A Physiological Approach to Renal Clearance From Premature Neonates to Adults

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Quick Read

Background

- A physiological basis to hepatic drug clearance has been widely applied based on the identification of hepatic blood flow as a limiting factor for hepatic clearance but no similar physiological quantity has been demonstrated for renal clearance.
- Gentamicin (gent), amikacin (amik) and vancomycin (vanc) are thought to be primarily eliminated by renal excretion and assumed to involve glomerular filtration.

Methods

- A mixed effects joint model (NONMEM 7.5.1) of the pharmacokinetics of gent, amik and vanc was developed by pooling data from 18 sources (the GAVamycin project).
- Renal function (RF), defined by the ratio of estimated glomerular filtration rate (eGFR) to normal GFR (nGFR), is used to describe individual differences in kidney function.
- nGFR is the predicted GFR with normal kidney function. eGFR predicts the current GFR. Details of the calculation of eGFR, nGFR, and renal function (RF) are described in (O'Hanlon 2023).
- Normal fat mass (Holford 2017) was used to account for differences in mass and body composition (Size).
- GFR clearance is predicted by an asymmetrical sigmoid function of RF.
- Non-GFR clearance is predicted by a simple linear function of RF.
- CLGFRstd=6.96 L/h 70 kg male RF=1
- Maturation function uses postmenstrual age (PMA) and postnatal transition (PNT) using postnatal age (PNA) (Matn).

Results

- Wide dispersion of age, total body mass, height, serum creatinine and renal function.
- Prediction corrected visual predictive checks show good agreement between median observations and predictions when evaluated by time, total body mass (TBM), renal function (RF), and postnatal age (PNA).

Conclusion

- GFR provides a physiological basis to identify renal clearance components.
- Because of different links to RF it seems that non-GFR clearance is describing a different mechanism of renal excretion that is not explained by GFR clearance.

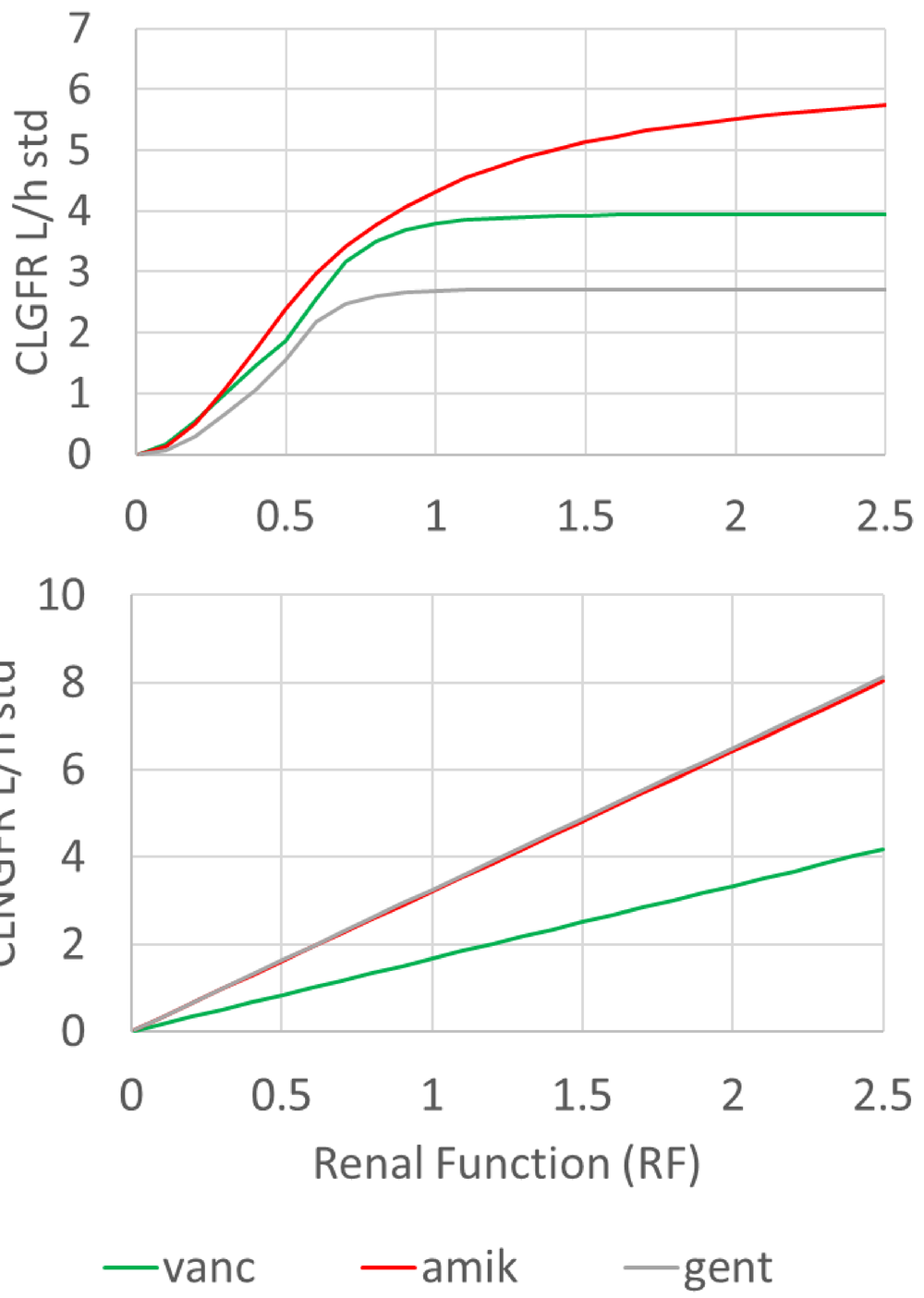
What You Need to Know

- Forget creatinine clearance OFV=83818 (Matthews (2004))
- Renal Clearance requires:

GFR clearance: limited by GFR as asymptote (CLGFR)

Non-GFR clearance: not limited by GFR (CLNGFR)

OFV=81743 ; dOFV=2075

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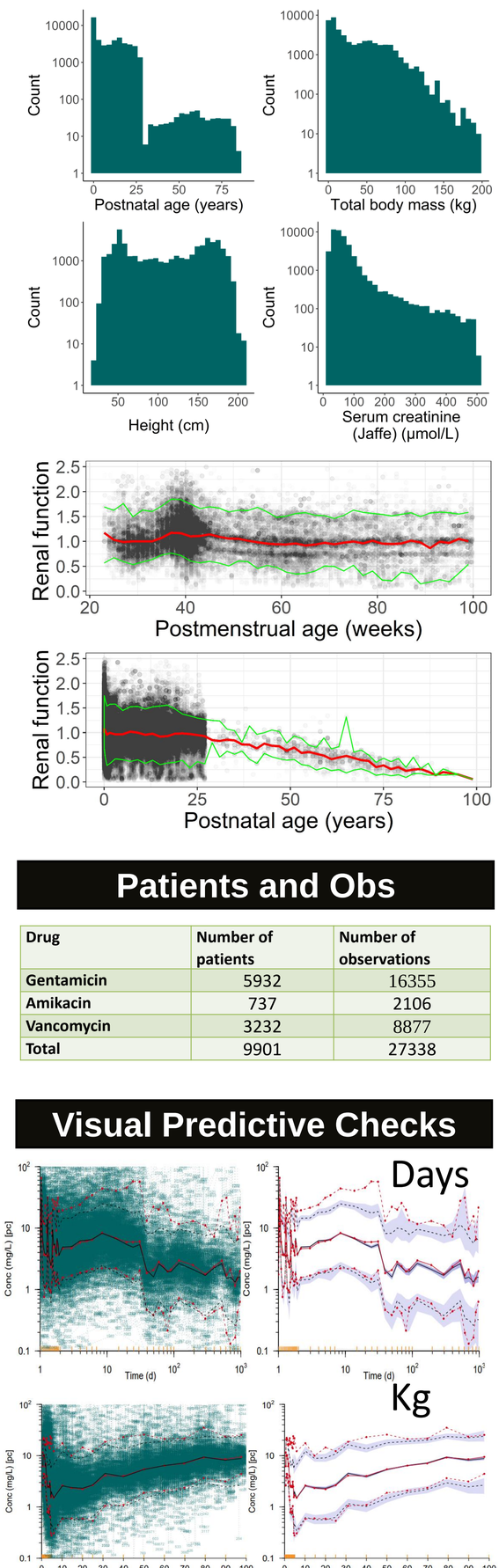
GFR CL     = nGFR   * f(RFgfr)
non-GFR CL = CLNGFR * f(RFngfr)

if (is_GFR CL) then ; Holford et al. PAGE (2023)
      f(RFgfr)=1/(1+(RF/CLGFR_RF50)**(-CLGFR_HILL))
      f(RFgfr)=RF
else ; Matthews (2004)
      f(RFngfr)=RF ; nGFR*RF = eGFR ~= eCLcr
      f(RFngfr)=1
endif
```

The Details

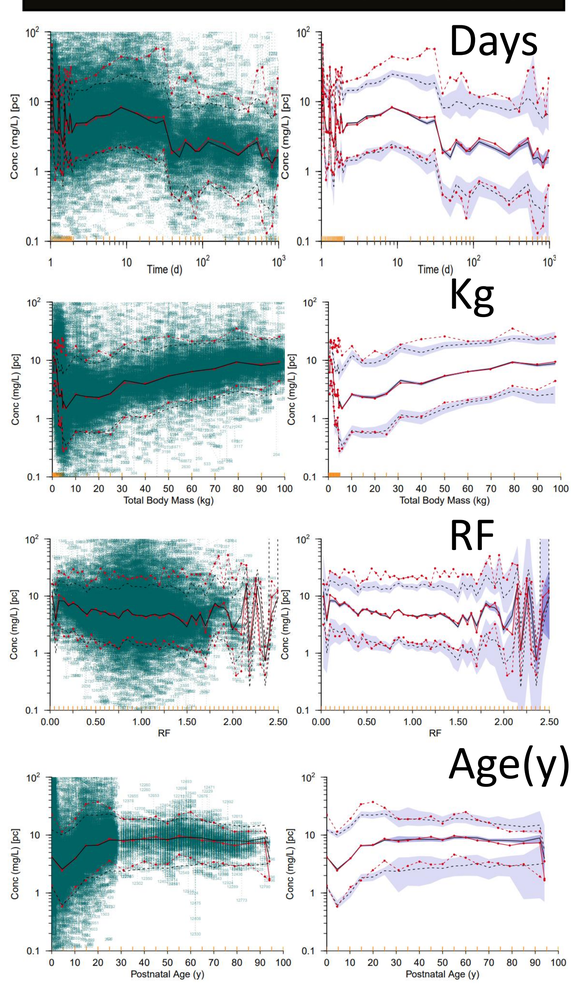
Covariates



Patients and Obs

Drug	Number of patients	Number of observations
Gentamicin	5932	16355
Amikacin	737	2106
Vancomycin	3232	8877
Total	9901	27338

Visual Predictive Checks



Prediction corrected visual predictive checks for gent, amik and vanc concentrations.

- The 5%, median and 95% percentiles of the distribution of the observations (red lines) and predictions (black lines) compare the distributions.
- The numbers in the left-side plot link observations in the same individual.
- The 95% confidence intervals for the prediction percentiles are shown by the purple-shaded areas in the right-side plot.
- The yellow lines on the x-axis show the data bins used in the construction of the VPC.

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Matthews, I., C. Kirkpatrick and N. Holford (2004). "Quantitative justification for target concentration intervention--parameter variability and predictive performance using population pharmacokinetic models for aminoglycosides." Br J Clin Pharmacol 58(1): 8-19.
O'Hanlon, C. J., N. Holford, A. Sumpter, H. S. Al-Sallami (2023). "Consistent Methods for Fat Free Mass, Creatinine Clearance and Glomerular Filtration Rate to describe Renal Function from Neonates to Adults." CPT Pharmacometrics Syst Pharmacol 12: 401-412.