengroep is na toediening van de standaard startdosering. Als deze bijvoorbeeld gemiddeld lager is dan bij patiënten die niet kritisch ziek zijn, dan kan het zinvol zijn om standaard te starten met een hogere dosering.

Een tweede strategie is om de startdosering alleen aan te passen bij patiënten met bepaalde kenmerken die een kleinere kans op het bereiken van adequate antibiotica concentraties voorspellen. Deze voorspellende patiëntenkenmerken worden covariaten genoemd. Voorbeelden van mogelijke covariaten zijn leeftijd, geslacht, lichaamsgewicht, aanwezigheid van chronische ziekten, mate van acuut ziek zijn en nierfunctie. Covariaten kunnen worden vastgesteld met behulp van een zogenaamde populatie-farmacokinetische analyse. Bij zo'n analyse worden ingewikkelde statistische en wiskundige modellen gebruikt om farmacokinetische processen te beschrijven op basis van gemeten geneesmiddelconcentraties in een specifieke groep patiënten, in dit geval antibioticaconcentraties bij kritisch zieke patiënten. Het daaruit voortkomende model heet een populatie farmacokinetisch (PopPK) model. Hiermee wordt het gemiddelde tijdsbeloop van de concentraties beschreven voor deze patiëntengroep na toediening van bepaalde doseringen van het antibioticum. Bovendien worden ook de verschillen in deze concentraties tussen patiënten beschreven, waarbij belangrijke covariaten kunnen worden vastgesteld die voorspellen of een individuele patiënt bij dezelfde dosering hogere of juist lagere concentraties zal hebben dan de gemiddelde patiënt. Deze analyses kunnen worden uitgevoerd met "non-linear mixed-effects modelling" (NONMEM) software.

Een derde strategie is om, na de al dan niet aangepaste startdosis, de volgende dosis aan te passen bij elke individuele patiënt met behulp van "Therapeutic Drug Monitoring" (TDM). Bij TDM wordt een bloedmonster afgenomen waarin de concentratie van het toegediende antibioticum wordt gemeten. Zo kan dus feitelijk worden gemeten of de concentratie adequaat, te laag of te hoog is ten opzichte van een van tevoren vastgestelde doelconcentratie en dus of de dosis respectievelijk gehandhaafd, verhoogd of verlaagd moet worden. De meest precieze schatting van de benodigde dosis voor de individuele patiënt wordt bereikt door een combinatie van TDM en een PopPK model, oftewel door het combineren van de gemeten concentraties, de individuele patiëntenkenmerken

en de informatie over de gemiddelde concentraties en de mate van variatie van de concentraties in de hele patiëntengroep.

Wat “adequate” antibiotica doelconcentraties zijn verschilt van antibioticum tot antibioticum. De beste strategie om snel adequate antibiotica concentraties te bereiken kan hierdoor ook verschillen. In dit proefschrift onderzoeken we bovengenoemde strategieën om de kans op adequate antibiotica concentraties te vergroten bij kritisch zieke patiënten die worden behandeld met gentamicine, vancomycine of ceftazidim. Bij behandeling met gentamicine is het voor effectieve behandeling met name belangrijk dat de maximale concentratie die in de individuele patiënt bereikt wordt vlak na intraveneuze toediening, oftewel de topspiegel, hoog genoeg is. Om bijwerkingen te voorkomen is het daarnaast van belang dat de gentamicine dalspiegel, d.w.z. de concentratie vlak voor de volgende toediening, laag genoeg is. Bij behandeling met vancomycine is het niet de maximale of laagste concentratie maar de gemiddelde concentratie van het antibioticum in de tijd die zowel de effectiviteit als de kans op bijwerkingen bepaalt. Bij behandeling met ceftazidim is het voor de effectiviteit belangrijk dat de concentratie lang genoeg boven een bepaalde minimale waarde blijft.

In **hoofdstuk 2** hebben we onderzocht of bepaalde patiëntenkenmerken een kleinere kans op het bereiken van adequate gentamicine topspiegels voorspellen. Met behulp van een PopPK model voor gentamicine in kritisch zieke patiënten hebben we bekeken welke covariaten van invloed zijn op de topspiegels en dus bruikbaar zijn om de startdosering gentamicine op te baseren, in plaats van dezelfde startdosering voor iedere IC patiënt te gebruiken. Albumine concentraties <15 g/L in bloed bleken het risico op een te lage gentamicine topspiegel sterk te vergroten: bij patiënten met een albumine concentratie <15 g/L was 100% van de piekspiegels te laag, bij patiënten met een albumine concentratie >15 g/L was 44% van de piekspiegels te laag. Waarschijnlijk is een hogere startdosering gentamicine nodig in patiënten met zeer lage albumine concentraties.

Het ontwikkelde popPK model hebben we daarnaast ook gebruikt om te bekijken welke maat voor nierfunctie (de belangrijkste covariaat voor uitscheiding van gentamicine) bij kritisch zieke patiënten het beste de dalspiegel voorspelt, wat van belang is om het risico op bijwerkingen te verminderen. Schattingen van de nierfunctie op basis van bepalingen van de lichaamseigen stof kreatinine in bloed bleken de uitscheiding van gentamicine te overschatten, wat zou kunnen leiden tot het te vroeg geven van een volgende toediening van gentamicine en

daardoor een verhoogd risico op bijwerkingen. Schattingen van de nierfunctie op basis van kreatinine bepalingen in urine bleken een betere voorspeller van de gentamicine dalspiegel en zouden dus de voorkeur hebben boven kreatinine bepalingen in bloed om te bepalen wanneer de volgende gentamicine toediening veilig kan worden gegeven.

In **hoofdstuk 3** hebben we onderzocht of het PopPK model voor gentamicine uit hoofdstuk 2 ook bruikbaar is voor het aanpassen van doseringen bij andere Intensive Care patiënten dan de groep patiënten met wiens gegevens het model ontwikkeld is. Het model bleek bruikbaar voor een nieuwe patiëntengroep van de Intensive Care van het Academisch Medisch Centrum, maar niet bruikbaar voor een patiëntengroep van de Intensive Care van het universiteitsziekenhuis in het Franse Nîmes, omdat het model de concentraties na toediening van gentamicine in deze groep overschatte. Dit illustreert dat men voorzichtig moet zijn met het gebruik van PopPK modellen in andere patiëntengroepen die zijn opgenomen op de IC. We adviseren om dan eerst te testen of het PopPK model de concentraties in de nieuwe patiëntengroep goed kan voorspellen.

In **hoofdstuk 4** hebben we onderzocht of het standaard meten van gentamicine topspiegels na de eerste toediening in het kader van TDM de kans vergroot dat kritisch zieke patiënten na de volgende toediening adequate gentamicine topspiegels hebben. Met behulp van een PopPK model voor gentamicine in kritisch zieke patiënten hebben we topspiegels geschat na de eerste toediening (dus voor TDM) en na volgende giften gebaseerd op TDM. TDM van topspiegels bleek de kans op adequate gentamicine topspiegels iets te vergroten, maar ook na TDM had de helft van de patiënten te hoge of te lage topspiegels, waarschijnlijk door de grote variatie van de farmacokinetische processen binnen individuele patiënten tijdens de verschillende stadia van de infectie en de daarop volgende afweerreactie. Daarnaast hebben we met behulp van computersimulaties bekeken wat het effect zou zijn van een hogere startdosering voor alle IC patiënten op de topspiegel na de eerste gentamicine toediening. Na een gesimuleerde hogere startdosering bleek het percentage patiënten met een te lage gentamicine topspiegel te dalen van 59% naar 36%. TDM bleek na deze hogere dosering geen verdere daling meer op te leveren van het percentage patiënten met een te lage topspiegel. We adviseren daarom om een hogere startdosering te gebruiken dan in deze studie werd gebruikt, maar zijn van mening dat TDM van gentamicine topspiegels toch verstandig kan zijn om extreem hoge of lage topspiegels vast te stellen.

In **hoofdstuk 5** bespreken we de gepubliceerde literatuur over de farmacokinetiek van gentamicine in volwassen patiënten en in groepen patiënten met andere farmacokinetiek, zoals patiënten met overgewicht, kritisch zieke patiënten, kinderen, pasgeborenen, ouderen en patiënten met een slechte nierfunctie die nierfunctievervangende (dialyse) behandeling krijgen. Hierbij beschrijven we de gevolgen van de farmacokinetiek voor optimale dosering en geven startdoseringsadviezen per patiëntengroep.

In **hoofdstuk 6** hebben we onderzocht of het standaard geven van een eenmalige hogere startdosering (een oplaaddosis) vancomycine de kans vergroot dat kritisch zieke patiënten adequate vancomycine concentraties hebben in de eerste 24 uur van de behandeling. Met behulp van een PopPK model voor vancomycine in kritisch zieke patiënten hebben we de gemiddelde concentraties in de eerste 24 uur vergeleken in patiëntengroepen met en zonder oplaaddosis. Een oplaaddosis bleek de kans op adequate vancomycine concentraties in de eerste 24 uur te vergroten van 54% naar 88%. Daarnaast hebben we bekeken of de verhoogde concentraties na een oplaaddosis zouden leiden tot meer acute nierfunctiestoornissen, omdat dit een mogelijke bijwerking van vancomycine is. We vonden geen significant verhoogd risico op acute nierfunctiestoornissen na een oplaaddosis, maar wel een verhoogd risico voor patiënten met een adequate vancomycine concentratie: 39% van de patiënten met een adequate concentratie ontwikkelde acute nierfunctiestoornissen vergeleken met 15% met een te lage concentratie. Dus hoewel hogere vancomycine concentraties het risico op acute nierfunctiestoornissen verhogen, blijft het onduidelijk of het geven van een oplaaddosis een extra risico vormt. Onze studie bevatte te weinig patiënten om een verhoogd risico op acute nierfunctiestoornissen na een oplaaddosis geheel uit te sluiten. We adviseren om een oplaaddosis vancomycine te gebruiken bij kritisch zieke patiënten en vervolgens met behulp van TDM de volgende dosis te verlagen als er een te hoge concentratie vastgesteld wordt.

In **hoofdstuk 7** hebben we onderzocht welk doseringsschema de grootste kans biedt op adequate ceftazidim concentraties in de eerste 24 uur van behandeling met antibiotica bij kritisch zieke patiënten die (mogelijk) een infectie hebben met *Pseudomonas aeruginosa*, een bacterie die relatief ongevoelig is voor ceftazidim en bovendien gemakkelijk nog minder gevoelig kan worden onder behandeling met antibiotica. Met behulp van een PopPK model voor ceftazidim in kritisch zieke patiënten hebben we de kans op adequate ceftazidim concentraties in de eerste 24 uur met verschillende doseringsschema's geschat. Zowel het gebruik van een oplaaddosis als het gebruik van hoog gedoseerde continue intraveneuze

toediening bleek de kans op adequate ceftazidim concentraties in de eerste 24 uur sterk te vergroten: met een standaard dosering continue intraveneuze toediening zonder oplaaddosis was de kans op adequate concentraties bij normale nierfunctie slechts 11%, terwijl dit met hoog gedoseerde continue intraveneuze toediening na een oplaaddosis 98% was. We adviseren daarom om een oplaaddosis te gebruiken, gevolgd door hoog gedoseerde continue intraveneuze toediening van ceftazidim. Daarnaast hebben we bekeken of adequate ceftazidim concentraties het risico verkleinen dat *Pseudomonas aeruginosa* ongevoelig wordt onder behandeling. Maar hoewel *Pseudomonas aeruginosa* regelmatig ongevoelig werd onder behandeling, was het aantal patiënten in deze studie te laag om hier een betrouwbare uitspraak over te doen.

In **hoofdstuk 8** bespreken we de bevindingen van ons onderzoek, de mogelijke toepassingen in de klinische praktijk en de ontbrekende informatie die onderwerp kan zijn van toekomstige studies.

Appendices

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Name PhD student: Caspar Hodiamont
PhD period: 2015 - 2023
Names of PhD supervisor(s) & co-supervisor(s): Ron Mathôt, Menno de Jong, Reinier van Hest, Nicole Juffermans

1. PhD training

	Year	ECTS
General courses		
- AMC Graduate School course Practical Biostatistics	2015	1.4
Specific courses		
- CHDR Introduction course to Population PK and PK/PD modelling with NONMEM	2015	1
Seminars, workshops and master classes		
- ESCMID Postgraduate Technical Workshop "A Statistical Approach to PK/PD Analysis in Practice"	2012	1
- Boerhaave (na)scholingscursus Infectieziekten	2015,2018	1.4
- Weekly research and journal club of the department of microbiology (AMC)	2015-2023	6.4
- Regional "infection evening" (Amsterdam UMC)	2016-2023	0.6
- Monthly NONMEM meeting (AMC)	2013-2020	5.5
Presentations		
- IDSA: Farmacokinetiek van antibiotica op de Intensive Care (oral)	2015	0.5
- ECCMID: Target vancomycin exposure of AUC0-24≥400 mg*h/l is not reached in the majority of critically ill patients after a loading dose of 25 mg/kg vancomycin (poster)	2015	0.5
- ECCMID: Emergence of ceftazidime resistant Pseudomonas aeruginosa during exposure to high concentrations of ceftazidime in vitro and in vivo (poster)	2016	0.5

- ISICEM: Optimization of gentamicin peak concentrations in critically ill patients (poster)	2016	0.5
- ECCMID: Relationship between ceftazidime exposure and development of resistance in critically ill patients with proven Pseudomonas aeruginosa infections (oral)	2019	0.5
- ECCMID: Impact of a vancomycin loading dose on the achievement of target vancomycin exposure in the first 24 hours (poster)	2019	0.5
(Inter)national conferences		
- European Congress of Clinical Microbiology & Infectious Diseases (ECCMID)	2015,2016,2019, 2021,2023	3.7
- International Symposium on Intensive Care and Emergency Medicine (ISICEM)	2016	0.6
- American Society of Microbiology (ASM) Microbe	2016	0.9
- International Society for Human and Animal Mycology (ISHAM) Congress	2018	0.6
- Congress on Trends in Medical Mycology (TIMM)	2021	0.4
- Scientific Spring Meeting Nederlandse Vereniging voor Medische Microbiologie (NVMM)	2021	0.5x
- Infectieziekten Symposium Amsterdam (IDSA)	2015-2021	1.5

2. Teaching

	Year	**ECTS**
Tutoring, Mentoring		
- Dedicated master mentoraat geneeskundestudenten	2014-2016, 2017-2019	3.2
Supervising		
- Master thesis Natalia Lechner “Relationship between ceftazidime exposure and microbiological cure and development of resistance in critically ill patients with proven *Pseudomonas aeruginosa* infections”	2018	2.3

- Bachelor thesis Gajanan Thurairajah "Onderdrukking van resistentievorming in *Pseudomonas aeruginosa* door optimalisatie van doseringsschema's voor ceftazidim en meropenem"	2019	1.1

3. Publications

	Year
Peer reviewed – this thesis	
- Determinants of gentamicin concentrations in critically ill patients: a population pharmacokinetic analysis.	2017
- Therapeutic Drug Monitoring of Gentamicin Peak Concentrations in Critically Ill Patients.	2017
- Predictive performance of a gentamicin population pharmacokinetic model in two western populations of critically ill patients.	2018
- Population Pharmacokinetics and Probability of Target Attainment of Different Dosing Regimens of Ceftazidime in Critically Ill Patients with a Proven or Suspected *Pseudomonas aeruginosa* Infection.	2021
- Impact of a vancomycin loading dose on the achievement of target vancomycin exposure in the first 24 h and on the accompanying risk of nephrotoxicity in critically ill patients.	2021
- Clinical Pharmacokinetics of Gentamicin in Various Patient Populations and Consequences for Optimal Dosing for Gram-Negative Infections: An Updated Review.	2022
Peer reviewed – other	
- Multiple-azole-resistant *Aspergillus fumigatus* osteomyelitis in a patient with chronic granulomatous disease successfully treated with long-term oral posaconazole and surgery.	2009
- *Kytococcus schroeteri* pneumonia in two patients with a hematological malignancy.	2010
- De ziekte van Chagas in Nederland: een schatting van het aantal patiënten.	2011
- Dengue in travellers: applicability of the 1975-1997 and the 2009 WHO classification system of dengue fever.	2012

- Imported leishmaniasis in the Netherlands from 2005 to 2012: epidemiology, diagnostic techniques and sequence-based species typing from 195 patients. 2013
- Pleurodynia caused by an echovirus 1 brought back from the tropics. 2013
- A case of meningoencephalitis by the relapsing fever spirochaete *Borrelia miyamotoi* in Europe. 2013
- Predominant association of *Raoultella* bacteremia with diseases of the biliary tract. 2014
- Performance of Kiestra total laboratory automation combined with MS in clinical microbiology practice. 2014
- Species-directed therapy for leishmaniasis in returning travellers: a comprehensive guide. 2014
- Inadequate vancomycin therapy in term and preterm neonates: a retrospective analysis of trough serum concentrations in relation to minimal inhibitory concentrations. 2014
- Diagnosis and management of aspergillosis in the Netherlands: a national survey. 2016
- Comparison of the PRNT and an immune fluorescence assay in yellow fever vaccinees receiving immunosuppressive medication. 2016
- Development of Antibiotic Resistance during Simulated Treatment of *Pseudomonas aeruginosa* in Chemostats. 2016
- The impact of trimethoprim-sulfamethoxazole as *Pneumocystis jiroveci* pneumonia prophylaxis on the occurrence of asymptomatic bacteriuria and urinary tract infections among renal allograft recipients: a retrospective before-after study. 2016
- Incidence, risk factors, and the impact of allograft pyelonephritis on renal allograft function. 2016
- Population Pharmacokinetics and Dosing Considerations for Gentamicin in Newborns with Suspected or Proven Sepsis Caused by Gram-Negative Bacteria. 2016
- Influenza-Associated Aspergillosis in Critically Ill Patients. 2017
- Optimization of therapy against *Pseudomonas aeruginosa* with ceftazidime and meropenem using chemostats as model for infections. 2017

- Fecal microbiota transplantation against intestinal colonization by extended spectrum beta-lactamase producing *Enterobacteriaceae*: a proof of principle study. 2018
- Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. 2018
- Population Pharmacokinetics of Ganciclovir in Critically Ill Patients. 2020
- Microbiological profile of nosocomial infections following cardiac arrest: Insights from the targeted temperature management (TTM) trial. 2020
- Venous thromboembolism is not a risk factor for the development of bloodstream infections in critically ill COVID-19 patients. 2021
- Population Pharmacokinetics and Dosing Optimization of Ceftazidime in Term Asphyxiated Neonates during Controlled Therapeutic Hypothermia 2023

Professional publications

- Een diepe mycose met mycobacteriële co-infectie aan de onderarm van een veearts - het belang van spiegelbepaling. 2016
- Evaluatie van een nieuwe Nederlandse vancomycine-doseerrichtlijn en populatiefarmacokinetiek van vancomycine bij preterme en a terme neonaten. 2019

List of Publications

This thesis

Hodiamont CJ, Juffermans NP, Bouman CS, de Jong MD, Mathôt RA, van Hest RM. Determinants of gentamicin concentrations in critically ill patients: a population pharmacokinetic analysis. **Int J Antimicrob Agents**. 2017 Feb;49(2):204-211. doi: 10.1016/j.ijantimicag.2016.10.022.

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Dankwoord

"*Gott gibt die Nüsse, aber er knackt sie nicht auf.*" – Johann Wolfgang von Goethe

Velen hebben academische of emotionele steun geboden in het traject dat heeft geleid tot dit proefschrift, bijvoorbeeld als begeleider, onderwijzer, co-auteur, mede-onderzoeker, (oud-)collega, vriend of familie. Een lijst van deze personen zou per definitie tekortschieten. Daarom wil ik bij deze mijn erkentelijkheid uitspreken aan iedereen die op directe of indirecte wijze heeft meegeholpen om de soms harde noten te kraken bij de totstandkoming van deze dissertatie.

Jullie waren onmisbaar. Mijn dank is groot!

Persoonlijk dankwoord

About the author

Caspar Jan Hodiamont (January 24th 1979) was born and raised in Nijmegen, The Netherlands. He started Medical School at the University of Amsterdam (UvA) in 1997 and has not left the Academic Medical Center since. In the final stages of his master study, he earned a scholarship to expand his academic horizon and spent an interlude at the Philosophy Department of the UvA, completing a minor in Political and Social Philosophy and Ethics and following courses in Philosophy of Science, Big History and the History of the Humanities.

Straight from the Philosophy lecture halls, now dressed preferably in black and sporting a beard, Caspar started his clinical internships in 2003. Although fascinated by the intricate workings of the human mind, he was also captivated by the microscopically small and drawn to the simple cause-effect relationship in bacterial infectious diseases: curing the patient by killing the pathogen using targeted antibiotics. After elective clinical internships at the Departments of Psychiatry and Medical Microbiology, he became a resident in clinical microbiology at the AMC in 2005 and subsequently acquired a medical staff position in 2010.

When confronted with a critically ill patient suffering from an ongoing infection with a *Pseudomonas aeruginosa* strain that gradually acquired resistance to every antibiotic that was administered, Caspar became intrigued by the question if optimal exposure to antibiotics could prevent resistance in these circumstances. Following conversations with prof. Ron Mathot and prof. Menno de Jong, a research project was started under the inspiring guidance of dr. Reinier van Hest and prof. dr. Nicole Juffermans focusing on pharmacokinetic dose optimization of antibiotic therapy in critically ill patients, which culminated in the publication of this thesis. They are still working on an answer to the original research question.

Caspar is married to Sarah Camaro and they have two daughters: Quirine and Aurélie. They live in Amsterdam.