

Pharmacokinetics of vancomycin in intensive-care patients

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Twenty-fifth PAGE meeting, Lisbon, 7-10 June 2016

Objectives

Since vancomycin is often used as a »drug of last resort« against Gram-positive bacteria, **individually adjusted treatment** is of utmost importance to achieve an efficient treatment. This is a critical need because of the increasing resistance of bacteria in the past years [1,2]. The aim of the study was to analyze and clarify the influence of personal characteristics on the pharmacokinetics of vancomycin and to provide a **population pharmacokinetic model** through which one could adjust and optimize dosing in an individual patient.

Methods

- a retrospective study of concentration-versus-time data for vancomycin in plasma,
- 33 critically ill patients from the Hospital Center Tondela – Viseu,
- a population pharmacokinetic approach,
- log-normal distribution of parameters,
- Adapt 5[3],
- »forward selection«,
- expectation-maximization algorithm,
- validation with bootstrapping with replacement (n=50).

Table 1: Population characteristics

Characteristic	Mean ± SD	Interval (min - max)
No of patients	33	/
No of conc. – time points	165	/
Age	64 ± 15	21 - 82
Sex	24 ♂ / 9 ♀	/
Weight	78.82 ± 17.05	55.92 - 122.2
Height	164.4 ± 8.940	147.0 - 180.0
CLCr	127.5 ± 50.52	41.20 - 244.60
ALT	58.61 ± 53.83	13.00 - 237.7
AST	56.47 ± 41.52	18.50 - 204.8
Coad. of furosemide	29 + / 4 -	/

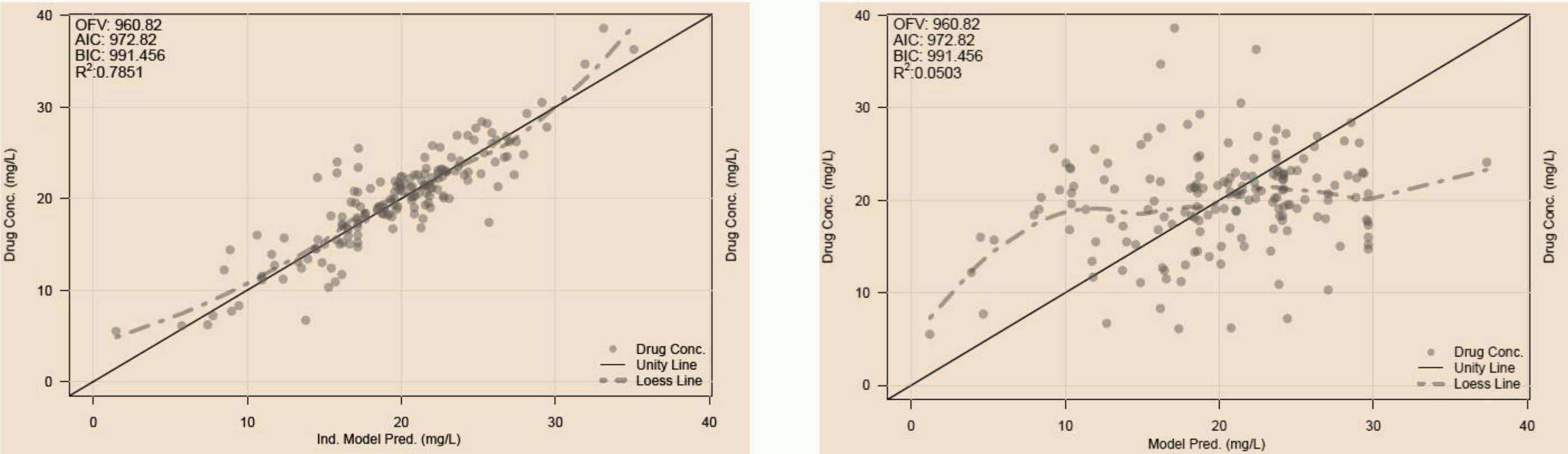
Results

The final pharmacokinetic model → **one-compartment** linear model with additive residual unknown variability and **total body weight** and **renal function** as covariates describing a between-subject variability (BSV). The **typical volume of distribution** (for the **average weight** – table 1) was **64.9 L** and was proportionally associated to the total body weight. BSV of Vd was **66.6%**. The **typical clearance of vancomycin** (for the **average CLCr** – table 1) was **4.02 L/h** and was associated to creatinine clearance as a marker of renal function. BSV of Cl was of **30.6%**. Residual unknown variability was 2.96 mg/L. The model was shown to be robust, since no 95% confidence intervals of parameters of bootstrap validation included zero and the results were within that interval.

Table 2: Final estimates: Base model vs. Final model

Parameter	Base model	Final model
	Estimate (RSE)	Estimate (RSE)
OFV	960.8	949.9
BIC	991.5	985.6
θ_{Cl} [L/h]	3.840 (9.75%)	2.210 (32.9%)
θ_{CLCr}	/	0.01420 (45.7%)
Cl ($\theta_{Cl} + \theta_{CLCr} * CLCr_{mean}$) [L/h]	/	4.021
θ_{Vd} [L]	67.20 (27.9%)	/
θ_{Vd} [L/kg]	/	0.823 (22.7%)
Vd ($\theta_{Vd} * Weight_{mean}$) [L]	/	64.87
BSV Cl	33.50% (22.6%)	30.60% (24.8%)
BSV Vd	68.00% (58.9%)	66.60% (30.2%)
Residual variability [mg/L]	2.990 (8.54%)	2.960 (6.46%)

Figures 1 and 2: Base model - Goodness of fit



Figures 3 and 4: Final model - Goodness of fit

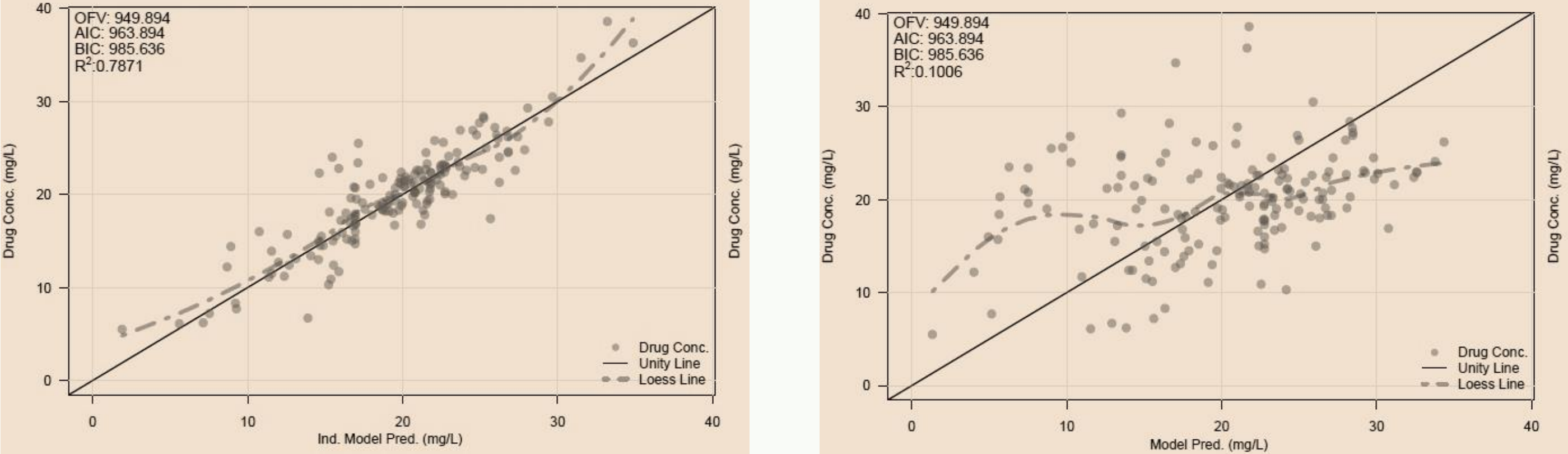


Figure 5: Final model - St. residuals vs individual prediction

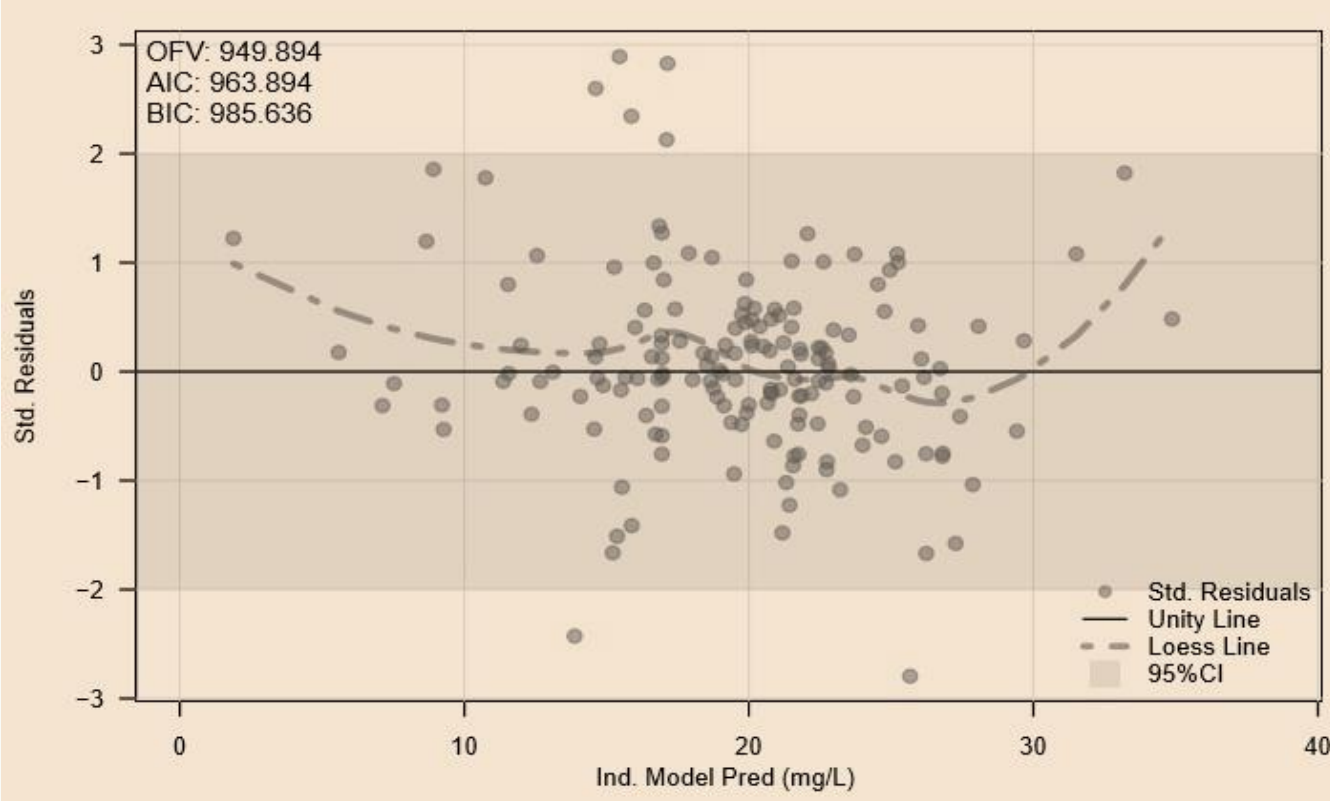


Figure 6: Final model - St. residuals vs model prediction

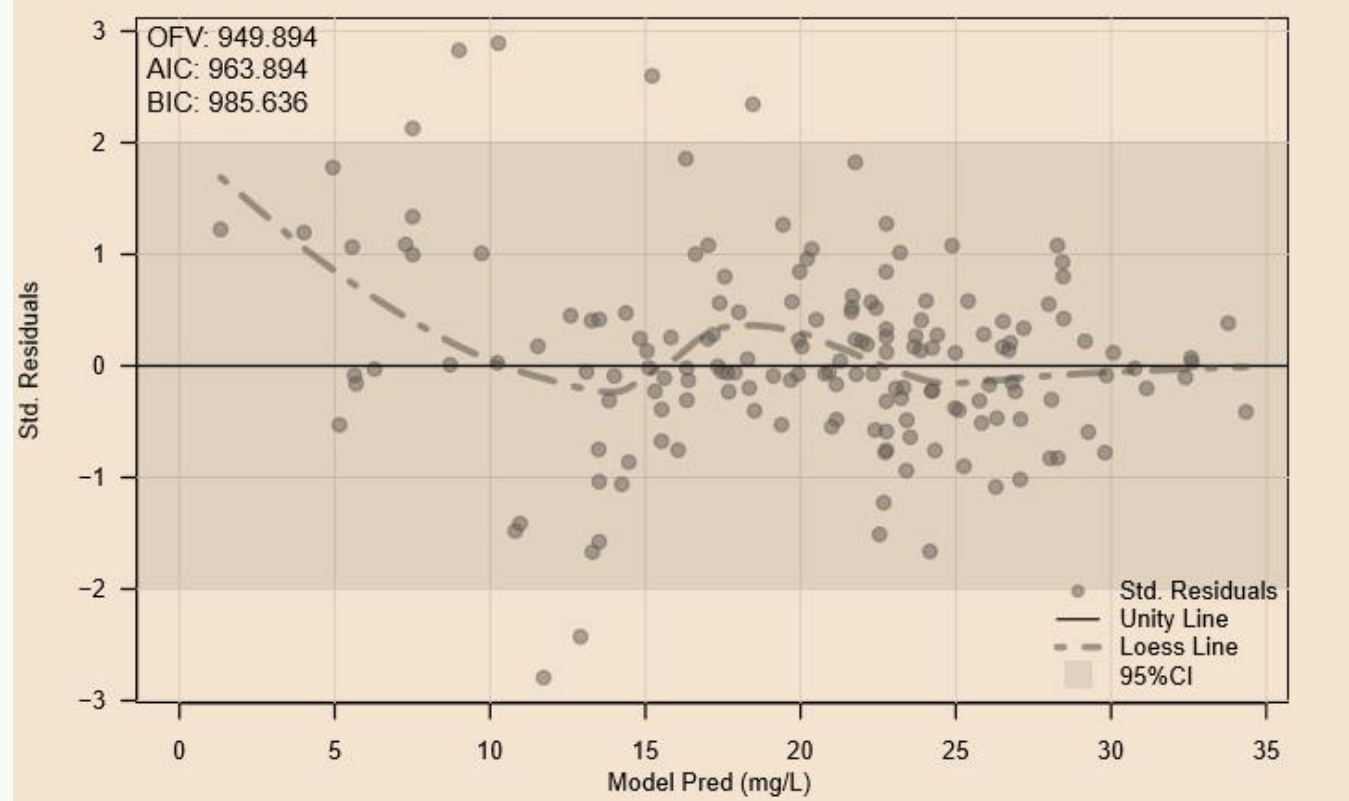
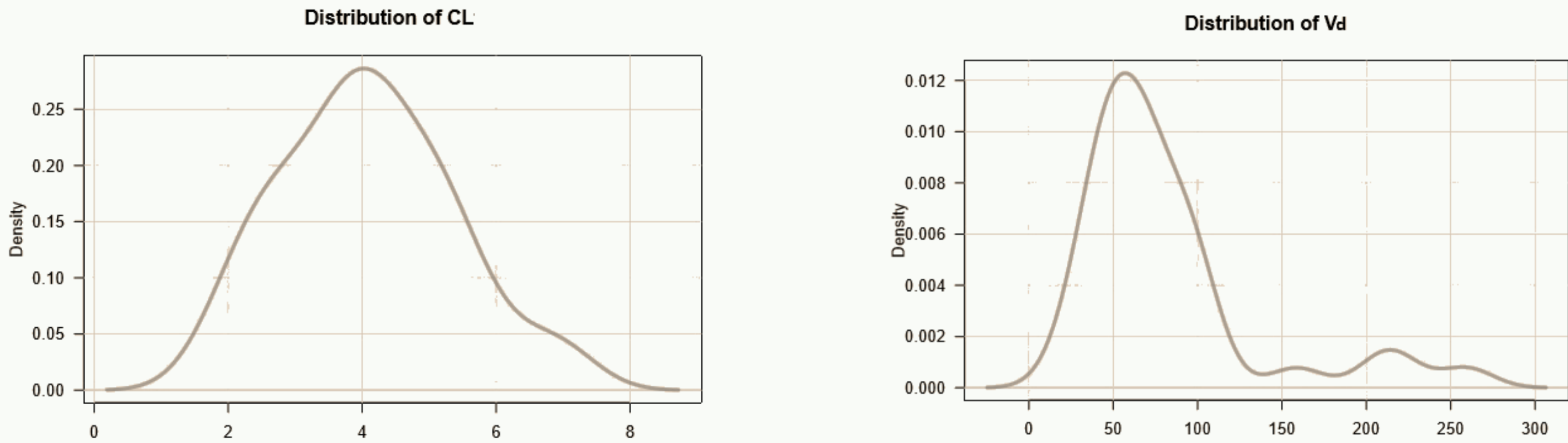


Table 3: Validation results

Parameter	Bootstrapping		Confidence intervals	Final model
	Mean	SD	(2.5 percentile – 97.5 percentile)	
θ_{Cl} [L/h]	2.147	0.739	0.914 - 3.560	2.21
θ_{CLCr}	0.0153	0.00727	0.000261 - 0.0286	0.0142
θ_{Vd} [L/kg]	0.883	0.197	0.514 - 1.262	0.823
BSV Cl [%]	28.34	5.712	14.93 - 37.93	30.60
BSV Vd [%]	59.23	17.32	29.38 - 87.75	66.60
Residual variability [mg/L]	2.849	0.611	1.712 - 3.752	2.96

Figures 7 and 8: Final model - distribution of parameters in the observed population

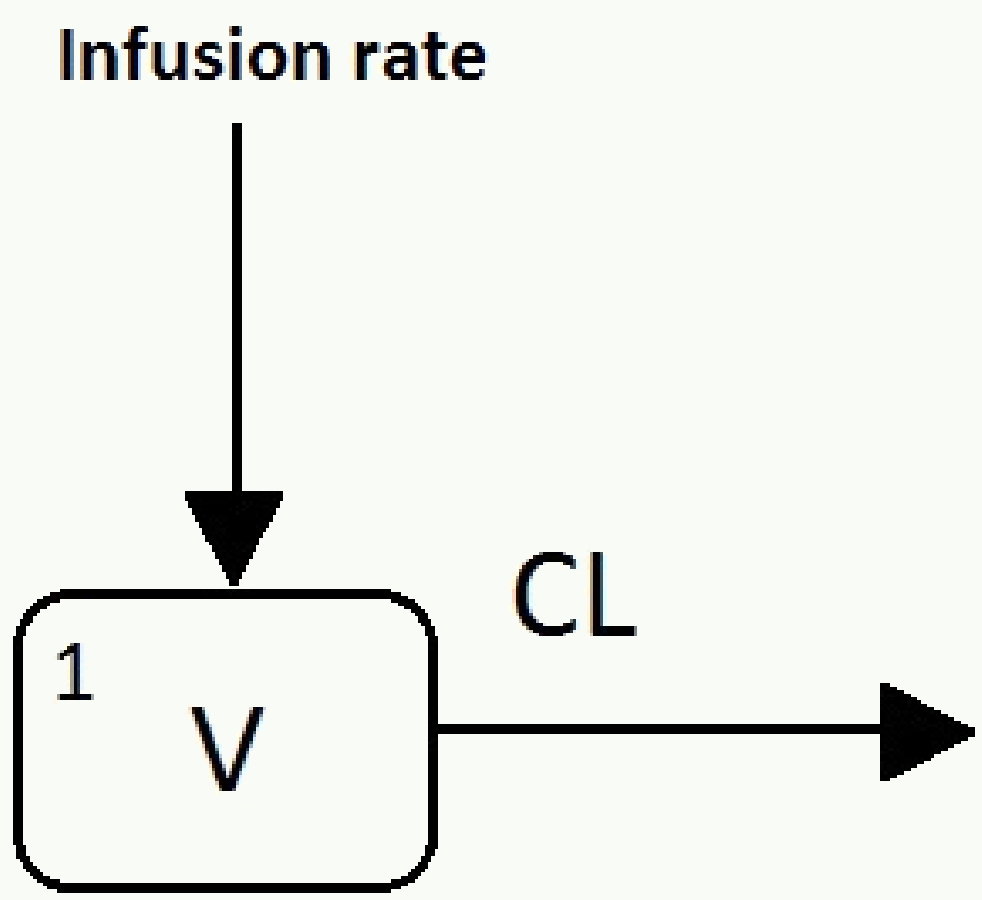


Conclusions

The study showed that the total body weight and renal function play an important role in the individualized therapy with vancomycin and that the dosing regime should be adjusted accordingly in order to achieve an optimized treatment.

Final model

- **1-compartment**
- $Cl_i = (\theta_{Cl} + \theta_{CLCr} * CLCr) * e^{n_i}$
- $Vd_i = (\theta_{Vd} * Weight) * e^{n_i}$



References

- [1] Levine D. (2006). Vancomycin: A History. *Clinical Infectious Diseases*, 42,55-12
- [2] Drugbank.ca, Vancomycin, (2005). *Drug bank*. [online] Available at: <http://www.drugbank.ca/drugs/DB00512> [Accessed May 2016]
- [3] D'Argenio D., Schumitzky A., Wang X. (2009). ADAPT 5 User's Guide: Pharmacokinetic/Pharmacodynamic Systems Analysis Software. *Biomedical Simulations Resource*, Los Angeles