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A Population Pharmacokinetic Modeling Approach to Determine the Efficacy of Intravenous Amikacin in Children with Cystic Fibrosis

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Background: In children with cystic fibrosis (CF), the currently recommended amikacin dose ranges between 30 and 35 mg/kg/d; however, data supporting this dosing efficacy are lacking. In this article, the objectives were to develop a nonparametric pharmacokinetic population model for amikacin in children with CF and investigate the efficacy and toxicity at different dose rates for distinct minimum inhibitory concentration (MIC) clinical breakpoints using Monte Carlo simulations.

Methods: Data from 94 children with CF (613 serum concentrations) from the Bordeaux University Hospital's CF-centre were analyzed. After determination of nonparametric pharmacokinetic population model parameters and associated influent covariates in Pmetrics, 1000 Monte Carlo simulations were performed for 7 different dose rates between 30 and 60 mg/kg/d, to predict the probability of obtaining peak serum amikacin $\geq 10 \times$ MIC and trough level ≤ 2.5 mg/L, for MIC values between 1 and 16 mg/L.

Results: The median (min–max) age and weight were 10 (0.3–17) years and 29 (6–71) kg, respectively, with only 2 children younger than 1 year of age. Body weight and creatinine clearance significantly impacted the amikacin volume of distribution and clearance. The mean relative bias/root mean squared error between observed and individual predicted concentrations was $-0.68\%/8.1\%$. Monte Carlo simulations showed that for sensitive bacteria with MICs ≤ 4 , 30 mg/kg/d was most appropriate for a 100% success rate; for bacteria with MICs ≥ 8 [eg, *Pseudomonas aeruginosa* (MIC_{amikacin} = 8)], a dose of at least 40 mg/kg/d allowed a high success probability (90%), with a trough level below 2.5 mg/L.

Conclusions: For intermediate pathogens, a dose of at least 40 mg/kg/d can improve efficacy, with an acceptable calculated residual trough level in cases of normal or hyperfiltration. Because amikacin undergoes renal clearance, which is immature until 1 year of age, dosing recommendations for this age group may be markedly high, warranting cautious interpretation.

Key Words: amikacin, cystic fibrosis, children, population pharmacokinetics, Pmetrics

BACKGROUND

Pulmonary exacerbations in patients with cystic fibrosis (CF) are life-threatening, and intravenous antibiotics, typically penicillins with aminoglycosides, are currently recommended treatment.¹ Amikacin is a frequently prescribed aminoglycoside because of its wide spectrum and synergistic effect with third-generation cephalosporins against *Pseudomonas aeruginosa*, a common pathogen causing exacerbations in CF.²

From a pharmacokinetic/pharmacodynamic (PK/PD) standpoint, amikacin demonstrates concentration-dependent and rapid bactericidal activity. However, prolonged and increased drug exposure escalates the risk of nephrotoxicity.^{3,4}

This has resulted in strong recommendations for therapeutic drug monitoring (TDM) of aminoglycosides. For efficacy, the PK/PD objective is to target a C_{max} value 8 to 10 times the minimum inhibitory concentration (MIC),⁵ whereas toxicity could be prevented by targeting trough concentrations below 2.5 mg/L (corresponding to the limit of detection of most immunochemistry methods), as proposed by the French National Authority for Health.⁶

For aminoglycosides, the PKs in adults with CF are modified when compared with non-CF subjects.⁷ Indeed, increased antibiotic clearance (CL) has been indicated to result in increased dosage regimens.⁸ Thus, the recommended amikacin dosing regimen is 30–35 mg/kg once daily, administered as a 30-minute infusion,^{9,10} regardless of the MIC of the bacteria. Notably, similar data in the pediatric population are extremely limited.

The aim of our study was to (1) develop a non-parametric population PK model for children with CF and (2) to determine the best dosage regimen to achieve the PK/PD

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objectives (both in terms of efficacy and prevention of toxicity) according to different MIC values.

MATERIALS AND METHODS

Ethics

Data used were anonymized in advance during collection, and patient consent was collected as authorized by French laws. This study was approved by the Ethical Committee of the Bordeaux University Hospital (approval number #GP-CE 2020-08).

Data

We developed our model using results obtained from routine-care standard amikacin blood sampling in children with CF, followed up at the Bordeaux University Hospital Paediatric CF center (CRCM) between January 2012 and December 2018. In all patients, dose individualization was performed using the Bayesian dose individualization program, PKJust (<https://pharmaco.chu-limoges.fr/>). Patients were characterized by a documented diagnosis of CF and pulmonary exacerbation treated with intravenous amikacin once daily for ≥ 10 days. For patients with repeated PK samples during the same episode of infection or with different episodes of infection, each PK profile was independently considered (no interoccasion variability was taken into account).

For each patient sampling, demographic and clinical data (age, sex, weight, and serum creatinine) were collected. The glomerular filtration rate (eGFR) was estimated using the Schwartz formula: $eGFR \text{ (mL/min)} = k \times \text{height (cm)} / \text{creatinine } (\mu\text{M})$, with different k values depending on patient age and sex.¹¹ In addition, the amikacin dose, the precise time of administration, dosing interval, and time of blood sampling were collected. For efficacy parameters, standard sampling was performed 30 minutes after the end of infusion, as well as 6 hours (before 2015) and 3 hours (after 2015) after infusion. Amikacin and creatinine concentrations were measured with the AU5400 analyzer (Beckman Coulter, Villepinte, France) using the QMS Amikacin Assay Application (Beckman Coulter, Villepinte, France), with a limit of quantification = 1.5 mg/L and a range of linearity from 1.5 to 50 mg/L, and the Creatinine Reagent OSR6678 (Beckman Coulter, Villepinte, France) with a limit of quantification = 0.2 mg/dL and a range of linearity in serum from 0.2 to 25.0 mg/dL, respectively.

Statistical Analysis

Demographic, clinical, and biological variables are reported as numbers and percentages for categorical variables, and as median and ranges (min–max) for continuous variables.

PHARMACOKINETIC MODELING

Population pharmacokinetic analysis was performed using Pmetrics version 5.2 (Laboratory of Applied Pharmacokinetics, University of Southern California, CA).¹²

A structural model was first developed without covariates by investigating 1-compartment and 2-compartment models with first-order elimination. Two

error models were tested: a combined analytical error model with a residual error represented by a proportional gamma term (residual error = $SD \times \text{gamma}$) or an additive lambda term [residual error = $(SD^2 + \text{lambda}^2)^{0.5}$]. Then, associations between covariates and PK parameters were investigated using visual examination (scatterplot and box-plots for continuous and categorical covariates, respectively) and statistical tests (regressions with linear and power relationships and Mann–Whitney tests for continuous covariates and categorical covariates, respectively). The clinical factors investigated were as follows: body weight, age, sex, serum creatinine concentrations, and eGFR. Then, a forward–backward selection was used to include the covariates in the intermediate model. The final model was selected based on a combination of statistical results [the lowest Bayesian information criterion (BIC), the bias, the root mean square error], and visual examination of graphs (population or individual observed–predicted plot, and weighted residuals versus time or individual predicted concentrations). Precision in parameter estimation was evaluated, not with the relative square error, which is not reported in Pmetrics, but by using the parameter weighted median and its 95% confidence interval (CI) after performing 1000 bootstraps of the marginal distribution of each parameter and calculating the median and 95% CI of the 1000 median values for each parameter.

INTERNAL EVALUATION

The final model was internally evaluated using a visual predictive check (VPC). The 5th, 50th, and 95th percentiles of 1000 simulated profile concentrations were plotted against the observed data.

Probability of Target Attainment

The final models were used to perform multimodal Monte Carlo simulations¹³ to generate 1000 concentration–time profiles for 7 amikacin dose regimens, ranging from 30 to 60 mg/kg. Simulations were performed as follows: (1) for the weight distribution observed in the study and the median eGFR value fixed; (2) for a fixed median weight and an altered eGFR (between 10 and 60 mL/min/1.73 m²). Then, the probabilities among the 1000 profiles for each dosing regimen were assessed for achieving both PKPD goals—peak concentration at 10 times the MIC and trough concentration below 2.5 mg/L and for MIC between 1 and 16 mg/L (corresponding to the EUCAST highest frequency for *P. aeruginosa*).

RESULTS

Population Characteristics

Data from 94 children were collected, totaling 282 PK profiles performed during pulmonary exacerbation (plus 27 additional PK profiles during the same antibiotic course considered independently) and 613 samples (flow chart is presented in the see **Fig. S1, Supplemental Digital Content 1**, <http://links.lww.com/TDM/A462>). Patient characteristics

are presented in Table 1. Thirty minutes after the end of infusion, 308 samples were obtained at a median (min–max) time of 1 (0.5–1.95) hours after initiating the amikacin infusion. The median serum concentration was 83.2 (25.1–138.9) mg/L. In addition, 305 samples were obtained at 3.22 (2.55–7) hours after initiating the infusion, with a median serum concentration of 20 (1.5–43.9) mg/L.

Pharmacokinetic Modeling

Data obtained from our pediatric population were best described by a monocompartmental model, parametrized in terms of amikacin clearance (CL) and volume of distribution (Vd), with a combined analytical error model ($0.25 \text{ mg/L} + \text{concentration} \times 0.1$) and a residual error term $\lambda = 0.1 \text{ mg/L}$ (BIC 1 and 2 compartment = 4541 and 4554, respectively).

Univariate analyses revealed significant associations using power relationships between (1) Vd and body weight ($P < 0.0001$), (2) CL and GFR ($P < 0.0001$), and (3) CL and body weight ($P < 0.0001$). No relationship was observed between the other investigated covariates and Vd or CL. In the final model, body weight was retained on Vd (Equation 1) and Schwartz-derived eGFR and body weight on CL (Equation 2), which significantly improved the model (BIC final model = 4099). The equations relating the covariates with exposure parameters are presented below:

$$Vd = Vd_0 \times \left(\frac{\text{weight}}{29} \right)^{\text{theta}_1} \quad (1)$$

29 kg is the median body weight in the population

$$Cl = Cl_0 \times \left(\frac{\text{eGFR schwartz}}{200} \right)^{\text{theta}_2} \times \left(\frac{\text{weight}}{29} \right)^{\text{theta}_3} \quad (2)$$

where eGFR is the estimated glomerular filtration rate and $200 \text{ mL/min/1.73 m}^2$ is the median eGFR in the population.

The estimated population pharmacokinetic parameters, their mean weighted median, and their 95% CI are presented in Table 2. There were 44 support points determined (available with the model file as see **Data, Supplemental Digital Content 2**, <http://links.lww.com/TDM/A461>).

TABLE 1. Patients Characteristics (Based on the 309 Pharmacokinetic Profiles; Each Profile was Considered as an Independent Patient)

Variable	Median (Min–Max) n = 309
Amikacin dose, mg/kg/d	35.0 (14.0–43.0)
Sex M/F	170/139
Height, cm	135 (65–186)
Weight, kg	29 (6–71)
Age, yrs	10.0 (0.3–17.0)
Serum creatinine, μM	35.0 (5.8–79.0)
Glomerular filtration rate using the Schwartz formula ¹¹ (mL/min/1.73 m ²)	200 (108–433)
Body surface area, m ² ²⁵	1.03 (0.32–1.82)

MODEL EVALUATION

The mean relative bias/root mean square error between the observed and modeled concentrations was $-0.68\%/8.1\%$. The scatter plots of individual or population predictions versus observed concentrations and weighted residuals as a function of individual prediction or time are presented in Figure 1.

INTERNAL EVALUATION

VPC for a median patient with a weight of 29 kg and an eGFR of $200 \text{ mL/min/1.73 m}^2$ (Fig. 2) revealed that 95% of the observed data were included in the 95% CI of the simulation and were homogeneously distributed around the median of the simulation.

Probability of Target Attainment

Probability of target attainment studies were performed for (1) a weight distribution characterized by a mean (min–max) = 29 (6–71) kg and a fixed eGFR = $200 \text{ mL/min/1.73 m}^2$ and (2) for a fixed weight = 29 kg and an eGFR distribution characterized by a mean (min–max) = 30 (10–60) mL/min/1.73 m^2 . The results of the PTA performed for both a $C_{\text{max}} > 10 \times \text{MIC}$ and a $C_{\text{min}} < 2.5 \text{ mg/L}$ and for 7 amikacin dosing regimens: 30, 35, 40, 45, 50, 55, and 60 mg/kg are presented in Figure 3 for the weight distribution, and see **Fig. S2, Supplemental Digital Content 3**, <http://links.lww.com/TDM/A463> for altered eGFR distribution.

When targeting these PK/PD objectives and for normal or hyperfiltration, organisms with MICs of 4 mg/L or less would likely achieve almost 100% PTA using a daily dose of 30 mg/kg. By contrast, a dose of at least 40 mg/kg would achieve at least 90% PTA for MICs of 8 mg/L (ie, *P. aeruginosa*).

DISCUSSION

In this study, we developed an amikacin population PK model for children with CF and performed PTA to determine the best dosing regimen to target a peak of $10 \times \text{MIC}$ and a trough $< 2.5 \text{ mg/L}$.

In children with CF, the currently recommended amikacin dose range lies between and 30–35 mg/kg/d, similar to the median in our cohort (35 mg/kg/24 hours). A 30 mg/kg dosing strategy allows the attainment of optimal concentrations for sensitive bacteria with a $\text{MIC} \leq 4 \text{ mg/L}$; however, as determined in the present work, a higher dose (40 mg/kg/24 hours) is required to attain the PK/PD objective in intermediate-resistant bacteria with a $\text{MIC} \geq 8 \text{ mg/L}$. The PTA assessment showed that this dosing scheme should be associated with efficacy without toxicity in patients with normal or glomerular hyperfiltration.

Only a few studies have aimed at developing amikacin PK models in patients with CF. A recent study performed in 6 adult CF patients treated with amikacin, using Monte Carlo simulations based on parameters obtained using noncompartmental analysis, has reported a dose of 45 mg/kg/d was needed to achieve optimal peak/MIC ratio for *P. aeruginosa*, with a MIC value of 8 mg/L.¹⁴ The dose proposed in this study is higher than that determined in this study (40 mg/kg)

TABLE 2. Final Parameters Estimates

Parameter (Unit)	Final Model Parameter Estimate			Bootstrapped Values	
	Median	CV%	Interpatient Variability (Range)	Mean Weighted Median	2.5–97.5 Percentile
V ₀ , L	7.86	25.4	5.62–22.02	7.78	7.86–8.11
Theta 1	0.79	20.0	0.61–1.96	0.78	0.76–0.89
CL ₀ , L·h ⁻¹	4.22	18.0	3.00–7.72	4.32	3.95–4.58
Theta 2	0.20	66.3	0.10–0.99	0.15	0.1–0.34
Theta 3	0.73	16.2	0.61–1.96	0.72	0.63–0.77

CL₀, the typical clearance for a median patient; Theta₁, the power parameter associated with weight; Theta₂, the power parameter associated with the glomerular filtration rate; Theta₃, the power parameter associated with weight; V₀, typical volume of distribution for a median patient.

and is also higher than current recommendations (30–35 mg/kg/d). These differences may be attributed to variations in patient age between the 2 investigations (adult versus children in our study) and mainly by differences in the number of patients investigated (6 versus 94 in our study).

Caceres Guido et al have performed parametric modeling for amikacin in 39 (114 concentrations) patients with CF. The developed parametric PK model was a 1-compartment model, with PK parameters reportedly similar to those determined in this study (CL for a median weight patient = 4.56 L/h and central Vd = 8.43 L); however, the interindividual variability was higher in their study (probably because of the lower number of concentrations available). Interestingly, they performed a simulation for an amikacin dose of 30 mg/kg administered

thrice, twice, or once a daily, and observed that the once-daily administration was the only dose rate that demonstrated a trough below the 2.5 mg/L threshold. In addition, they further noted that none of the simulations for this dose reached a peak of 60–80 mg/L, which was consistent with our results.¹⁵

Recently, Illamola et al¹⁶ have developed a 2-compartment PK model for amikacin in 49 adult patients, revealing that creatinine clearance (CrCL) and weight significantly influenced amikacin CL and Vd, and amikacin PK differed between patients with and without CF. However, PTA was not performed to determine the optimal dosing scheme. In this study, the reported PK parameters were in accordance with the values reported in the Illamola study for CL but 2-fold lower for Vd (Vd = 14.4 L and Cl =

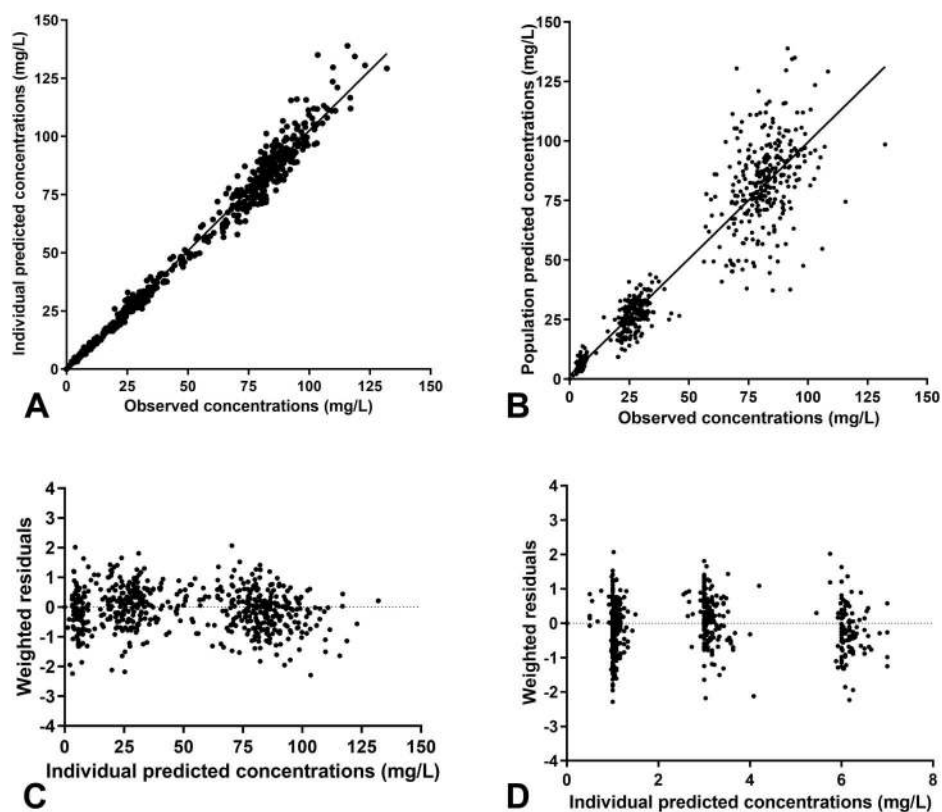


FIGURE 1. Scatter plots of amikacin. A, Individual-predicted concentrations versus observed concentrations ($R^2 = 0.98$). B, Population-predicted concentration versus observed concentration ($R^2 = 0.87$). C, Weighted residuals versus individual-predicted concentrations. D, Weighted residuals versus time postadministration.

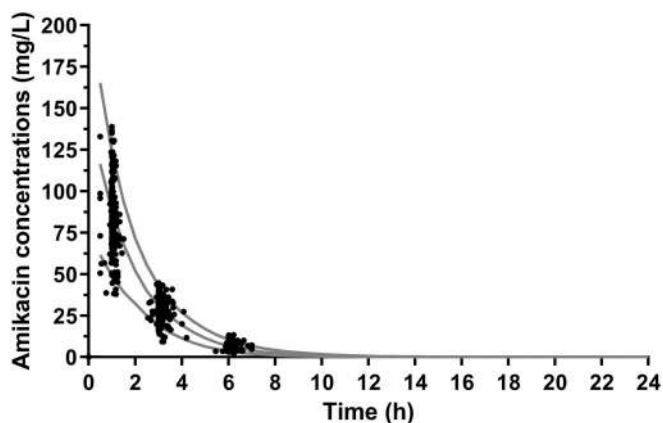


FIGURE 2. VPC of simulated concentrations for 30 minutes amikacin infusions in a typical patient with bodyweight = 29 kg and glomerular filtration rate estimated using Schwartz formula = 200 mL/min/1.73 m². The 5th, 50th, and 95th percentiles of simulated concentrations are plotted against the observed data.

3.06 L/h). A probable explanation for the difference in Vd is the difference in populations (adult/children) assessed. In comparison, in non-CF children, studies using a 1-compartment model to describe the PK of amikacin demonstrated a Vd of approximately 0.3–0.4 L/kg and CL around 0.124 L/h/kg,^{17,18} corresponding those children presenting a weight of 29 kg (median of our population) with Vd ~10 L and CL ~3.6 L/h. These marginal differences are consistent with the PK modification expected in patients with CF when compared with others patients.⁷

Unlike Illamola et al, in our study, a mono-compartmental model best described the data, but this is consistent with only 2 concentrations available per profile. Indeed, estimating additional parameters with only 2 samples would have resulted in difficulties in accurately estimating the intercompartmental CL and peripheral Vd. In addition, we used the Schwartz formula to estimate the eGFR, which is reportedly more suitable in pediatric populations, whereas Illamola et al used the Modification of Diet in Renal Disease equation in adult patients.

Notably, the simulation performed for a theoretical eGFR <60 mL/min/1.73 m² revealed that none of the amikacin dosing schemes allows reaching PTA of 100% due to increase in trough concentrations. However, these simulations must be interpreted cautiously because no such eGFR values were available in the data set, and a linear relationship between the drug CL and the renal function has to be hypothesized, which may not be accurate.

The exact time of sampling was collected because the data were prospectively entered into the website, probably leading to relatively accurate values. Indeed, TDM has been performed for a long time at the department, and nurses are well aware of the importance of precise sampling time. In addition, for routine TDM of aminoglycosides, samples are not drawn at C_{max} but 30 minutes later, which avoids the large uncertainty that would be observed if the sample was drawn at the end of infusion (given their low Vd). The large

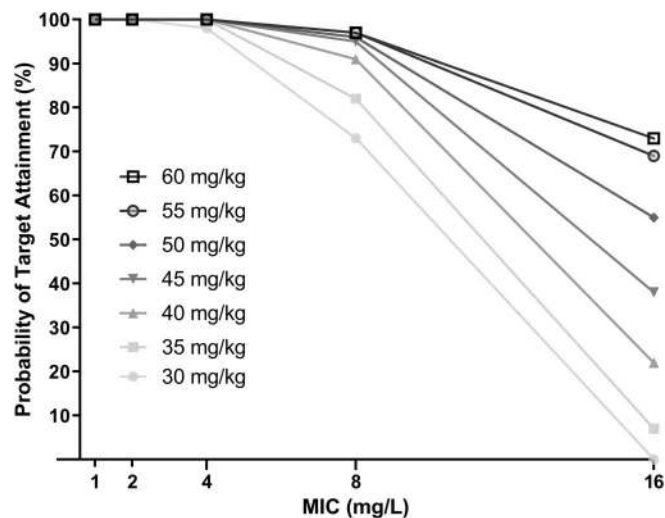


FIGURE 3. Probabilities of target attainment for a peak = 10 × MIC and a trough concentration <2.5 mg/L for 7 amikacin dosing schemes based on simulations for a weight distribution characterized by a mean (min–max) = 29 (6–71) kg.

range of peak values is linked to the difference in doses administered and interindividual variability. In this study, the choice of breakpoint was based on the EUCAST¹⁹ recommendations, but it is obvious that susceptibility to *P. aeruginosa* strains is highly variable in patients with CF²⁰ and that the susceptibility of a given bacterium should be assessed to use the appropriate dosing regimen.

The prevalence of amikacin resistance doubles every 4–5 years of lung residence time^{21,22} and parallels the increase in mexY mRNA expression and nonconservative mexZ mutations, indicating the overexpression of the efflux pump MexXY.²¹ This suggests the need to adapt antibiotic doses based on peak and residual antibiotic concentrations to improve efficacy and safety, which is the principle of TDM.

The main limitation of this study is that every profile was considered as an independent patient, that is, no interoccasion variability was investigated, but it only concerned 27 profiles (<10% of the PK profiles). In the preliminary phase, we investigated each patient by considering multiple drug measurements within the same antibiotic course. This showed that the fit of the subsequent visits was inadequate, suggesting that PK parameters are highly variable for a given subject over time, even for visits within an interval of a few days. Furthermore, this implied that it may be suitable to perform multiple drug measurements during a given course.

Another limitation is the use of the 1-compartment model that could have led to a biased estimation of the trough concentrations. In addition, we were unable to assess the accuracy of predictions as our data set did not include such data. However, accurate estimation of the trough is not an issue in children with CF, as the PK of aminoglycosides is characterized by an increase in their CL.⁸

In this cohort, median CrCL, estimated using the modified Schwartz equation, was markedly elevated. The

Schwartz formula tends to overestimate the actual CrCL because it is based on serum creatinine, which is often low in children because of low muscular mass, or fluid overload, related to their underlying condition,^{23,24} especially in children with CF. Similarly, the body surface area values are considerably lower than those in healthy populations. We believe that the use of eGFR could result in the overestimation of drug CL; however, this can also be observed with other creatinine-derived formulas.²⁴ In this study, even with 20 ml/min/m² overestimation, all the values would be higher than 88 ml/min/m² which still corresponds to a normal renal function

Finally, this model was developed in a population of children aged between 0.3 and 17 years, with only 2 children younger than 1 year of age. Because amikacin is subjected to renal CL and it is known to be underdeveloped until 1 year of age, dosing recommendations provided by our simulations in this age group may be markedly high and should be cautiously interpreted.

CONCLUSIONS

Based on the present results, to achieve a $10 \times$ MIC at peak and trough concentrations <2.5 mg/L, an initial dose of 40 mg/kg/d should be proposed as the starting dose for the treatment of acute pulmonary exacerbation in children with CF infected with *P. aeruginosa* with MIC ≥ 8 mg/L. Nevertheless, these dose recommendations are based on simulations and are useful for the first dose, but further dose adjustments should be performed based on typical TDM.

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