Covariates of amikacin disposition in a large pediatric oncology cohort

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What is known about this subject

1. Aminoglycoside antibiotics are frequently used in children with febrile neutropenia.
2. Physiologic changes during development are responsible for age-related differences in amikacin pharmacokinetics (PK) in children.
3. Amikacin PK in children differs *between* disease groups (e.g. burns versus oncology diagnoses).

What this study adds

1. We explored amikacin PK in pediatric oncology patients, including *within*-patient changes across the treatment episodes.
2. Maturation covariates and creatinemia determined amikacin clearance and volume of distribution in a large cohort of pediatric oncology patients, while positive blood culture, oncology diagnosis and nephrotoxic chemotherapy were not retained as significant covariates.
3. The combination of clinical and PK data is useful to feed dosing software programs in the future, to improve drug exposure in special pediatric populations.

Abstract

Objective: Amikacin pharmacokinetics (PK) in children displays large variability due to maturational and disease-related covariates. The objective was to explore amikacin PK in a large pediatric oncology cohort, taking into account *within*-patient changes.

Methods: Clinical data and amikacin therapeutic drug monitoring (TDM) observations were collected retrospectively from children with oncology diagnosis receiving amikacin during febrile neutropenia. Individual amikacin PK parameters were calculated using a one-compartment model with instantaneous input and first-order output. To explore covariates of clearance (Cl) and volume of distribution (Vd), linear mixed models were used, modelling a random effect for patient to account for clustering due to repeated measurements.

Results: Based on 188 amikacin treatment episodes in 114 patients, median (interquartile range) amikacin Cl was 1.37 (1.05; 2.46) L/h and Vd 7.98 (5.66; 12.73) L. Height and creatinemia were significant covariates for Cl (marginal R^2 71.1%), while weight, height and creatinemia determined Vd (marginal R^2 59.5%).

Conclusions: We described extensive variability of amikacin PK in a large cohort of pediatric oncology patients, including *within*-patient changes across treatment episodes. Maturational covariates and creatinemia determined amikacin Cl and Vd, while primary non-maturational covariates were not significant. Our observations, based on combined clinical and PK data in children with oncology diagnoses, can be useful to feed dosing software programs to improve drug exposure in special populations.

Key words: amikacin – pharmacokinetics - febrile neutropenia - children

Running title: Amikacin disposition in pediatric oncology patients

Introduction

Aminoglycosides are one of the oldest antibiotic classes, who have played a major role in antimicrobial therapy since their discovery in the 1940s. It are hydrophilic compounds displaying a concentration dependent efficacy, while the trough level is associated with toxicity. Within this class, amikacin has the broadest *in vitro* and *in vivo* activity against most aerobic gram-negative bacteria. ‘Once daily-dosing’ or ‘extended interval dosing’ has been proven to be superior in neonates, children and adults, compared to multiple daily dosing [1, 2, 3]. This specific approach can be applied due to concentration-dependent bactericidal activity with therapeutic peak concentration; a post-antibiotic effect which allows continued efficacy even when serum concentrations are below expected minimal inhibitory concentration (MIC); a decreased risk of adaptive resistance; and reduced renal accumulation due to achievement of low trough concentrations [4, 5, 6]. Physiologic changes during development are responsible for age-related differences in amikacin disposition in children. A decrease in the body-water content with age affects the apparent volume of distribution (Vd), while age-dependent renal maturation determines amikacin clearance (Cl). Consequently, these maturational covariates (like age, weight, renal function...) result in large inter- and intra-individual amikacin pharmacokinetic (PK) variability in children requiring optimized dosing regimens [2, 7, 8]. In addition, non-maturational covariates (like disease, co-medication, treatment) can further contribute to this PK variability, especially in high-risk pediatric populations (e.g. critically ill, febrile neutropenia, poly-pharmacy) [9]. The impact of disease condition on amikacin disposition has recently been documented in children with burn injuries compared to oncology patients [10]. Liu *et al* demonstrated that if other covariates (i.e. maturational covariates and creatinine clearance) remain the same, children with burn injuries exhibited higher central volume (+17%) and Cl (+55%) compared to oncology patients [10]. Besides these *between* group differences in amikacin PK parameters, variability in amikacin disposition *within* the

pediatric oncology subgroup also remains high. In this study we aim to explore which covariates mainly determine amikacin PK in a large pediatric oncology group, taking into account 1) both maturational and non-maturational covariates, and 2) *within-patient* alterations of these covariates.

Methods

Study population

Clinical data and amikacin therapeutic drug monitoring (TDM) observations were collected retrospectively from patient files of children with an oncologic diagnosis, admitted to the University Hospitals Leuven, Belgium, between January 2010 and June 2013, due to febrile neutropenia. This dataset in part overlays with Liu *et al* [10]. However, instead of only the first febrile neutropenia episode, now all episodes of individual patients are included, and data of 2 additional patients could be retrieved. Amikacin, co-administered with ceftazidim, was the empirical treatment for febrile neutropenia. The ethical board of the hospital approved the study (internal number S55690).

The following covariates were collected: sex, oncologic diagnosis (leukemia or solid tumor), induction phase chemotherapy (yes/no), previous administration of nephrotoxic chemotherapeutic drugs (i.e. carboplatin, cisplatin or ifosfamide), age (months), height (cm), weight (kg), creatinemia (mg/dL), albuminemia (g/L), c-reactive protein (CRP, mg/L), blood culture at the start of amikacin therapy (positive/negative) and in case of positive blood culture, type of organism. Biochemical parameters were included if available in 24 hours before or after the moment of TDM. Blood cultures were observed at the start of each treatment episode.

Drug administration

Amikacin was infused intravenously over 30 minutes. All patients were treated with the same dosing regimen i.e. 20 mg/kg once daily. Early exposure was evaluated, using the first trough ($C_{\min}$, measured prior to the second dose) and peak observation ($C_{\max 30}$, concentration 30 minutes after finalization of the second amikacin administration, or 1h after start of this administration) of each amikacin treatment episode.

Amikacin assay

Amikacin plasma concentrations were measured with fluorescence polarization immunoassay (Abbott TDx, Abbott Park, IL, USA). The assay was linear from 0.8 to 50.0 mg/L with intra-day and inter-day variability less than 7.6%. This analytical method was used until 31 May 2012, after which a kinetic interaction of microparticles in solution (KIMS) immunoassay (Roche/Hitachi Cobas c systems, Roche Diagnostics GmbH, Mannheim, Germany) was used for amikacin quantification with a coefficient of variation less than 5%. To avoid censoring of values below the lower limit of quantification (LLOQ 0.8 mg/L), these concentrations were replaced by LLOQ/2 (i.e. 0.4 mg/L) as suggested in literature [11].

Biochemical assay

Creatinine and albumin in plasma were measured on Roche Modular P before April 2012 and with Roche Cobas c702 from April 2012 (Roche Diagnostics, Mannheim, Germany). All creatinine measurements were isotope dilution mass spectrometry (IDMS) traceable. Creatinine was measured enzymatically in patients <5 years and based on modified Jaffé in patients ≥ 5 years until September 2012. From October 2012, creatinine was measured enzymatically in all patients. Albumin was measured using bromocresol green.

Pharmacokinetic parameters

Individual amikacin PK parameters were calculated based on C_{min} and $C_{max'30}$, using a one-compartment model with instantaneous input and first-order output. $C_{max'30}$ (concentration 30 minutes after finalization of the first amikacin administration, or 1h after start of this administration) was calculated as $C_{max30} - C_{min}$. Logarithm (Log) of $C_{max'30}$ and C_{min} were used to calculate the slope of the individual trendline (equation 1)

$$Slope = (Log_{C_{max'30}} - Log_{C_{min}}) / (t_{C_{max'30}} - t_{C_{min}}) \quad (\text{equation 1})$$

with $t_{C_{max'30}}$ and $t_{C_{min}}$ the time (h) corresponding to the respective concentrations at 1h and 24h after start of the first administration. Subsequently, the elimination rate constant (K_E) and elimination half-life ($T_{1/2}$, h) could be determined using equation 2 and equation 3 respectively.

$$Slope = -K_E / 2.303 \quad (\text{equation 2})$$

$$T_{1/2} = 0.693 / K_E \quad (\text{equation 3})$$

C_{max0} could be derived from equation 4

$$Log_{C_{max'30}} = Log_{C_{max0}} - [(K_E \cdot t) / 2.303] \quad (\text{equation 4})$$

With C_{max0} plasma amikacin concentration immediately after intravenous administration and $t = 1h$ after start of administration. Equation 4 represents a straight line indicating that the semi-logarithmic plot of Log_C versus time is linear with $Log_{C_{max0}}$ as Y-intercept. Based on the dose administered and C_{max0} , volume of distribution (V_d , L), and subsequently Clearance (Cl , L/h) can be calculated using equations 5 and 6.

$$V_d = Dose / C_{max0} \quad (\text{equation 5})$$

$$Cl = V_d \cdot K_E \quad (\text{equation 6})$$

Statistical analyses

Continuous data are reported as median and interquartile range (IQR) or mean (SD), categorical data as incidence and percentage. To explore the effect of covariates on Cl and Vd, linear mixed models were used, modelling a random effect for patient to account for clustering due to repeated measurements. A backward selection procedure was applied for multivariable model construction, with a 5% significance level for covariates to be removed from the model. Non-linear (quadratic) trends for continuous covariates were considered in the model building, if significant in univariable analysis. Given the presence of repeated measurements in the data, a classical R^2 value could not be determined. As an alternative, we estimated the marginal R^2 , proposed by Nakagawa and Schielzeth for such clustered data settings, providing the proportion of variance explained by the fixed factors [12]. Based on the multivariable model, predicted Cl and Vd can be obtained as the weighted sum of the covariate measurements, with the parameter estimates as weights. The effect estimate is considered as the change in Cl or Vd for the indicated increase of the predictor level.

Analyses have been performed using SAS software (version 9.4, SAS System for Windows) and MedCalc version 19.1.5 (MedCalc Software, Ostend, Belgium). A p-value <0.05 was considered statistically significant.

Results

Between January 2010 and June 2013, 780 amikacin TDM results were available. Observations with missing TDM, TDM after sampling error and TDM collected later in the treatment episode (i.e. follow-up TDM) were excluded. From this dataset, treatment episodes for which both the first peak and trough, as well as dosing were available, were selected. Observations in non-oncologic cases were excluded. Finally, first peak and trough of 188 amikacin treatment episodes, collected in 114 patients were retained for further analysis. The flowchart of included

observations is presented in **Figure 1**. In total, n=38/114 patients (33%) had ≥ 2 amikacin treatment episodes (n=16 patients with 2 episodes, n=16 with 3, n=3 with 4, n=1 with 5, n=1 with 6 and n=1 with 9 episodes), counting for 112/188 episodes. Overall 105 trough levels were $< \text{LLOQ}$ and replaced by 0.4 mg/L.

Descriptive statistics

Median (IQR) age of the included treatment episodes was 80 (40.50-151.50) months, and median weight 21.15 (14.30-45.45) kg. **Table 1** summarizes the clinical and biochemical characteristics. Twenty-five blood cultures were positive, 153 were negative and 10 unknown. The top 3 of isolated pathogens were *Staphylococcus epidermidis* (n=8), *Escherichia coli* (n=5) and *Staphylococcus hominis* (n=4).

Pharmacokinetic parameters

Median observed amikacin trough level ($C_{\min}$) was 0.40 (0.40-1.15) and peak ($C_{\max 30}$) 48.65 (38.40-60.60) mg/L. Median amikacin Cl was 1.37 (1.05-2.46) L/h with half-life ($T_{1/2}$) 3.56 (3.3-4.33) h, and Vd 7.98 (5.66-12.73) L. To explore the impact of (non-)maturational covariates on Cl and Vd, first univariable analyses were performed. For Cl, age, weight, height, creatinemia and CRP were significant in univariable analyses. Blood culture (positive vs negative) and oncologic diagnosis (solid tumor vs leukemia) were no significant covariates of amikacin Cl (**Table 2**). In a final multivariable model, height and creatinine remained significant covariates of Cl, with a marginal R^2 of 71.1% (**Table 3a**). In **Table 3b**, the effects per covariate are presented. Due to the quadratic effect, the change in Cl for a 1 cm increase in height varies over the range of height. This means that the change in Cl is e.g. different when height goes from 100 to 101 cm compared to 120 to 121 cm. The nonlinear trend for Cl by height and the linear trend for Cl by creatinine are presented in **Figure 2a** and **2b** respectively.

The same covariates, significant in univariate analysis for Cl, were retained for Vd (**Table 4**). In a final multivariable model, weight, height and creatinine remained significant covariates of Vd, with a marginal R² of 59.5% (**Table 5**). The trends for Vd by height and creatinine are presented in **Figure 3a** and **3b** respectively.

Discussion

In a large cohort of pediatric oncology patients, we explored covariates of amikacin PK. Height and creatinemia were significant covariates of Cl, and weight, height and creatinemia determined amikacin Vd. The strengths of this analysis are the extensive cohort, with availability of combined (non-)maturational clinical and PK data, and the fact that *within-patient* changes are taken into account. Since 112/188 episodes originated from patients with ≥ 2 amikacin courses, these observations count for a substantial part (almost 60%) of the dataset. Amikacin is frequently used in critically ill children. Our analysis confirms the substantial remaining PK variability. As a consequence, it is recommended to continue TDM assessments in special populations. Recently, amikacin disposition in pediatric subgroups e.g. neonates with asphyxia and hypothermia [13], children with burns [14], cystic fibrosis [15] and cancer [16] have been reported. Implementation of PK covariates in optimized dosing regimens, can improve safe and effective amikacin therapy in these populations. The maturational covariate height was retained on Cl instead of weight, which is more often retained in earlier reports. In a recent review, Illamola *et al* summarized the most common significant determinants of amikacin PK in parametric population PK analyses in neonates and children [7]. In the included (non-oncology) studies (n=8), 6 involved neonates up to 3 months, 2 investigated children >2 years (burn/ non-burn group). Current BW (cBW) was a Cl covariate in 7/8 studies, followed by age-related covariates and predictors of glomerular filtration rate (GFR) as most important

Cl covariates in the neonatal studies. In addition, cBW was found as covariate for Vd in all studies. Also in a recent study of n=67 children with (suspected) Gram-negative infection cBW was included as only covariate for both Cl and Vd in an amikacin PK/PD model [17]. In our cohort, exclusively containing oncology children, height was a more powerful predictor of Cl. This might be related to the fact that weight displays larger *within*-patient fluctuations in oncology patients, compared to height. To further explore this, weight and height data of the 38 cases with multiple treatment episodes were selected. Mean (SD) percentage (%) difference between first and last value, as well as maximal difference versus first value for weight were 3.658 (11.179) and 3.866 (11.488)%, while 0.868 (2.178) and 0.854 (2.273)% for height, respectively. Furthermore, additional analyses of Cl, first expressed by L/h.BSA, (BSA=body surface area) were performed. Both height and weight were competing variables for inclusion in this model, of which the model building procedure selected height, in addition to creatinine (**Table S1**). Multivariable analysis of Cl, expressed in L/kg/h revealed only creatinine as significant covariate (**Table S2**). Overall, these additional explorations did not reveal new predictors. Since height did not substantially change within an individual during the study, amikacin Cl variability in our cohort seems mainly attributed to variation in creatinemia. Mean (SD) % difference between first and last value, and maximal difference versus first value for creatinine were 24.026 (60.030) and 31.670 (9.729)% respectively, indicating large intra-patient creatinine alterations. Creatinemia is a ‘mixed covariate’, reflecting a combined effect of maturation and non-maturational factors affecting renal function like disease, co-medication or treatment modalities.

Blood culture, CRP, oncology diagnosis and nephrotoxic chemotherapy were also explored as specific non-maturational predictors. Although CRP was significant in univariate analysis of Cl, CRP nor blood culture were retained in the final multivariate selection. Theoretically, antibiotic Cl during sepsis can increase or decrease depending on renal function [18]. In

addition, increased Vd due to sepsis-induced third space losses, fluid resuscitation and/or altered protein binding affects Vd of hydrophilic compounds. This is even more pronounced in burn patients with sepsis [19]. Oncology diagnosis was not significant in our analysis. In contrast, in a dataset including 207 adults with hematological malignancies, cBW and renal function, but also acute myeloblastic leukemia (amikacin Cl +20%) and hypoalbuminemia (amikacin Vd +30.4%) were found as most important covariates of amikacin disposition [20].

Amikacin Cl in our study is slightly higher compared to general ward and ICU children [mean Cl 1.78 (median 1.37) vs 1.2 L/h] [17], and comparable to critically ill children with normal renal function [mean Cl 0.07 (median 0.06) vs 0.068 L/h/kg] respectively [21]. This is in line with findings in adults with hematological and solid malignancies, in whom increased aminoglycoside Cl and Vd are reported earlier [22, 23, 24, 25]. As summarized by Hartman *et al*, critically ill children generally show a higher Cl and larger Vd for antibiotics than healthy children and critically ill adults, resulting in a failure to achieve target concentrations for many antibiotics, including amikacin [26]. In contrast to renal dysfunction, hemodynamic changes during critical illness may result in increased renal clearance, known as augmented renal clearance (ARC) [27]. This is interesting, since amikacin is eliminated completely by glomerular filtration. Higher Cl during critical illness (e.g. sepsis) is partly attributed to this phenomenon, with ARC reported in up to 67% of critically ill children [28]. In children with cancer, ‘glomerular hyperfiltration’ is a recently recognized, short-lived phenomenon, present in >40% of patients at diagnosis and during initial chemotherapy cycles [29]. The mechanism is not completely understood, but seems related to tumor volume with subsequent cell breakdown [30]. In addition, a hypermetabolic state is hypothesized to contribute to this hyperfiltration pathophysiology in children with cancer [29]. This might explain increased Cl of hydrophilic compounds in febrile neutropenia. For vancomycin, Hirai *et al* documented that

febrile neutropenia indirectly increased Cl in children, due to this elevated GFR [31]. Consequently, increased Cl warrants higher dosing to achieve predefined targets. In a previous analysis of our group, simulations for children with cancer indeed indicated that higher amikacin doses than currently used are needed to achieve optimal peak and trough concentrations [10].

Our study has limitations. First, it concerns a retrospective analysis which only explored ‘early’ amikacin exposure, using an individual PK approach. Second, a 1-compartment model was selected. Also for other aminoglycosides in pediatric neutropenic fever, individual PK calculations using a 1-compartment model have been used [32]. For amikacin, both 1- and 2-compartment models have been published in neonates and/or children [7, 17]. The a priori selection of a 1-compartment approach, is a limitation based on the pragmatic study design as TDM (peak/trough) observations as collected during clinical care were used. With 2 TDM samples per treatment episode, it is not feasible to estimate 2- or multiple compartment models.

As a future perspective, pooling of available amikacin observations in pediatric oncology cohorts might help to better understand PK determinants, and to improve dosing in this population. In addition, further exploration of PD aspects e.g. adaptive resistance (AR) during an amikacin treatment episode using *in vivo* MIC results, is needed. Alhadab *et al* developed an amikacin population PK model of pediatric oncology patients (n=34) [16]. An AR(PD) model of *Pseudomonas aeruginosa* from available *in vitro* time-kill curve data was combined with the PK model. Simulations based on this PK-ARPD approach suggested twice-daily dosing (45 mg/kg BID) for safe and effective therapy, while limiting bacterial resistance for this pathogen [16]. This type of analysis is important since dynamic evolution of bacterial growth and killing need to be considered. Especially, since mortality of *P.aeruginosa*

bacteremia in this population remains constant last 20-30 years [33]. Recently, 30-day mortality of *P. aeruginosa* bacteremia in children with neutropenic fever was 38.9%, and in 36.1% of bacteremia a multi-drug resistance strain was identified [33]. However, susceptibility of the isolated strains for amikacin was 100%, compared to 67.6% for piperacillin/tazobactam and 72.2% for meropenem. This illustrates the potential importance of aminoglycosides in neutropenic fever, usually as part of empiric combination therapy.

Conclusion

We described extensive variability of amikacin PK in a very large cohort of pediatric oncology patients with febrile neutropenia, taking into account *within*-patient changes across amikacin treatment episodes. Maturational covariates and creatinemia determined amikacin Cl and Vd, while primary non-maturational covariates were not significant. Our observations, based on combined clinical and PK data in children with an oncology diagnosis, are useful to feed dosing software programs to improve drug exposure in special populations. To achieve this, multidisciplinary collaboration between clinicians, microbiologists, pharmacologists and pharmacists is important [34]. Besides exploration of PK covariates, integrated PK/PD analyses with prospective *in vivo* MIC data over time, are useful to gain additional knowledge in clinical evolution of amikacin PD and to further improve amikacin exposure.

Table and Figure legends

Table 1: Clinical and biochemical characteristics of the included observations.

Table 2: Univariable analyses of (non-)maturational covariates of clearance (Cl, L/h)

Table 3: Table 3a presents the final multivariable model for clearance (Cl, L/h) resulting from a backward selection procedure; i.e. the selected covariates with their parameter estimates and significance. Table 3b presents the covariate effects with 95% confidence intervals. Given that height follows a nonlinear trend, its effect on outcome is not constant over time, hence the effect is estimated at 3 different heights (i.e. percentile p25-50-75 of the study population, presented as rounded values 100-120-150 cm).

Table 4: Univariable analyses of (non-)maturational covariates of volume of distribution (Vd, L).

Table 5: The final multivariable model for volume of distribution (Vd, L) resulting from a backward selection procedure; i.e. the selected covariates with their parameter estimates and significance as well as the covariate effects with 95% confidence intervals.

Supplementary Table S1: The multivariable model for clearance (Cl, L/h.BSA) resulting from a backward selection procedure; i.e. the selected covariates with their parameter estimates and significance as well as the covariate effects with 95% confidence intervals (BSA= Body Surface Area).

Supplementary Table S2: a) presents the multivariable model for clearance (Cl, L/kg/h) resulting from a backward selection procedure; i.e. the selected covariates with their parameter estimates and significance. b) Presents the covariate effects with 95% confidence intervals. Given that creatinemia follows a nonlinear trend, its effect on outcome is not constant over time, hence the effect is estimated at 3 different creatinine values (i.e. percentile p25-50-75 of the study population, presented as rounded values 0.3-0.5-0.7 mg/dL).

Figure 1: Flowchart of included amikacin therapeutic drug monitoring (TDM) results and amikacin treatment episodes.

Figure 2: The nonlinear trend (+ 95% confidence interval in dashed lines) for amikacin clearance (Cl, L/h) by height, for median creatinine of the entire dataset, is presented in Figure 3a. The linear trend (+ 95% CI in dashed lines) for Cl by creatinine, for median height of the entire dataset, is presented in Figure 3b. Within the multivariable model, Cl is expressed as $Cl (L/h) = 1.1968 - 0.0179 * height + 0.0002 * height * height - 1.1032 * creatinine$ (with height in cm, creatinine in mg/dL).

Figure 3: Graphs presenting the linear trends for volume of distribution (Vd, L) by height, for median creatinine and weight (Figure 5a), and by creatinine, for median height and weight (Figure 5b). Medians are calculated based on the entire dataset. In the multivariable model, Vd is expressed as $Vd (L) = -3.5156 + 0.0936 * weight + 0.1041 * height - 7.0313 * creatinine$ (with weight in kg, height in cm, creatinine in mg/dL).

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Conflict of interest

The authors have no conflict of interest to declare.

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Figure 1

Figure 2: The nonlinear trend (+ 95% confidence interval in dashed lines) for amikacin clearance (Cl, L/h) by height, for median creatinine of the entire dataset, is presented in Figure 2a. The linear trend (+ 95% CI in dashed lines) for Cl by creatinine, for median height of the entire dataset, is presented in Figure 2b. In the multivariable model, Cl is expressed as $Cl (L/h) = 1.1968 - 0.0179 * height + 0.0002 * height*height - 1.1032 * creatinine$ (with height in cm, creatinine in mg/dL).

Figure 2a

Figure 2b

Figure 3: Graphs presenting the linear trends for volume of distribution (Vd, L) by height, for median creatinine and weight (Figure 3a), and by creatinine, for median height and weight (Figure 3b). Medians are calculated based on the entire dataset. In the multivariable model, Vd is expressed as $Vd (L) = -3.5156 + 0.0936 * \text{weight} + 0.1041 * \text{height} - 7.0313 * \text{creatinine}$ (with weight in kg, height in cm, creatinine in mg/dL).

Figure 3a

Figure 3b

Table 1: Clinical and biochemical characteristics of the included observations.

Continuous characteristic	Median	IQR
Age (months)	80.00	40.50; 151.50
Height (cm)	118.75	100.00; 156.65
Weight (kg)	21.15	14.30; 45.45
Creatinemia (mg/dL) ^a	0.31	0.24; 0.49
Albuminemia (g/L) ^b	36.70	33.00; 39.30
CRP (mg/L)	73.80	33.25; 149.15
Amikacin dose (mg/kg)	20.00	19.45; 20.52
Dichotomous characteristic	Incidence	Percentage (%)
Sex (male)	100/188	53.19
(female)	88/188	46.81
Diagnosis (leukemia)	113/188	60.11
(solid tumor)	75/188	39.89
Induction phase (yes)	23/188	12.23
(no)	165/188	87.77
Cisplatinum (yes)	7/188	3.72
(no)	181/188	96.28
Carboplatinum (yes)	15/188	7.98
(no)	173/188	92.02
Ifosfamide (yes)	46/188	24.47
(no)	142/188	75.53
Blood culture ^c (positive)	25/178	14.04
(negative)	153/178	85.96

^a creatinemia available in 187/188 cases; ^b albuminemia available in 182/188 cases; ^c blood culture data unknown in 10/188 cases. CRP: C-reactive protein; IQR: interquartile range.

Table 2: Univariable analyses of (non-)maturational covariates of clearance (Cl, L/h)

Covariate	Test	Estimate (95% CI)	P-value	N obs.
Age	+1 month	0.01354 (0.01194;0.01514)	<0.0001*	188
Weight	+1 kg	0.04685 (0.04172;0.05199)	<0.0001*	188
Height	+1 cm	0.02613 (0.02335;0.02892)	<0.0001*	188
Height	Quadratic trend		0.0003*	188
Albuminemia	+1 g/l	-0.0006 (-0.0274;0.02609)	0.9626	182
Creatinemia	+0.1 mg/dl	0.17576 (0.10310;0.24842)	<0.0001*	187
Creatinemia	Quadratic trend		0.0105*	187
CRP	+1 mg/l	0.00150 (0.00014;0.00286)	0.0306*	188
CRP	Quadratic trend		0.0130*	188
Carboplatinum	Yes vs no	-0.0117 (-0.6035;0.58018)	0.9688	188
Cisplatinum	Yes vs no	-0.4083 (-1.340;0.52303)	0.3852	188
Diagnose	Solid tumor vs leukemia	0.32424 (-0.0551;0.70358)	0.0927	188
Sex	Female vs male	-0.2123 (-0.5893;0.16470)	0.2655	188
Blood culture	Positive vs negative	-0.2217 (-0.6157;0.17223)	0.2654	178
Ifosfamide	Yes vs no	0.32358 (-0.1146;0.76180)	0.1454	188
Induction phase	Yes vs no	0.00393 (-0.3779;0.38576)	0.9837	188

CI: confidence interval; CRP: C-reactive protein. For continuous covariates the estimate provided is the slope (change in outcome for 1-unit increase in predictor), for dichotomous covariates the estimate provided is the difference [$>$ ($<$) 0 means higher (lower) outcome level in the first category]. * P-values <0.05 were considered significant.

Table 3a: Table 3a presents the final multivariable model for clearance (CL, L/h) resulting from a backward selection procedure; i.e. the selected covariates with their parameter estimates and significance.

Covariates	Parameter estimate	SE	P-value	N obs.
Intercept	1.1968	0.6129	0.0533	187
Height	-0.0179	0.01017	0.0827	.
Height*Height	0.0002	0.000041	<0.0001	.
Creatinemia	-1.1032	0.3132	0.0008	.

SE: standard error.

Table 3b: Table 3b presents the covariate effects with 95% confidence intervals. Given that height follows a nonlinear trend, its effect on outcome is not constant over time, hence the effect is estimated at 3 different heights (i.e. percentile p25-50-75 of the study population, presented as rounded values 100-120-150 cm).

Covariate	Test	Effect estimate (95% CI)	P-value
Height 100 cm	+1 cm	0.0212 (0.0163;0.0261)	<0.0001
Height 120 cm	+1 cm	0.0290 (0.0255;0.0326)	<0.0001
Height 150 cm	+1 cm	0.0407 (0.0347;0.0467)	<0.0001
Creatinemia	+0.1 mg/dL	-0.1103 (-0.1728;-0.0479)	0.0008

CI: confidence interval. The effect estimate is the change in CL (L/h) for the indicated increase of the predictor level.

Table 4: Univariable analyses of (non-)maturational covariates of volume of distribution (Vd, L).

Covariate	Test	Estimate (95% CI)	P-value	N obs.
Age	+1 month	0.06272 (0.05283;0.07261)	<0.0001*	188
Weight	+1 kg	0.21191 (0.17830;0.24552)	<0.0001*	188
Weight	Quadratic trend		0.0487*	188
Height	+1 cm	0.12316 (0.10574;0.14059)	<0.0001*	188
Albumin	+1 g/l	-0.0378 (-0.1771;0.10155)	0.5902	182
Creatinemia	+0.1 mg/dl	0.59499 (0.20376;0.98621)	0.0034*	187
Creatinemia	Quadratic trend		0.0207*	187
CRP	+1 mg/l	0.00706 (0.00000;0.01413)	0.0499*	188
CRP	Quadratic trend		0.0451*	188
Carboplatinum	Yes vs no	-0.2230 (-3.325;2.8793)	0.8865	188
Cisplatinum	Yes vs no	-2.316 (-7.214;2.5829)	0.3493	188
Diagnose	Solid tumor vs leukemia	0.93094 (-1.083;2.9452)	0.3601	188
Gender	Female vs male	-1.197 (-3.179;.78520)	0.2327	188
Blood culture	Positive vs negative	-1.541 (-3.587;.50453)	0.1374	178
Ifosfamide	Yes vs no	1.8253 (-.4768;4.1273)	0.1184	188
Induction phase	Yes vs no	0.20673 (-1.774;2.1871)	0.8358	188

CI: confidence interval; CRP: C-reactive protein. For continuous covariates the estimate provided is the slope (change in outcome for 1-unit increase in predictor), for dichotomous covariates the estimate provided is the difference [$>$ ($<$) 0 means higher (lower) outcome level in the first category]. * P-values <0.05 were considered significant.

Table 5: The final multivariable model for volume of distribution (Vd, L) resulting from a backward selection procedure; i.e. the selected covariates with their parameter estimates and significance as well as the covariate effects with 95% confidence intervals.

Covariate	Parameter estimate	SE	Test	Effect estimate (95% CI)	P-value	N obs.
Intercept	-3.5156	1.8479			0.0597	187
Weight	0.0936	0.04336	+ 1 kg	0.0936 (0.0071;0.1800)	0.0344	.
Height	0.1041	0.02368	+ 1 cm	0.1041 (0.0569;0.1513)	<.0001	.
Creatinemia	-7.0313	1.9118	+ 0.1 mg/dl	-.7031 (-1.084;-.3218)	0.0005	.

SE: standard error. The effect estimate is the change in Vd (L) for the indicated increase of the predictor level.

Table S1: The multivariable model for clearance (Cl, L/h.BSA) resulting from a backward selection procedure; i.e. the selected covariates with their parameter estimates and significance as well as the covariate effects with 95% confidence intervals.

Covariate	Parameter estimate	SE	Test	Effect estimate (95% CI)	P-value	N obs.
Intercept	1.2241	0.1656			<0.0001	187
Height	0.0075	0.0017	+ 1 cm	0.0075 (0.0041;0.0109)	<0.0001	.
Creatinemia	-1.0520	0.2836	+ 0.1 mg/dL	-0.1052 (-.1618;-0.0486)	0.0004	.

SE: standard error. Predicted Cl (L/h.BSA) is the weighted sum of covariate measurements, with parameter estimates as weights

The effect estimate is the change in Cl (L/h.BSA) for indicated increase of the predictor level. A p-value <0.05 is considered statistically significant.

Table S2: a) presents the multivariable model for clearance (CL, L/kg/h) resulting from a backward selection procedure; i.e. the selected covariates with their parameter estimates and significance. **b)** Presents the covariate effects with 95% confidence intervals. Given that creatinemia follows a nonlinear trend, its effect on outcome is not constant over time, hence the effect is estimated at 3 different creatinine values (i.e. percentile p25-50-75 of the study population, presented as rounded values 0.3-0.5-0.7 mg/dL).

a)

Covariate	Parameter estimate	SE	P-value	N obs.
Intercept	0.0991	0.0065	<0.0001	187
Creatinemia	-0.1228	0.0296	<0.0001	.
Creatinemia*Creatinemia	0.0748	0.0288	0.0114	.

SE: standard error. Predicted CL (L/kg/h) is the weighted sum of variable measurements, with parameter estimates as weights. A P-value <0.05 is considered statistically significant.

b)

Covariate	test	Effect estimate (95% CI)	P-value
Creatinemia 0.3mg/dL	+0.1 mg/dL	-0.0070 (-0.0094;-0.0047)	<0.0001
Creatinemia 0.5mg/dL	+0.1 mg/dL	-0.0041 (-0.0058;-0.0023)	<0.0001
Creatinemia 0.7mg/dL	+0.1 mg/dL	-0.0011 (-0.0044;0.0023)	0.5275

CI: confidence interval. The effect estimate is the change in CL (L/kg/h) for indicated increase of the predictor level. Creatinemia: due to the quadratic effect, the change in CL (L/kg/h) for a 0.1mg/dL increase varies over the range of creatinemia. e.g. the change in CL (L/kg/h) is different when creatinine goes from 0.3mg/dL to 0.4mg/dL compared to 0.5mg/dL to 0.6mg/dL. A P-value <0.05 is considered statistically significant.