

Current vancomycin dosing recommendations for pediatric patients: a pharmacokinetic evaluation

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Introduction

- Vancomycin
 - First-line treatment for suspected MRSA infections in neutropenic children
 - Few pediatric pharmacokinetic data available
 - AUC/MIC is preferred parameter
 - Current dose regimens appear insufficient to obtain $AUC/MIC \geq 400$
 - Vancomycin clearance increased in hematology-oncology patients

Le et al. Pediatr Infect Dis J 2013

Fernandez et al. Clin Pharmacokinet 2009

Problem

- Initial dose regimen in UZ Brussel: 15mg/kg 4 times daily, adjusted afterwards according trough levels
- However:
 - Initial trough levels far too low
 - Several days (up to 1 week) often needed to obtain adequate trough levels

Research questions

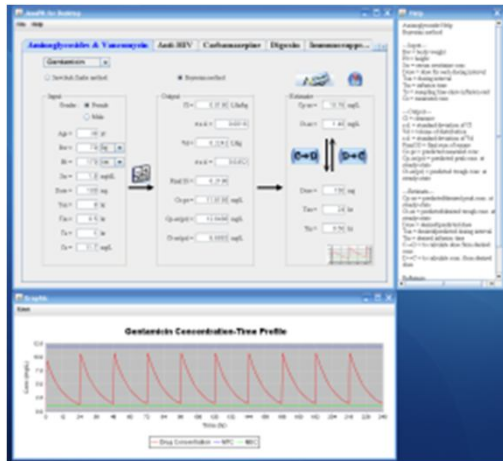
- Influential factors on vancomycin clearance, trough levels and AUC/MIC in pediatric patients?
- Doses needed for therapeutic trough level and AUC/MIC \geq 400?
- “Normal” pediatric patient vs. hematology/oncology: different dose needed for AUC/MIC \geq 400?

Methods

- Retrospective study: 2011-2013
- Inclusion criteria
 - Intermittent vancomycin infusion
 - Dose frequency: 4 times daily
 - Patient age: > 1 y and <18y
 - Steady state (≥ 4 doses)
 - Serum creatinin values available
 - ≥ 2 trough values available
 - Not on intensive care
- Data collected from electronic patient files
 - Vancomycin dose, frequency, infusion time, trough levels
 - Age, gender, weight, length
 - Diagnosis, comorbidities
 - Creatinin clearance, administered fluids, (nephrotoxic) co-medication

Methods

- One-compartment first-order model with Bayesian analysis: simulation possible when only trough levels available
- PK software : JPKD (*JavaPK for Desktop*), Kaoshiung Medical University Taiwan



 **JPKD** v3.1
JavaPK for Desktop

- Input : gender, body weight, body length, VANC dose, dosing interval, infusion time, serum creatinin, trough value
- Output : Volume of distribution, vancomycin clearance

Wrisko et al. Ther Drug Monit 2000

Methods

- Renal clearance: Schwartz equation
- MIC = 1 mg/L (conservative approach)
- Adequate trough levels: 10-20mg/L
- Patients stratified according age: < 6 year , 6 -12 year , > 12 year

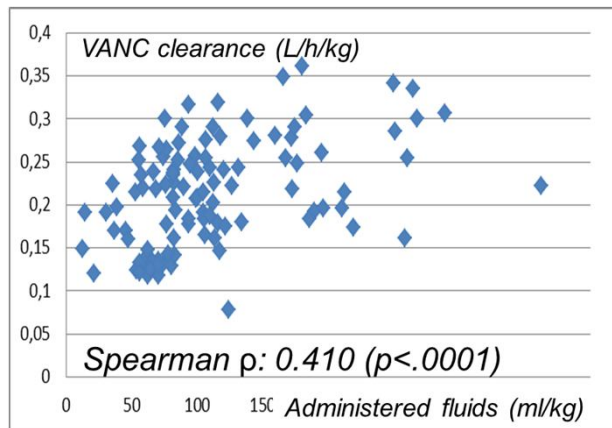
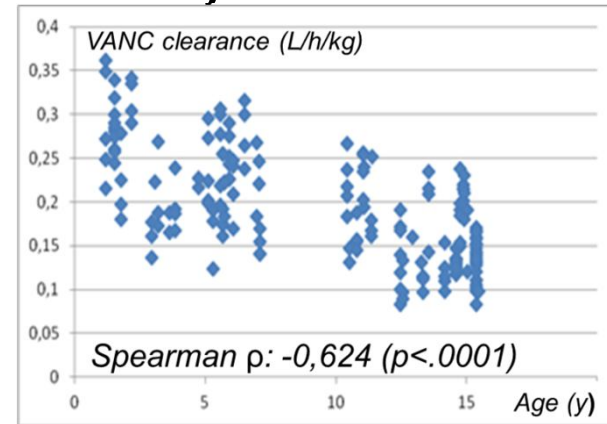
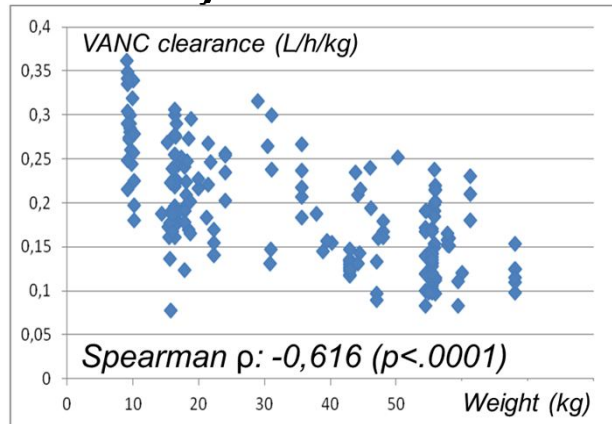
Results

- 24 patients (21 hematology/oncology) → 183 trough levels available for analysis
- Patient characteristics

Patient variables (N=24)	Median (interquartile range)
Age (year)	6.3 (range 1 - 15)
Gender (male/female)	15/9
Hematological/oncological malignancy	21
Body weight (kg)	19.98 (16.35 - 43.00)
Length (cm)	114.50 (102.60 - 156.00)
Serum creatinin (mg/dL)	0.38 (0.30 - 0.45)
VANC trough level (mg/L)	10.13 (7.14 - 13.54)
Vancomycin clearance (L/hr/kg)	0.186 (0.14 - 0.24)
Creatinin clearance (ml/min/1,73m ²)	195.08 (156.58 - 244.44)
VANC distribution volume (L/kg)	1.08 (1.06 - 1.11)

Results

■ Vancomycin clearance: univariate analysis



Significant correlations with:

- Weight
- Fluids
- Age

Results

- Overall impact of age

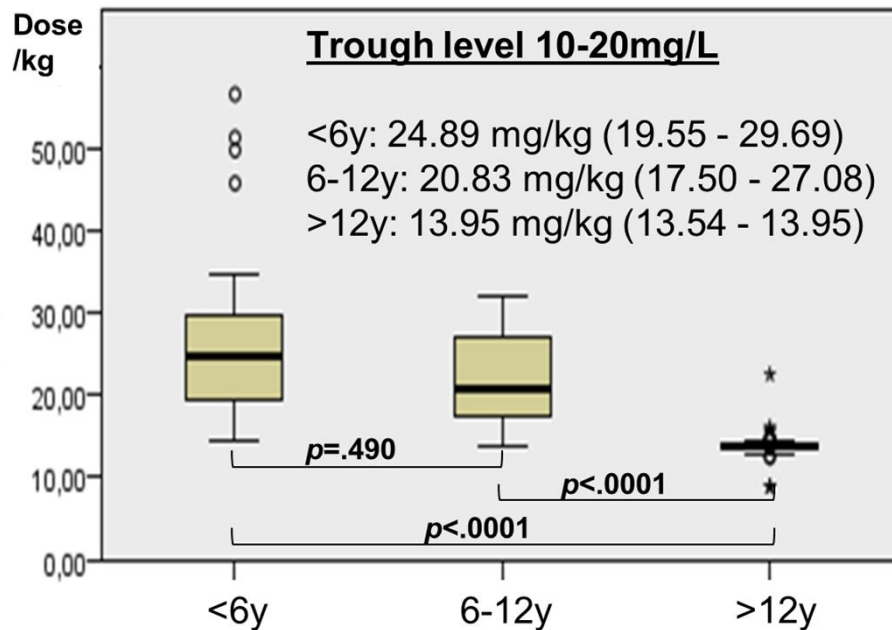
Age (years)	Number of patients	Median VANC clearance (L/h/kg)	Median dose (mg/kg)	Median trough (mg/L)
< 6	9	0.2260	24.31	9.89
6 -12	11	0.2071	18.38	10.55
> 12	4	0.1350	13.95	11.41

- Agreement between AUC/MIC and trough levels: 86% (PPV: 80%)

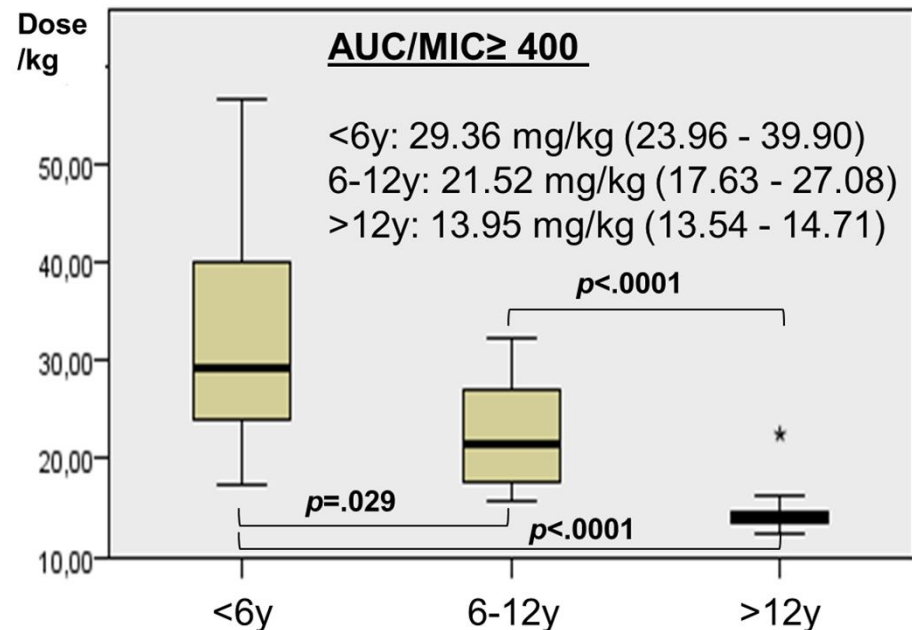
AUC/MIC	Trough level (mg/L)		
	< 10	10 - 20	> 20
< 400	85.4% (70)	14.0% (13)	0% (0)
≥ 400	14.6% (12)	86.0% (80)	100% (8)

Results

Median dose needed for trough levels 10-20mg/L per age group

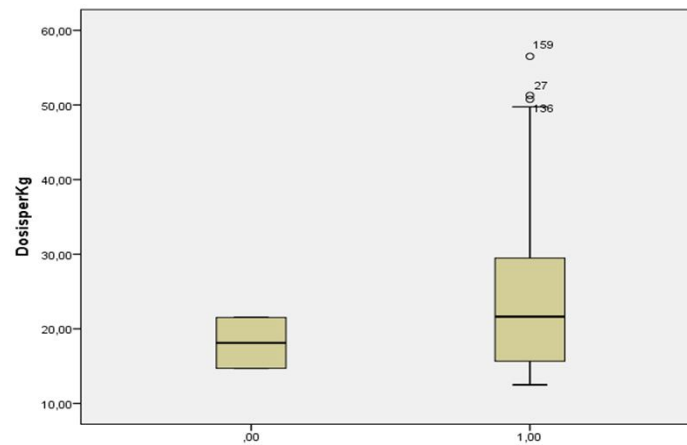


Median dose needed for AUC/MIC ≥ 400 per age group



Results

- Different dose needed for hematology-oncology patients?



For $AUC/MIC \geq 400$

- No malignancy: median dose 18,12 mg/kg QDS
- Malignancy: median dose 21,63 mg/kg QDS

Discussion & conclusion

- Current VANC dose regimen insufficient for our patients
- Age, weight, administered fluids affect VANC clearance
- Therapeutic trough levels + $AUC/MIC \geq 400$: significant differences between age groups
- Possible dosing algorithm
 - < 6 year: 25 – 30 mg/kg QDS
 - Only in case of malignancy? 6 - 12 year: 20 mg/kg QDS
 - > 12 year : 15 mg/kg QDS

*Sanders Pharmaceutisch Weekblad 2012
Cardoso Braz J Infect Dis 2012*

Discussion & conclusion

■ Limitations

- Small population
- No data on clinical outcome
- Data imbalance between patients
- AUC/MIC ≥ 400 & trough levels not validated for children
- Retrospective

■ Future

- Prospective study
- Additional focus on toxicity
- Both peak and trough levels
- Larger patient population
- Clinical outcome