

Model-informed simulation for optimal vancomycin dosage in pediatric patients with febrile neutropenia: implication of augmented renal clearance on appropriate dosing

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Background & Methods

BACKGROUND

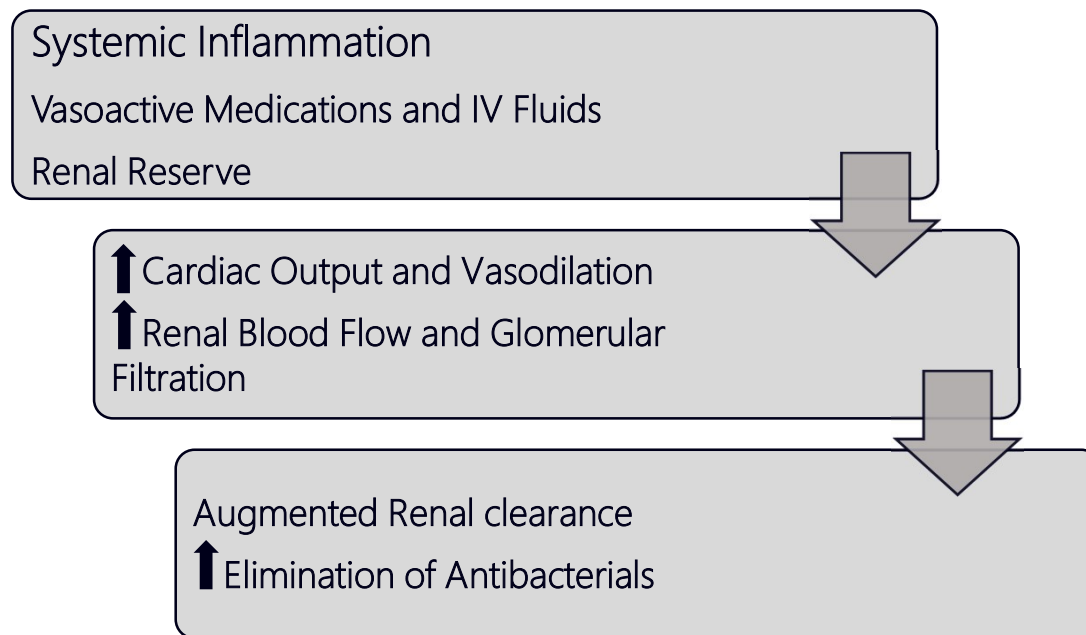
- The recommended dose of vancomycin (VCM) for children is 40-60 mg/kg/day. (*Liu C et al., 2011, Clin Infect Dis 52: e18-55*)
- Febrile neutropenia (FN) associated with augmented renal clearance (ARC) is reported, which is a form of enhanced renal function/clearance.
- We characterized VCM pharmacokinetics in a population of children with FN after hematopoietic stem cell transplantation (HSCT), and propose a new dosing schedule to improve VCM exposure and limit acute kidney injury (AKI).

METHODS

- Inclusion criteria: children (age 0-17), treatment with VCM for FN following HSCT from 2009 to 2014 in SickKids.
- PK modeling: Population PK analysis using a 2-compartment model structure in NONMEM.
- Dosing simulation: $AUC/MIC = 400-650$ was used for target exposure for Monte Carlo simulation.

What is ARC?

- ARC is enhanced renal function, which can be seen in critically ill patients, including febrile neutropenia.
- Increased cardiac output, concomitant use of vasoactive drugs and fluid therapy may contribute.



Udy AA et al. (2011) *Curr Pharm Biotechnol* 12 (12):2020-2029.

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Patient demographics

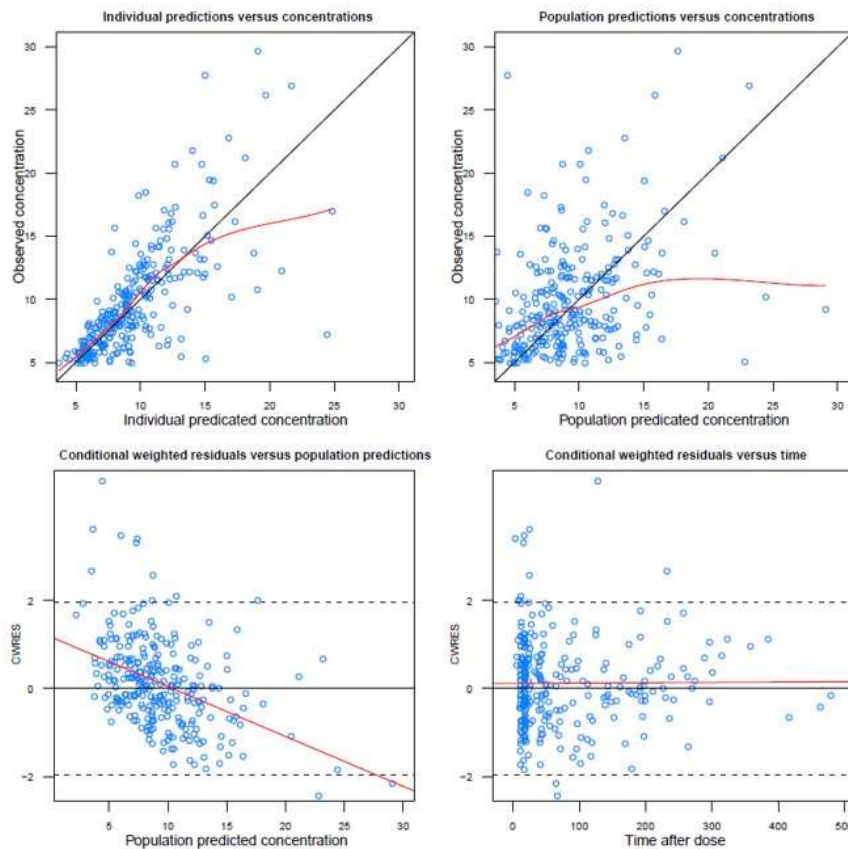
Parameter	Median (IQR)
N	165
Sex (male/female)	93/72
Age (years)	6 (2-12)
Body weight (kg)	20.7 (13.5-46.5)
Serum creatinine (mg/dL)	0.34 (0.25-0.45)
Estimated GFR (mL/min/1.73m ²)	143.3 (116.8-168.4)
Serum albumin (g/L)	31 (28-35)
Serum total bilirubin (μmol/L)	6 (3-10)
Neutrophil count (/mm ³)	10 (0-30)
Body temperature (°C)	38.6 (37.5-39.4)
Transplant type (n)	Bone marrow: 82 Peripheral blood stem cell: 47 Cord blood stem cell: 36

- High eGFR was observed. (Reference value: 120-130 mL/min/1.73m²)

Final model for vancomycin clearance

$$CL = 5.94 \times (BW/70)^{0.75} \times PMA^{3.4} / (47.7^{3.4} + PMA^{3.4}) \times (eGFR/120)^{0.626} \times 1.12^{flag}$$

$(BT \geq 38.0 \text{ } ^\circ\text{C}; flag=1, BT < 38.0 \text{ } ^\circ\text{C}; flag=0)$



- The model fit improved significantly by including body weight, PMA, eGFR and body temperature as covariates.

Initial dosing recommendations for vancomycin

Age	eGFR (mL/min/1.73 m ²)							
	60	80	100	120	140	160	180	200
3 m-6 m	37	44.5	51	57.5	63	69	74	79
6 m-1 y	44.5	53	61	68.5	75.5	82	88	94
1 y-2 y	46.5	55.5	64	72	79	86	92.5	99
2 y-6 y	45.5	54	62	70	77	83.5	90	96
6 y-12 y	38	45.5	52.5	58.5	65	70	76	81
12 y-17 y	32	38.5	44	49	54	59	63.5	68

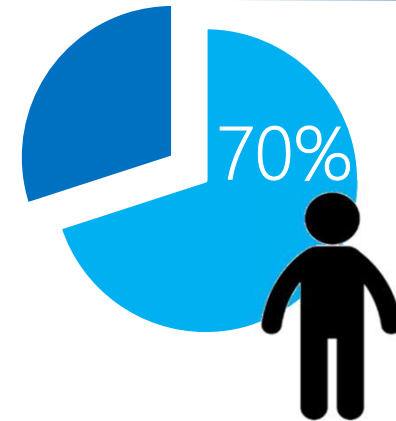
Dose unit: mg/kg/day, divided every 6 hours.

- eGFR > 120 mL/min/1.73m²: 70% of population in this study
- Higher dose is required than guidelines

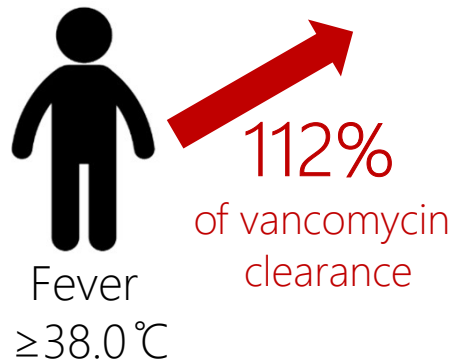


Results

- 70% of patients have augmented renal clearance that further enhances clearance of vancomycin



Augmented renal clearance



- Fever ($\geq 38.0^{\circ}\text{C}$) increases vancomycin clearance by 12%

- Higher vancomycin dosage is required for children with FN



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Conclusions

- ✓ We successfully identified an increased VCM clearance attributed to an increased eGFR by ARC in children with FN.
- ✓ Dosing simulations indicated that children with FN require higher doses than the current standard dose to improve target exposure attainment.