

Implications of being born Small for Gestational Age on the exposure of vancomycin and gentamicin in neonates

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INTRODUCTION

- o (Pre)term neonates are dosed based on weight, in combination with gestational age (GA) or postnatal age (PNA).
- o Currently, no attention is paid to neonates that are born small for gestational age (SGA).
- o **SGA** neonates: neonates with a birth bodyweight (bBW) < 10th percentile of the bBW for their GA.

AIM

- 1. To determine the influence of being born SGA on the clearance (CL) of vancomycin and gentamicin in neonates.
- 2. To quantify its influence on exposure (AUC) when dosing vancomycin and gentamicin according to a national dosing guideline.

METHODS

Patient demographics

Table 1: Patient demographics of vancomycin and gentamicin datasets [1-4].

	Vancomycin [1,2]	Gentamicin [3,4]
Number of patients	437	733
Gestational age (wks)	30 (23-41)	34 (23-42.1)
Postnatal age (days)	12 (1-31)	3 (1-30)
Birth bodyweight (g)	1310 (385-4680)	2320 (440-5240)
Current bodyweight (g)	1368 (415-4860)	2320 (440-5420)
SGA (n (%)) ^[5]	100 (22.9%)	84 (11.5%)

Values are expressed as median [range], except stated otherwise.

Software

o NONMEM 7.5, PsN 5.2.6, Pirana 3.0.

Influence Small for Gestational Age (SGA) on CL

o In a two-compartment model for vancomycin and gentamicin ^[6] SGA was studied together with GA or bBW (as antenatal predictor) and PNA (as postnatal predictor) for CL.

Model-based simulations of influence of SGA

- O Stochastic simulations (n=500).
- **Vancomycin:** dosed on current bodyweight based on 4 subgroups: bBW (< and > 2.5 kg) and PNA (< and > 7 days) (Dutch Pediatric Formulary ^[7]).
 - Efficacy: AUC 400 600 mg*h/L.
- **Gentamicin:** dosed on current bodyweight based on 4 subgroups: GA (< 32, 32-37, > 37) and PNA (< and > 7 days) (Dutch Pediatric Formulary [8]).
 - Efficacy: AUC > 80 mg*h/L & peak levels 8 12 mg/L.
 - Toxicity: trough levels < 0.5 1 mg/L.

CONCLUSIONS

- o Being born **Small for Gestational Age (SGA) has a significant impact on CL** of both vancomycin and gentamicin in neonates. SGA neonates have a **higher CL** of these renally excreted drugs, likely due to a higher GA compared to AGA neonates of the same bBW and PNA.
- o Model-based evaluations show that **below-target AUC occurs more often in SGA neonates** when dosed according to a national dosing guideline, particularly for **vancomycin**, which requires further attention in neonatal dosing guidelines.

RESULTS

Influence Small for Gestational Age (SGA) on CL

In a model with birth bodyweight (p<0.001) and postnatal age (p<0.001) as covariates, **SGA** proved a **significant covariate** for CL for both vancomycin and gentamicin:

- o **Vancomycin:** CL **30% higher** (RSE 4%) in SGA vs AGA neonates with the same bBW and PNA (p < 0.001)
- o **Gentamicin:** CL **20% higher** (RSE 4%) in SGA vs AGA neonates with the same bBW and PNA (p < 0.001)

Model-based simulations of influence of SGA

O **Vancomycin:** lower AUC in SGA vs AGA neonates with 54.1% vs 25.8% of the individuals with an AUC < 400 mg*h/L on day 3 (**Figure 1**). Particularly for neonates with a GA of 36 weeks because of allocation to different dosing groups based on birth bodyweight between SGA and AGA neonates in the Dutch Pediatric Formulary.

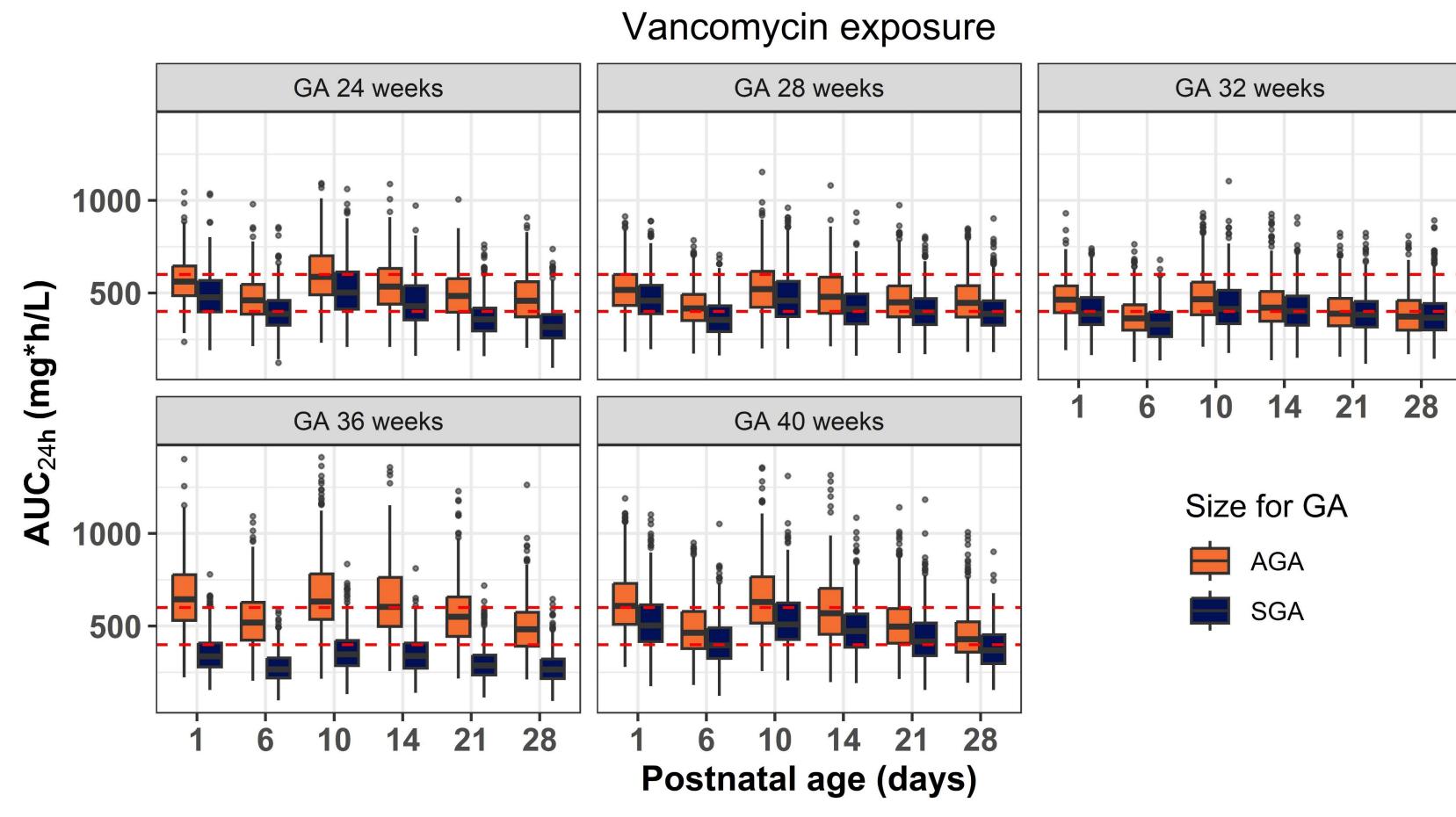


Figure 1: Vancomycin exposure (AUC_{24h} mg*h/L) vs PNA for GA of 24, 28, 32, 36 and 40 weeks for SGA and AGA neonates on day 3 of vancomycin treatment according to the Dutch Pediatric Formulary. Target AUC = 400-600 mg*h/L (red dotted lines).

- O Gentamicin: small differences in AUC between SGA and AGA neonates were observed (74.7% vs 70.4% < 80 mg*h/L) (Figure 2).
- O Gentamicin: small differences in peak levels (20.7% vs 8.9% < 8 mg/L) and no major differences in trough levels between SGA and AGA neonates were observed, with 34.5% vs 37.6% showing trough levels > 1 mg/L, respectively (data not shown).

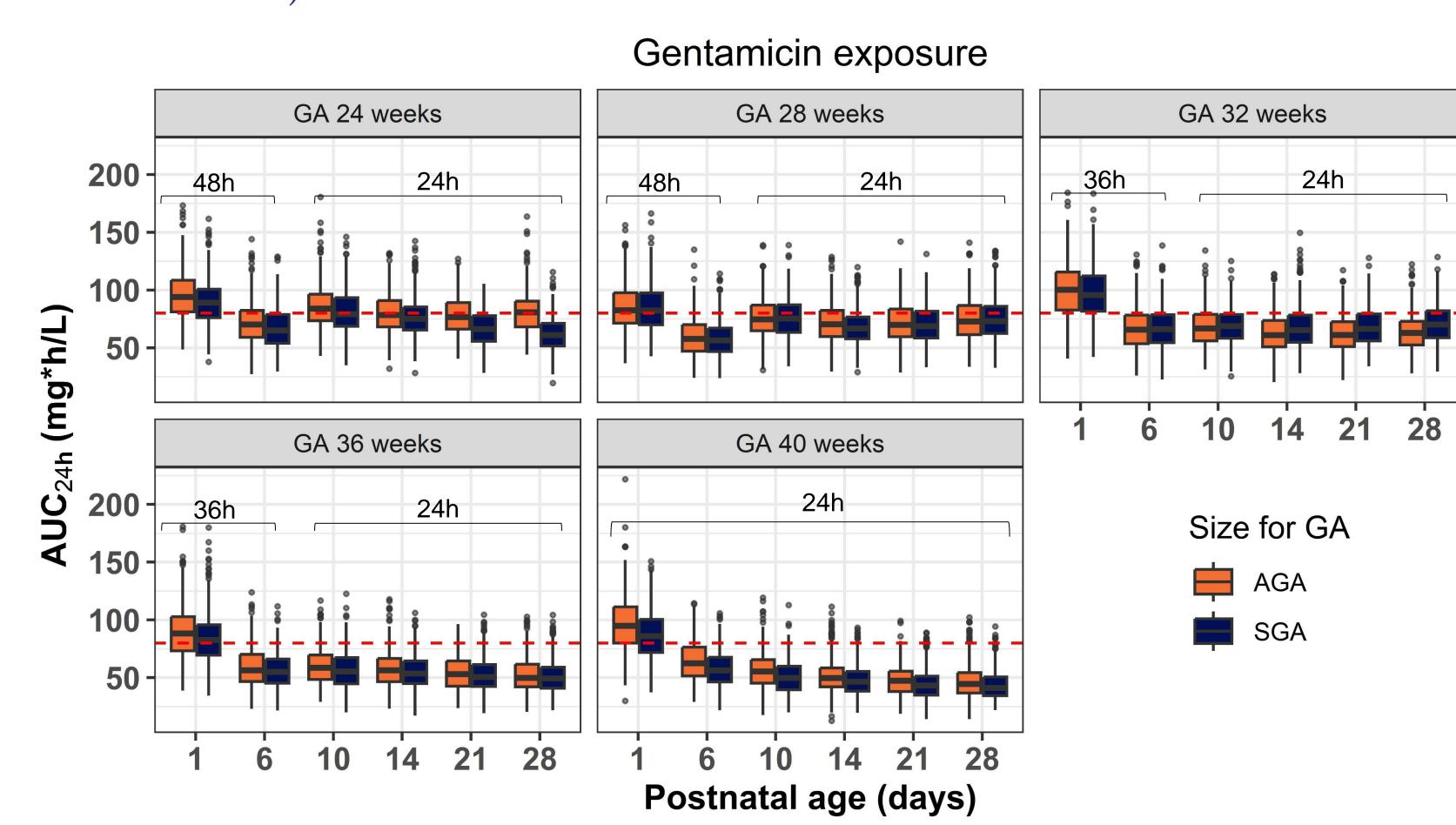


Figure 2: Gentamicin exposure (AUC_{24h} mg*h/L) vs PNA for GA of 24, 28, 32, 36 and 40 weeks for SGA and AGA neonates before the second gentamicin dose according to the Dutch Pediatric Formulary. Target AUC > 80 mg*h/L. 48h, 36h, 24h: patients received gentamicin in a 48h, 36h, 24h dosing scheme as indicated in the panels according to the Dutch Pediatric Formulary.



