Poster **R-50**

In silico studies to evaluate dosing intervals associated with low risk of amikacin accumulation in preterm neonates

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Introduction

- The Swiss national dose recommendation (SwissPedDose) of amikacin in neonates is 15 mg/kg every 24h-48h depending on post-menstrual age (PMA) and post-natal age (PNA), defining six subpopulations (Table 1).
- In the group of preterm neonates PMA 30-35 weeks/PNA <14 days, elevated C_{trough} were clinically observed (subpopulation 3) under an initially proposed 24h-dosing-interval.

Table 1: Amikacin dosage recommendations for neonates (SwissPedDose) and open questions.

SWISSPEDDOSE
Amikacin (IV)
Indication: General use (Neonatology)
Dosage recommendation

Subpopulation	Postmenstrual age (PMA)	Postnatal age (PNA)	Amikacin dosage recommendation
1	<30 weeks	<14 days	15 mg/kg every **48h**
2	<30 weeks	≥14 days	15 mg/kg every 24h
3	30-35 weeks	<14 days	15 mg/kg every 24h* → or better every 36h or 48h?
4	30-35 weeks	≥14 days	15 mg/kg every 24h
5	35-44 weeks	<14 days	15 mg/kg every 24h
6	35-44 weeks	≥14 days	15-20 mg/kg every 24h

*for practical reasons and after literature review during the harmonization process, an initial 24h dosing interval was proposed disregarding PNA.

Methods

demographic data[1]
(Figure 1: real-life neonatal population, receiving antibiotics on a neonatal ward)

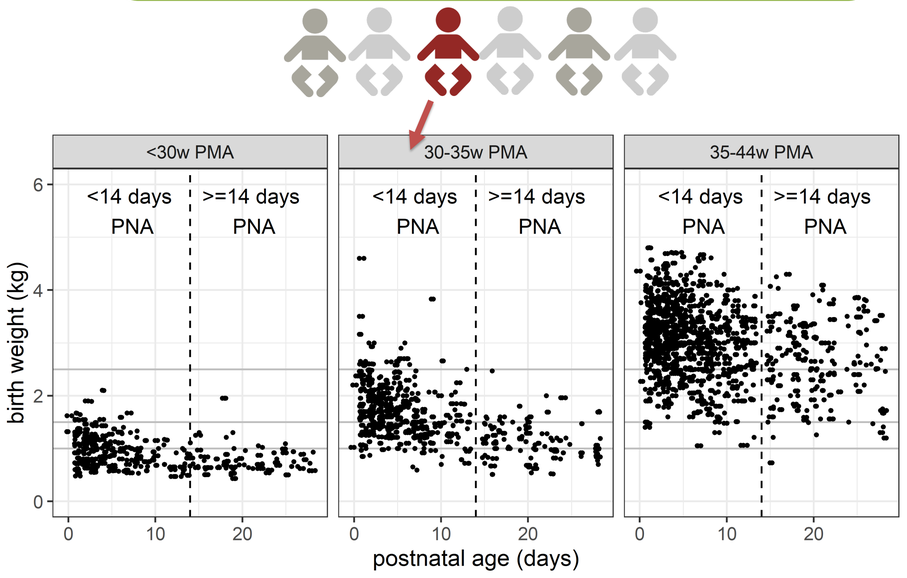

Figure 1: Depicition of real-life population demographic data[1]: birth weight *versus* postnatal age (PNA) as clearance-relevant covariates, depicted by postmenstrual age (PMA) split into 6 subpopulations according to SwissPedDose recommendations.

+ Amikacin dosing scenarios (Table 1)

+ Published population pharmacokinetic model[1]
Clearance = *function(birth weight and PNA)*
Volume of distribution = f(current weight)

SIMULX

In silico studies
(Monte Carlo simulations)
(n=500 individuals sampled with replacement per each of the 6 subpopulations)

Outcome:
- C_{trough} before the 3rd dose

Endpoint:
- **% of patients with C_{trough}<5 mg/L**

References:
[1] Hufnagel et al. JPIDS 2019
[2] Cristea et al. Antimicrob Agents Chemother. 2017

Objective

→ To evaluate the potential of extended intervals (36h-48h) to achieve amikacin target C_{trough} of <5 mg/L (associated with decreased oto-/nephrotoxicity) in a typical population of preterm neonates PMA 30-35 weeks/PNA <14 days, treated with antibiotics on a neonatal ward[1].

Results

In silico studies I: Results for initial dose recommendations

The proportion of neonates predicted with C_{trough}<5 mg/L was (Figure 2):

- **61%** in preterm neonates PMA 30-35w/PNA<14d (24h-interval)
- 80-100% in the other subpopulations

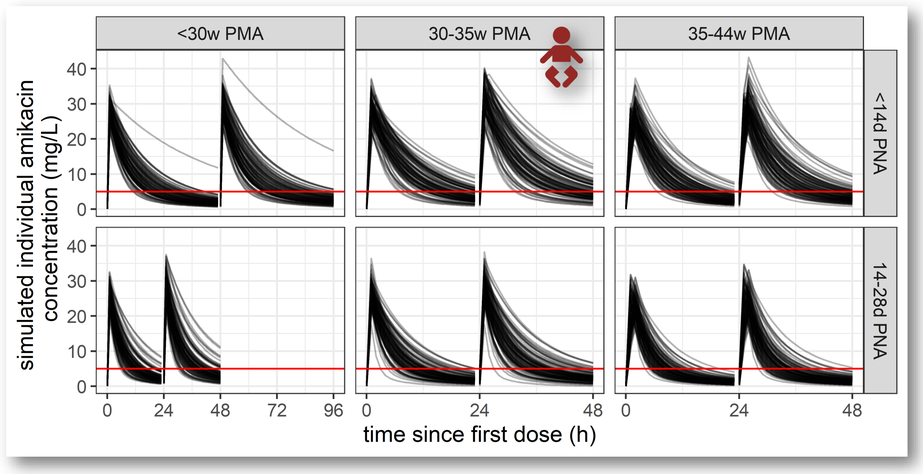

Figure 2: Illustration of simulated individual amikacin concentration-time profiles for each of the 6 subpopulations following two dose administration according to intial SwissPedDose recommendations. C_{trough} before the 3rd dose was extracted for each patient and the % of neonates with C_{trough} < 5 mg/L (*red horizontal line*) was calculated.

In silico studies II: Results for extended interval dosing

In the population of preterm neonates PMA 30-35w/PNA <14d, extended interval dosing increased the proportion of patients with predicted C_{trough}<5 mg/L to **93%-98%** (36-48h interval) (Figure 3)

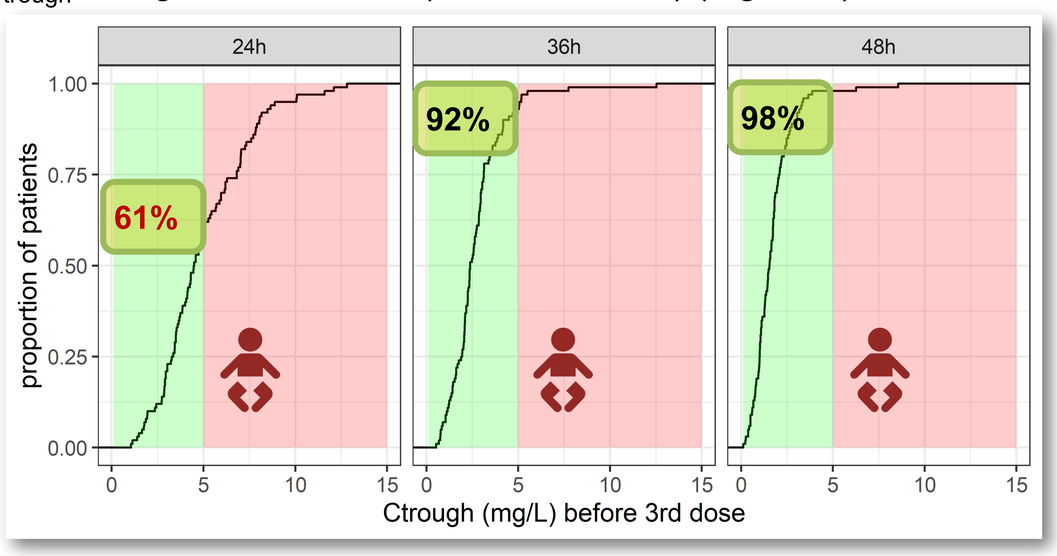

Figure 3: Summary of cumulated simulated main outcomes (C_{trough} before 3rd dose) and predicted outcome (proportion of patients with Ctrough < 5 mg/L, *green boxes*) for subpopulation 3 following extended interval dosing.

Conclusions

- ***In silico* studies confirmed a pharmacologically expected risk of amikacin accumulation in a typical population of preterm neonates 30-35 weeks/0-14 days receiving antibiotics on a neonatal ward following 24h-interval dosing.** Simulations suggest appropriateness of 36h-interval to reach C_{trough}<5 mg/L in >90% of patients.
- Such pharmacometric approach combined with real-wold demographic data may prove useful also in other situations to guide development of neonatal dose recommendations.