Impact of the use of different PK/PD indexes on Amikacin Dosing requirements in Severely Ill Children: A Population Pharmacokinetic Approach

Van herteryck Isis[1,2], Tan Zhiyuan[2], Dhont Evelyn[2,3], Devreese Mathias[1], De Wilde Bram[4], Hermans Eline[1,2], De Paepe Peter[2,5], De Cock Pieter[2,6]

[1]Department of Pathobiology, Pharmacology and Zoological Medicine, Faculty of Veterinary Medicine, Ghent University, [2]Department of Basic and Applied Medical Sciences, Faculty of Medicine and Health Sciences, Ghent University, [3]Department of Paediatric Intensive Care, Ghent University Hospital, [4]Department of Pediatric Hematology-Oncology. [5]Department of Emergency Medicine, Ghent University Hospital, [6] Department of Pharmacy, Ghent University Hospital

Introduction

- Pediatric patients exhibit developmental physiological changes that increase pharmacokinetic (PK) variability.
- Severely ill children frequently experience augmented renal clearance (ARC), leading to an increased risk of subtherapeutic exposure.
- Amikacin remains a cornerstone therapy for severe hospital-acquired Gram-negative infections; however, dosing is challenging due to high inter-individual PK variability and a narrow therapeutic window.
- Current dosing simulations primarily target a maximal concentration (C_{max}) /Minimal inhibitory concentration (MIC) ratio, while there is an emerging shift toward area-under the concentration-time curve (AUC)/MIC-based targets.

Objectives

- Develop a pediatric amikacin population PK (PopPK) model and identify the most predictive estimating glomerular filtration rate (eGFR) equation for clearance.
- Evaluate the impact of alternative probability of target attainment (PTA) targets on recommended dosing regimens.

Methodology

Clinical study

- Observational study at Ghent University Hospital in children (< 16 years) admitted to the intensive care or oncology units. Patients received standard-of-care amikacin doses, 20 mg/kg intravenously (IV) over 30 minutes.

Demographic characteristics (n=38 patients)	
Department (PICU/oncology)	22 (65.8%)/ 16 (42.1%)
Sex (Male/Female)	23 (60.5%)/ 15 (39.5%)
Age (y)	4.21 (0.05-14.00)
Weight (kg)	15.3 (2.9-63.0)
eGFR Bouvet (mL/min/1.73 m²)	136.5 (25.1-258.7)
eGFR Bouvet (mL/min)	66.7 (2.9-139.0)

Table 1: Demographics table of 38 children.
Continuous variables are presented as median (range). Categorical variables are depicted as a number (percentage).

PICU: paediatric intensive care
eGFR: estimated glomerular filtration rate

Model fitting

- Population PK analysis with Monolix (Lixoft, Version 2024R1)
  - 15 different paediatric eGFR equations were evaluated, such as Bouvet
  - Internal validation was performed using, Monte Carlo simulation-based Bootstrap (n=1000) and prediction corrected Visual Predictive Check (pcVPC).

Table 2: Paediatric estimated glomerular filtration rates (eGFR).

Bouvet combined serum Cystatin C (CysC) + serum Creatinine (Cr)
$eGFR\ (\text{mL/min/1.73}) = 63.2 \times \left(\frac{Cr\ (\frac{\text{mg}}{\text{dL}})}{96}\right)^{-0.35} \times \left(\frac{CysC\ (\frac{\text{mg}}{\text{L}})}{1.2}\right)^{-0.56} \times \left(\frac{weight\ (\text{kg})}{45}\right)^{0.3} \times \left(\frac{age\ (\text{years})}{14}\right)^{-0.4} \times \left(\frac{1.73}{body\ surface\ area\ (\text{m}^2)}\right)$

Simulations

- Dosing simulations were performed using the Mrgsolve package in Rstudio (Posit, Version 4.5.2)
- Dosing regimens were evaluated for once-daily administration across dose levels of 5-30 mg/kg (n=3000 patients per covariate category)
- Different probability of target attainment (PTA) criteria were evaluated
  - PTA1: AUC/MIC ≥ 62.5 + Cmax/MIC ≥ 8 + Cmin ≤ 5 mg/L.
  - PTA2: AUC/MIC ≥ 62.5 + Cmax ≥ 8 + Cmin ≤ 5 mg/L.
  - PTA3: AUC/MIC ≥ 62.5 + Cmax ≥ 8 + Cmin ≤ 5 mg/L.

Results

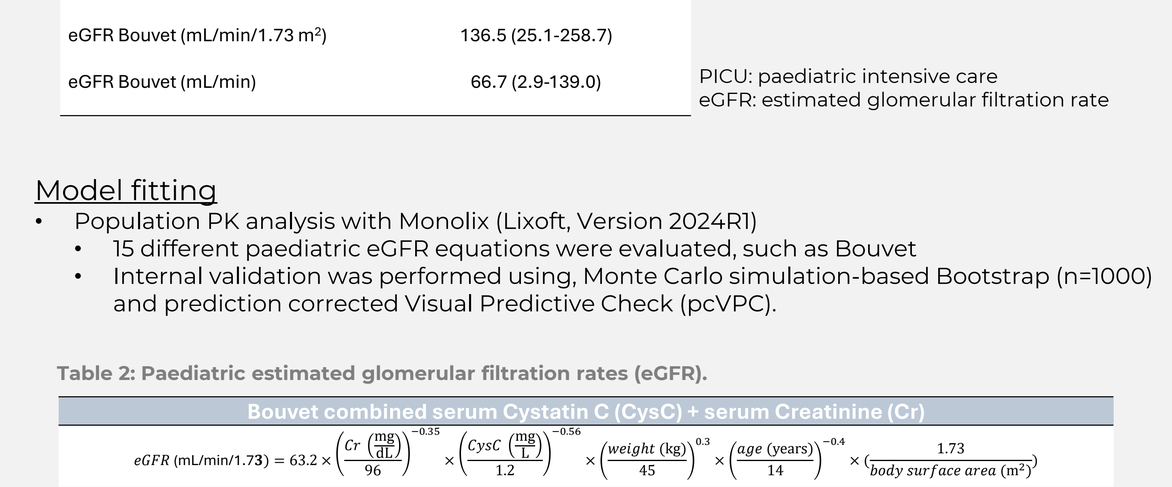

Figure 1: Two-compartment design and relevant covariates of the Amikacin model.
Scheme of the model and related equations.

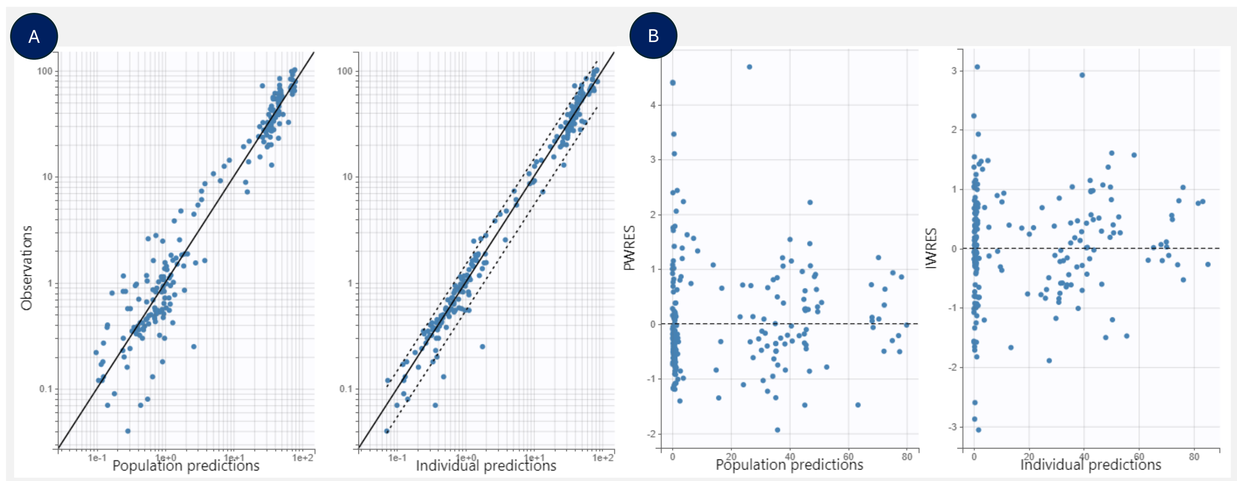

Figure 2: Diagnostic plots.
A. Population (left) and individual predicted (right) plasma concentrations (210 observations) plots. The dotted line represents the 90% confidence interval. B. Population (left) and individual (right) weighted residuals (PWRES, IWRES) plots.

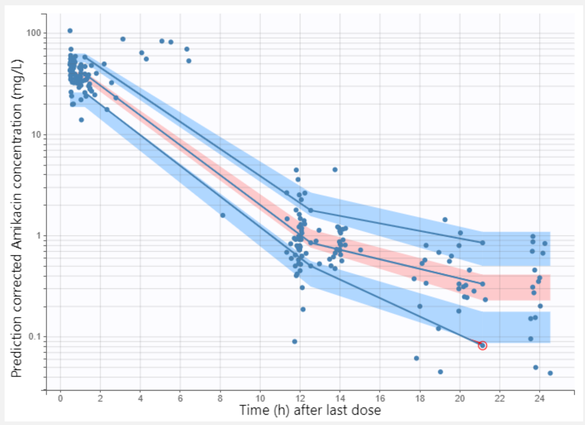

Figure 3: Predicition corrected Visual Predictive Check.
The middle line denotes the median values. The other lines represent 10% and 90% percentiles of the observed values. The shaded areas represent 90% confidence intervals.

ε_{prop}: probability error term (µg/mL), CI: confidence interval, Cl_{pop} : population clearance, eGFR: estimated glomerular filtration rate using the Bouvet combined formula (mL/min/1.73 m²), department: oncology (1) or PICU (0), Q_{pop}: intercompartmental flow, Vc_{pop}: central volume of distribution, Vp_{pop}, peripheral volume of distribution, WT: bodyweight (kg),

Table 3: Population Pharmacokinetic Parameters.
Parameter estimates of amikacin in the paediatric population are depicted together with the internal validation bootstrap results of 1000 simulations.

PK parameters	Estimate (precision %)	Bootstrap (n=1000) Median (95% CI)
Fixed population effects		
Cl_{pop} (L/h)	7,40 (6.08)	7.47 (6.22-8.96)
$\beta_{Cl,WT}$	0.75 (fixed)	
$\beta_{Cl,eGFR}$	0.74 (13,40)	0.80 (0.46-1.03)
Vc_{pop} (L)	25.35 (6.88)	24.58 (19.61-29.15)
$\beta_{Vc,WT}$	1 (fixed)	
$\beta_{Vc,Department}$	-0.52 (24.6)	-0.48 (-0.69--0.22)
Vp_{pop} (L)	13.76 (16.30)	14.48 (9.76-23.42)
$\beta_{Vp,WT}$	1 (fixed)	
Q_{pop} (L/h)	1. 60 (23.20)	1.64 (0.71-3.86)
$\beta_{Q,WT}$	0.75 (fixed)	
Inter individual variability		
ω_{Cl}	0.23 (22.81)	0.22 (0.15-0.30)
ω_{V1}	0.24 (24.51)	0.23 (0.05-0.39)
Residual variability		
ε_{prop}	0.28 (6.04)	0.28 (0.22-0.33)

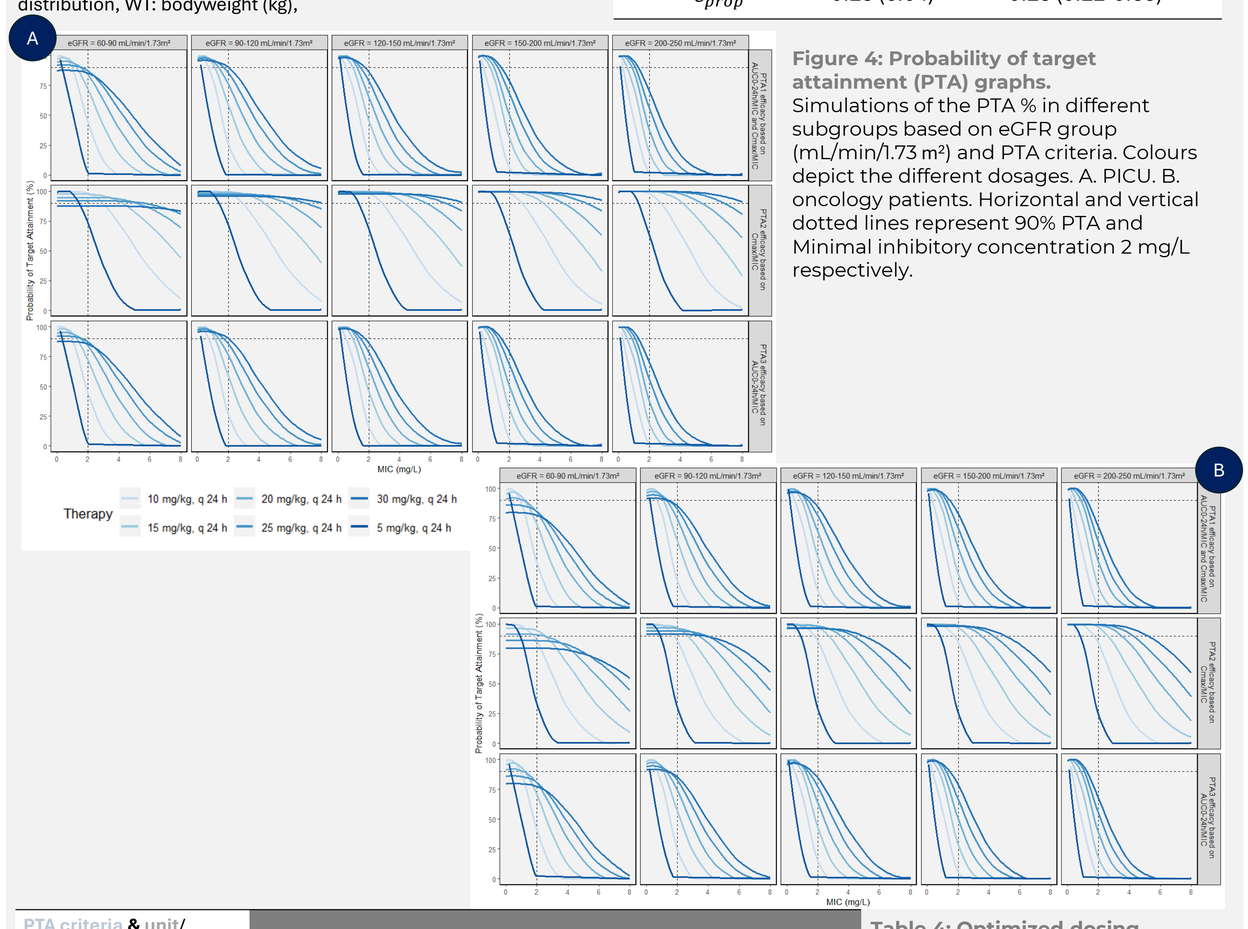

Figure 4: Probability of target attainment (PTA) graphs.
Simulations of the PTA % in different subgroups based on eGFR group (mL/min/1.73 m²) and PTA criteria. Colours depict the different dosages. A. PICU. B. oncology patients. Horizontal and vertical dotted lines represent 90% PTA and Minimal inhibitory concentration 2 mg/L respectively.

PTA criteria & unit/ eGFR (mL/min/ 1.73 m²)		60-90	90-120	120-150	150-200	200-250
PTA1	PICU	25 mg/kg, q24h(81%)	30 mg/kg, q24h(86%)	30 mg/kg, q24h(85%)	30 mg/kg, 18h(83%)	30 mg/kg, q18h(94%)
	Oncology	25 mg/kg, q24h(88%)	30 mg/kg, q24h(90%)	30 mg/kg, q24h(86%)	30 mg/kg, q18h(86%)	30 mg/kg, q18h(96%)
PTA2	PICU	15 mg/kg, q24h(95%)	15 mg/kg, q24h(97%)	20 mg/kg, q24h(99%)	20 mg/kg, 24h(99%)	25 mg/kg, q24h(100%)
	Oncology	10 mg/kg, q24h(99%)	15 mg/kg, q24h(100%)	15 mg/kg, q24h(100%)	15 mg/kg, q24h(100%)	20 mg/kg, q24h(100%)
PTA3	PICU	25 mg/kg, q24h(81%)	30 mg/kg, q24h(86%)	30 mg/kg, q24h(85%)	30 mg/kg, 18h(83%)	30 mg/kg, q18h(94%)
	Oncology	25 mg/kg, q24h(88%)	30 mg/kg, q24h(90%)	30 mg/kg, q24h(86%)	30 mg/kg, q18h(86%)	30 mg/kg, q18h(96%)

Table 4: Optimized dosing regimens for personalized therapy of amikacin in children.
Dosing regimens categorised based on eGFR, department of admission, and PTA criteria administered after a 0.5h infusion. Values represent the recommended dose (mg/kg) and frequency (h) with their resulting PTA % value, when evaluating for a Minimal inhibitory concentration of 2 mg/L.

Conclusion

- A two-compartment PK model best described amikacin disposition in this population.
- The eGFR equation by Bouvet, Creatinine and Cystatin C-based, provided the most accurate description of amikacin elimination.
- Low PTA values are observed when AUC/MIC > 62.5 must be achieved certainly for ARC patients, higher doses are recommended. Dosing recommendations based on department, and eGFR could be beneficial.

Acknowledgements.
This study is funded by BOF (BOF/24J/2023/068).
Figures were made with BioRender and Rstudio.

References
- Dhont E. PhD thesis. 2025.
- Dia N. et al., Ther Drug Monit. 2025 47(3).
- Illamola SM. et al., Clin Pharmacokinet. 2018 57(10).
- EUCAST. 2024.

Contact
Isis Van herteryck
Isis.vanherteryck@ugent.be
LinkedIn