Evaluation of exposure to vancomycin in neonates under existing dosing regimens using a population pharmacokinetic approach

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Introduction & Objectives

- Several neonatal vancomycin dosing algorithms already exist based on various pharmacokinetic (PK) models[1]
- Most dosing approaches (international guidelines, protocols used in neonatal intensive care units (NICUs), published models) use age, renal function and body weight as covariates to establish the initial dosage
- No consensus for the best suited dosing regimen for neonates is observed

Study aims:

- **Build a population PK model of vancomycin in a large cohort of neonates**
- **Compare by simulation vancomycin exposures under existing dosage recommendations**
- **Contribute to harmonize vancomycin dosing in neonates admitted in NICUs**

Materials & Methods

Data

- 1848 vancomycin concentrations measured in 405 neonates
- Demographics: gestational age (GA), postnatal age (PNA), postmenstrual age (PMA = GA + PNA), current body weight (WT), birth weight (BW), gender, small for gestational age (SGA), creatinine (CRT), Apgar score, umbilical venous and arterial pH (pH_v/pH_a), antenatal steroids

Demographics

Population median (IQR, min-max)	
WT [g]	1200 (879-2335, 462-5660)
BW [g]	1050 (790-2170, 462-4330)
Gender (male, %)	231 (57%)
GA [weeks]	29 (26.7-34.9, 24-42.1)
Preterm (N)	331 (26.4-30.7, 24-36.9)
Full term (N)	74 (38.1-39.2, 37-42.1)
PMA [weeks]	32 (28.3-36.5, 24.6-61.0)
PNA [days]	16.8 (-, 0-245)
CRT [µmol/L]	52 (31-68, 5-276)
SGA (N)	88 (22%)
Apgar score at 5 min	8 (-, 0-10)
pH_v	7.25 (-, 6.93-7.93)
pH_a	7.28 (-, 6.71-7.45)
Antenatal corticoids (N)	261 (64%)

1) Model development

- One-compartment model with first-order elimination (NONMEM®) most appropriate
- Body weight allometric scaling on CL and V in the structural model
- Interindividual variability on CL and V + additive and proportional residual error model (intra-patient variability)

2) Simulation Study

- Dosing regimens tested:
  - 9 empirical dosing regimens used in NICUs across Switzerland
  - 7 international guidelines (Lexicomp, Red Book, BNFC, Neofax, Neonatal Formulary 7, Frank Shann's booklet, Dutch Children Form)
  - 4 from the literature: Janssen *et al*[4], Grimsley *et al*[5], Capparelli *et al*[6], McDougal *et al*[7]

Study population: exposure simulated for 405 neonates with the same demographic and clinical characteristics

Efficacy marker (after 24 hours and 7 days of treatment):
- **$AUC_{0\text{-}24h}$** derived by numerical integration (NONMEM®)
- **Trough concentrations (C_{min})**

Targets: **$AUC_{0\text{-}24h}$/MIC:** > 400 (considering a MIC ≤ 1 mg/L)[2]
$AUC_{0\text{-}24h}$: < 700 mg·h/L[3]
C_{min}: 10 – 20 mg/L

❖ **Expressed as a proportion of patients within/over the target**

Results

Final model

Parameter	*Population mean*			
	Estimate	*RSE (%)*	*IIV(%)*	*RSE (%)*
CL (L/h)	0.268	17	22.5	8
V (L)	0.629	2	-	-
θ_{WT}	0.438	18		
T_{50} (week)	46	-		
Hill	3.57	14		
θ_{CRT}	0.483	16		
σ_{prop} (CV%)	0.228	6		
σ_{add} (CV%)	2.22	10		

$$TVCL = CL \cdot \left(\frac{WT}{WT_{median}}\right)^{\theta WT} \cdot \left[\left(\frac{CRT_{median}}{CRT}\right)^{\theta CRT}\right] \cdot \left[\left(\frac{PMA^{Hill}}{PMA^{Hill} + T_{50}{}^{Hill}}\right)\right]$$

$$TVV = V \cdot \left(\frac{WT}{WT_{median}}\right)^{1}$$

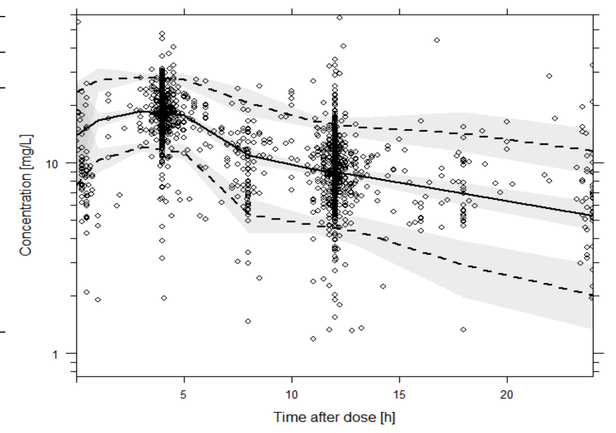

Figure 1: Prediction corrected visual predictive check, with vancomycin concentrations (circles) and population prediction (solid line) and 95% prediction interval (semi-solid line). Grey fields represent the model-based percentile confidence interval.

Simulations

Proportion of neonates within/over target:

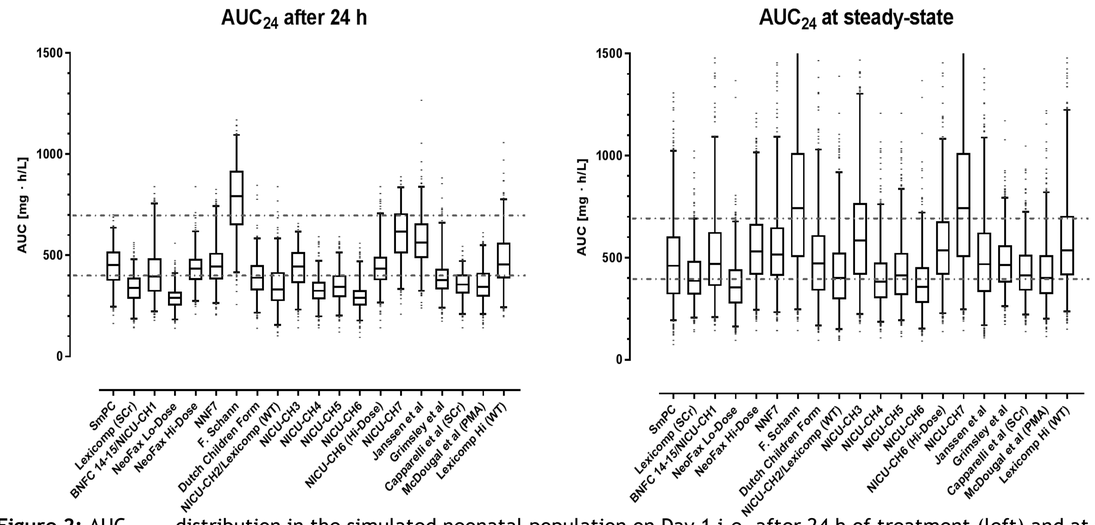

Figure 2: $AUC_{24/MIC}$ distribution in the simulated neonatal population on Day 1 i.e. after 24 h of treatment (left) and at steady-state (right). Dotted lines represent an $AUC_{24/MIC}$ between 400-700 Boxes represent the median and interquartile ranges, whiskers percentiles 5 and 95.

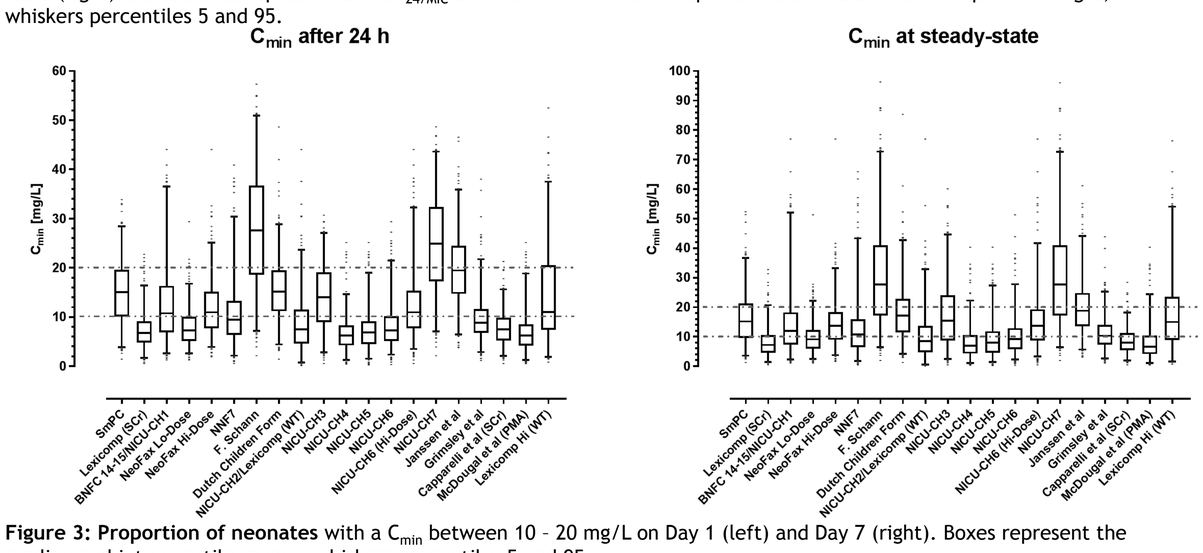

Figure 3: Proportion of neonates with a C_{min} between 10 – 20 mg/L on Day 1 (left) and Day 7 (right). Boxes represent the median and interquartile ranges, whiskers percentiles 5 and 95.

Best regimens on Day 1 according to the target AUC/MIC :

1) Janssen *et al* (73%): dose stratifications with 19 levels *f*(PMA,BW,WT) + loading dose
2) Neonatal Formulary (67%): 5 levels *f*(PMA, WT)
3) NeoFax -Hi-Dose (66%): 7 levels *f*(PMA, PNA, WT)

- Adding a loading dose of 25 mg/kg to the Neonatal Formulary regimen improves exposure on Day 1: 78% patients within target
- A model-based algorithm *f*(WT, CRT, PMA) directly derived from our model further improves exposure and reaches optimal exposure in 95% of patients (DAY 1) and 75% (DAY 7).

Conclusions

- **A majority of current neonatal vancomycin dosing regimens are inappropriate to reach optimal $AUC_{0\text{-}24h}$/MIC ratio (400-700) or C_{min} of 10-20 mg/L in a large proportion of patients**
- Better neonatal regimens leading to higher drug exposure are needed
- Complexity of regimen seems to marginally improve exposure
- Adding a loading dose to a simple dose regimen (e.g. Neonatal Formulary) significantly improves exposure on Day 1

References

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