MW Pharm

MwPharm Online for ICU

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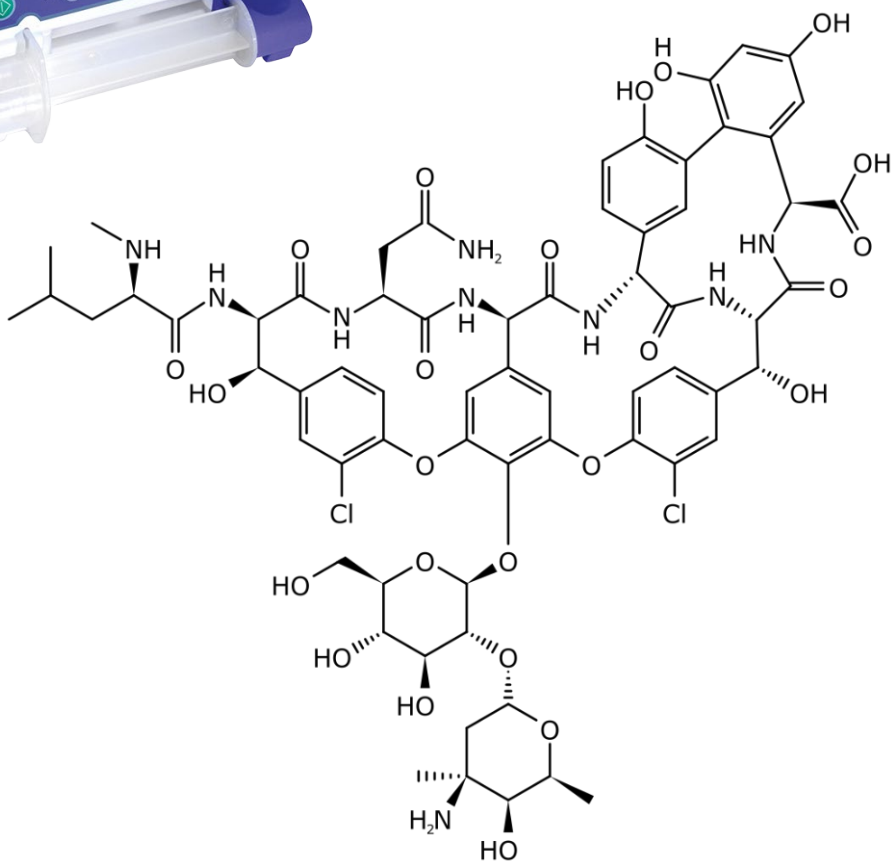
Revision	Date	Author	Description
1.0	14/12/2021	Mediware a.s.	1st revision



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1 INTRODUCTION

1.1 Intensive Care Unit (ICU) Patients

Patients on the ICU represent a very different population compared to non-ICU patients. ICU patients are typically connected to many different medical devices as shown in Figure 1.

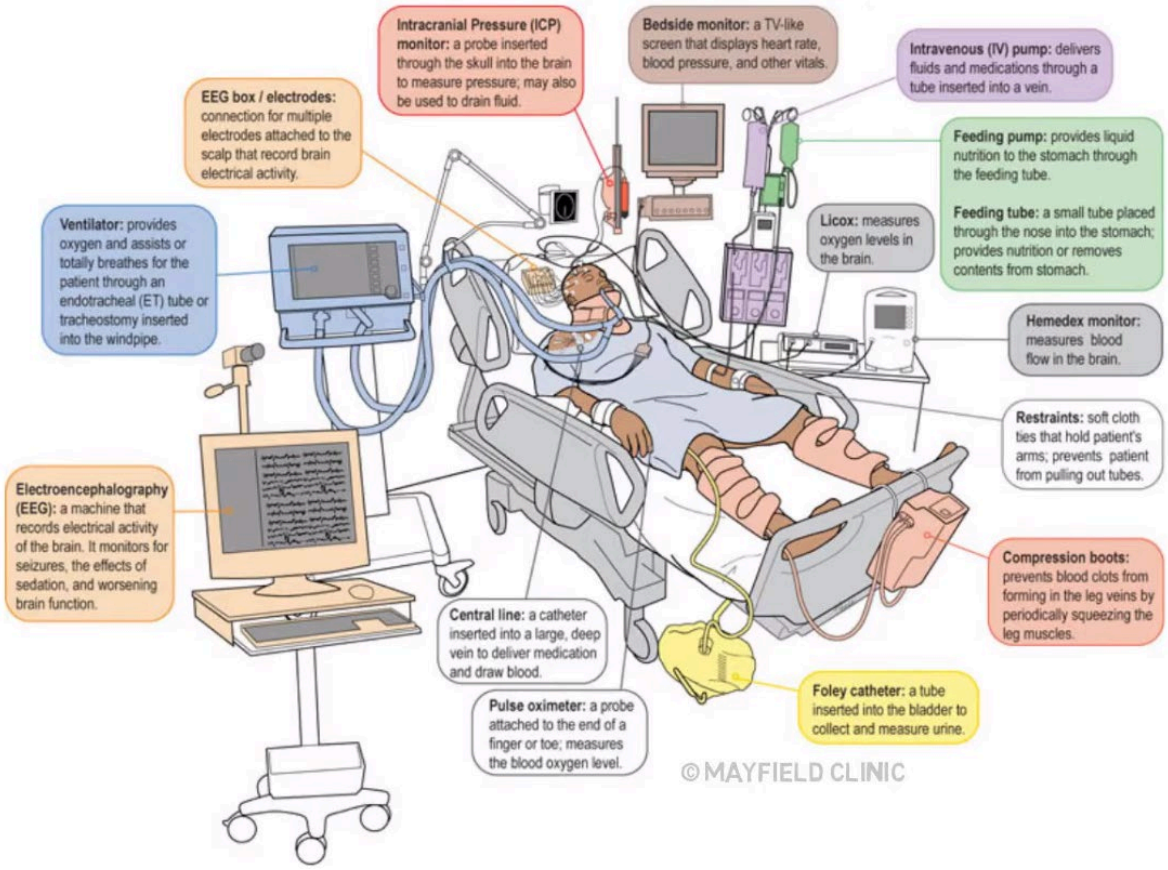

Figure 1. Typical intensive care patient (source: Mayfield Clinic).

Often the ICU patient is unconscious, which requires drugs to be administered using an intravenous pump. Devices that may directly affect the pharmacokinetics of a drug are the ventilator and the dialysis unit.

1.2 Altered Pharmacokinetics of Antibiotics in ICU Patients.

Critically ill patients experience drastic derangements in their physiological parameters, subsequently impacting on the pharmacokinetics of drugs. Physiological parameters include:

- Sepsis and septic shock
- Augmented renal clearance (ARC)

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- Impaired renal clearance
- Liver failure
- Hypoalbuminemia
- Oedema

The effect of these changing physiological parameters dependents on the physicochemical properties of the drugs as shown in Figure 2.

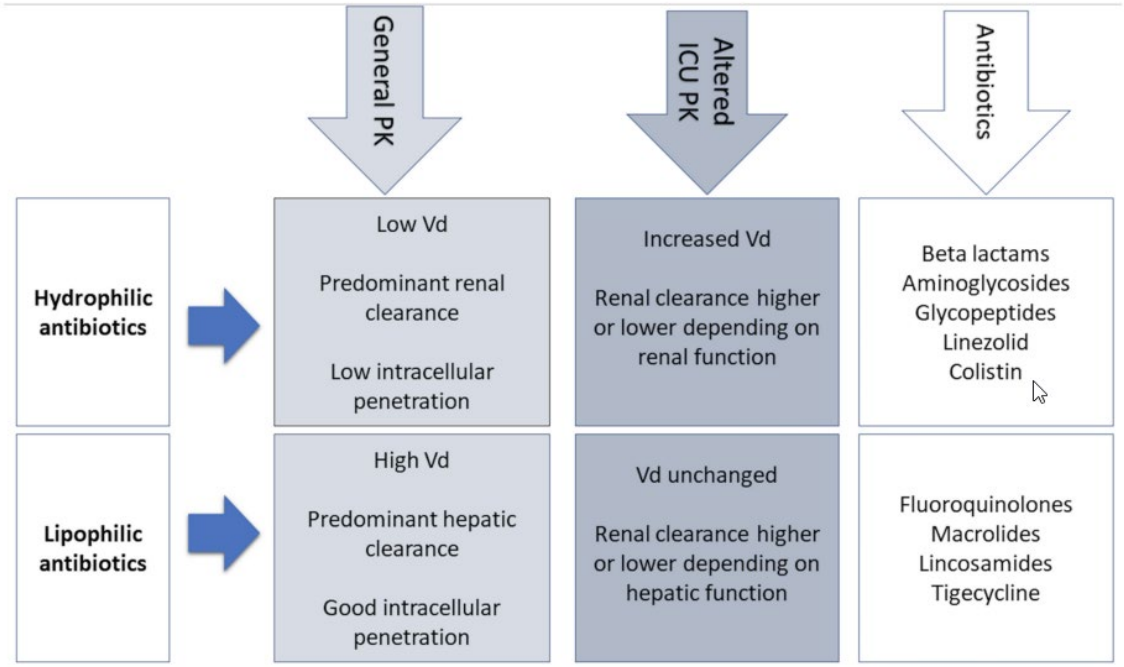

Figure 2. Altered pharmacokinetics of antibiotics in ICU patients (Tsai et al., 1).

1.3 Vancomycin

Vancomycin, a glycopeptide, is hydrophilic, has a low Vd, and elimination is mainly renal. Altered Vd and drug clearance, namely ARC, in the critically ill may lead to low drug exposure (2). The preferred dosing method for vancomycin is a continuous infusion, which is believed to have the following benefits (1).

- Reduced nephrotoxicity
- Faster target attainment
- Lower incidence of subtherapeutic concentrations

The dosing target of vancomycin is an AUC24 > 400 mg.h/L. At the start of therapy, the AUC24 is relatively low, which may cause therapeutic failure. A loading dose is therefore highly recommended. The loading dose of vancomycin is determined by the volume of distribution, whereas the maintenance dose (infusion rate) is determined by the clearance.

Guo et al. (3) evaluated several population models for vancomycin. The model of Roberts at al. (4) performed best with a prediction error (PE) lower than 20% for patients from two Dutch hospitals.

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2 VANCOMYCIN ICU POPULATION MODEL

2.1 NONMEM Model

The final parameter estimates of the Roberts vancomycin ICU model (4) are shown in Figure 3.

TABLE 2. Bootstrap parameter final estimates of the final covariate model

Parameter	Mean	95% confidence interval	
		2.5 percentile	97.5 percentile
Fixed effects			
Clearance (liters/h)	4.58	4.09	5.19
Volume of distribution (liters/kg)	1.53	1.31	1.71
Random effects: between-subject variability, Ω_{BSV} (% coefficient of variation)			
Clearance	38.9	28.3	55.6
Volume of distribution	37.4	16.6	54.9
Random error			
Residual unexplained variability (% coefficient of variation)	19.9	14.5	24.6
SD (mg/liter)	2.4	1.3	3.0

Figure 3. Parameter estimates of the Roberts vancomycin ICU model (4).

The clearance is modulated by the normalized creatinine clearance (mL/min/1.73m²) and the volume by body weight (kg) as shown in the equations below.

Clearance (L/h) $$CL = 4.58 \cdot \frac{CLcrN}{100}$$

Volume (L) $$V = 1.53 \cdot BW$$

This model is a simple 1-compartment model compared to many other non-ICU models, which use 2-compartments. However, 2-compartments are not required here, since in the ICU the primary mode of administration is a continuous infusion, in which the steady state concentration is only determined by the clearance.

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2.2 EDSIM Model

The Edsim representation of the Roberts vancomycin ICU model is shown in Figure 4.

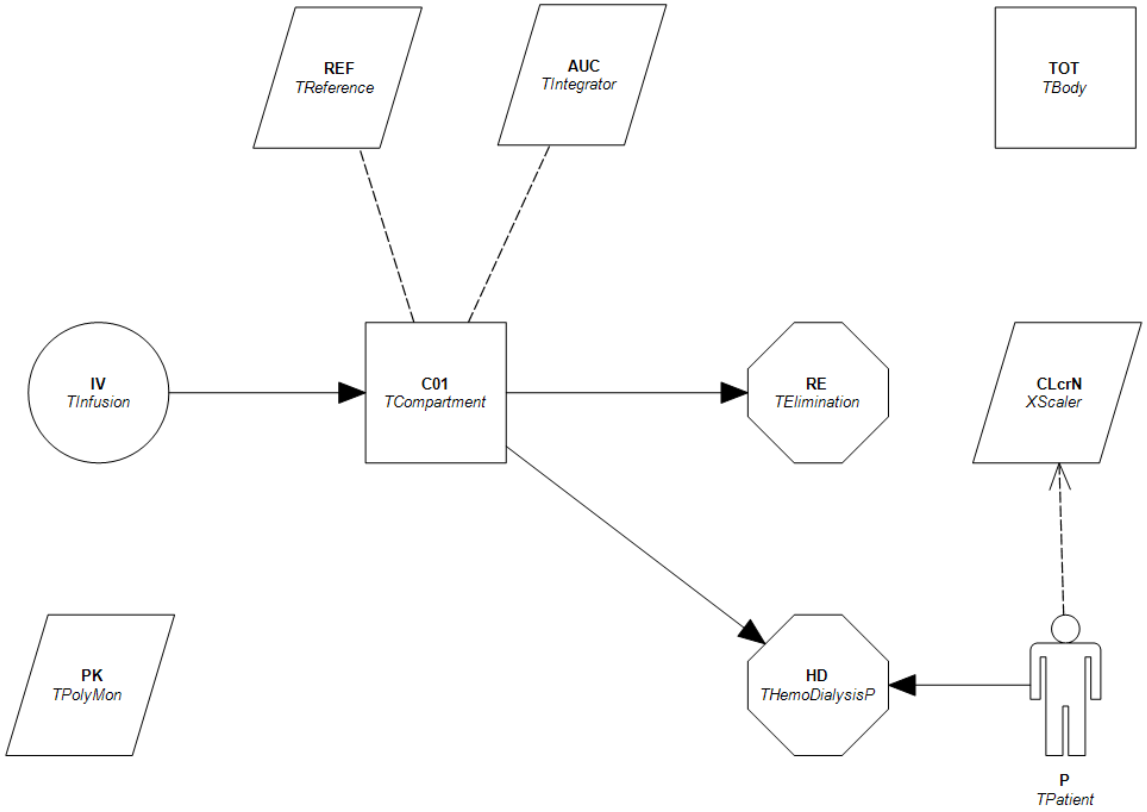

Figure 4. Edsim representation of the Roberts vancomycin ICU model.

The volume is directly scaled by body weight as shown in Figure 5.

PARAMETERS	All ☐	Pop ☑					Allometry		
Name	PopValue	SD	Unit	Fit	Bayes	Log	Scaler	Expo	Format
C01.V	1.53 ±	0.572	L/kg	☑	☑	☑	P.Bw		0

Figure 5. Scaling of volume by body weight.

We did not use the same method for scaling the drug clearance, because the creatinine clearance is a calculated quantity which makes it more difficult to define a reference value (100 mL/min/1.73m²). Instead, we use an external XScaler object named "CLcrN" for calculating the modulation factor.

PARAMETERS	All ☐	Pop ☑					Allometry			Covariate
Name	PopValue	SD	Unit	Fit	Bayes	Log	Scaler	Expo	Format	Symbol
RE.CL	4.58 ±	1.782	L/h*	☑	☑	☑		1	3	CLcrN.CoFactor

Figure 6. Scaling of drug clearance by creatinine clearance.

However, for testing purposes we must find the required creatinine levels causing a particular creatinine clearance. These values are listed in Table 1 for the Jelliffe-21 renal function method. Please note that body weight also affects the calculated creatinine clearance.

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Ccr	Bw	CLcrN
µmol/L	*kg*	*mL/min/1.73m²)*
122.838	70	50
42.506	35	100
62.839	70	100
47.49	140	100
42.218	70	150
25.488	70	250

Table 1. Creatinine levels vs creatine clearance (Jelliffe-21).

2.3 Validation of Covariate Effects

A special validation spreadsheet was used to validate the effects of different covariate values. Here the by Excel calculated values were compared with Edsim reported values (Figure 7).

PARAMETERS

Name	Value	Unit
PK.CL	4.5800265	L/h
PK.CL12	0	L/h
PK.CL13	0	L/h
PK.CL14	0	L/h
PK.fe	1	-
PK.Thalf_01	16.208654	h
PK.Thalf_02	0	h
PK.Thalf_03	0	h
PK.Thalf_04	0	h
PK.V1	107.1	L
PK.V2	1	L
PK.V3	1	L
PK.V4	1	L
PK.Vb	107.1	L
PK.Vmax	0	mg/h
PK.Vss	107.1	L

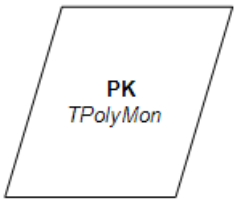

Figure 7. Denormalized PK-parameters of the TPolyMon object.

2.4 Validation of Simulation Output

The Roberts paper contains 3 figures with simulation output (figures 2, 3 and 4). The highest and lowest curves in these figures were digitized (ScanIt software). The resulting data sets were pasted as observations in the Edsim model in order to

compare the results (see chapter 3). Please note that higher loading doses require longer infusion times as shown in paragraph 3.1.

There was an excellent match between the Edsim simulation output and the digitized samples.

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3 VANCOMYCIN SIMULATIONS IN EDSIM

3.1 Roberts et al. Figure 2

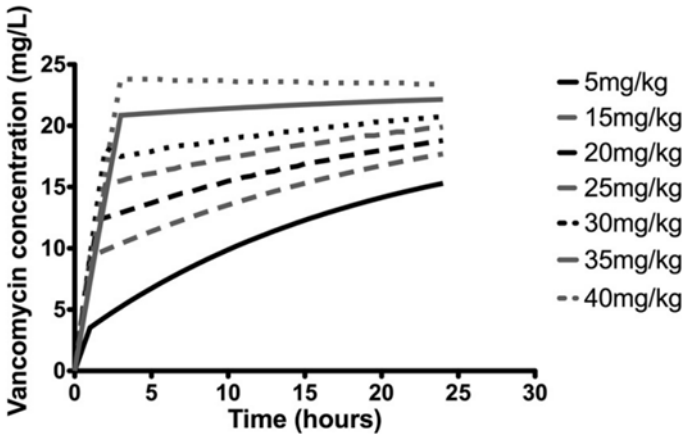
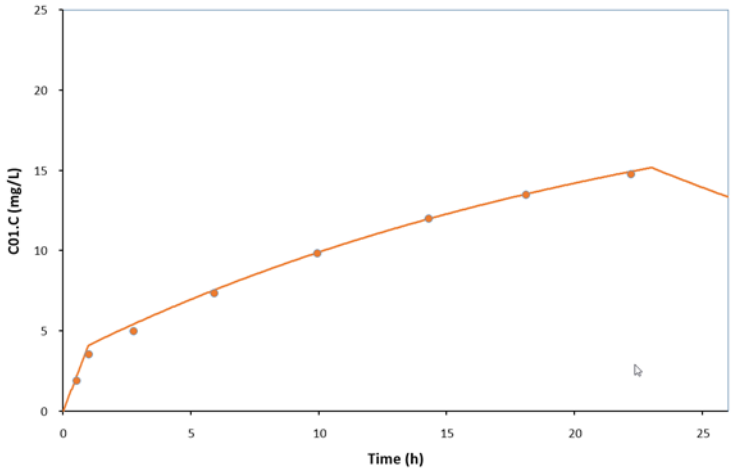


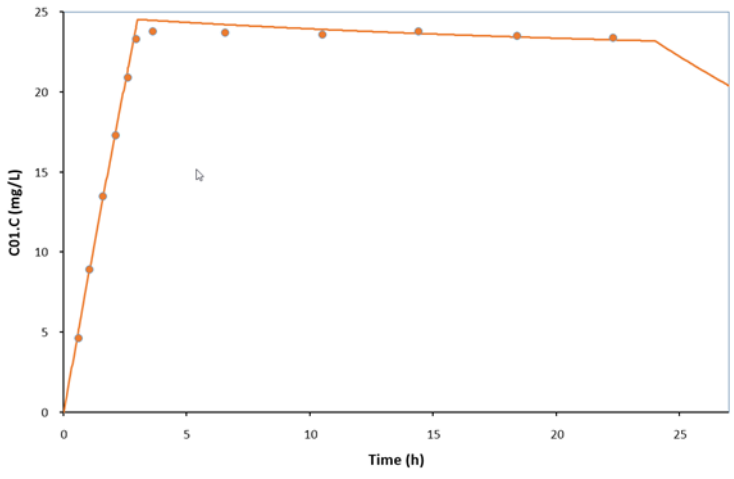
FIG. 2. The effect of loading dose on rapid attainment of target vancomycin concentrations. Different weight-based doses are simulated for a critically ill patient with a creatinine clearance of 100 ml/min/1.73 m^2, followed by administration as a 35-mg/kg/day continuous infusion.

Load (mg/kg)	Tinf (h)
5	1
15	1
20	1.5
25	2
30	3
35	3
40	3



5 mg/kg

infused in 1 hour



40 mg/kg

infused in 3 hours

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3.2 Roberts et al. Figure 3

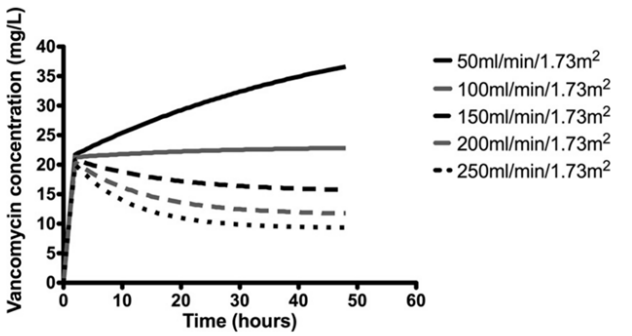
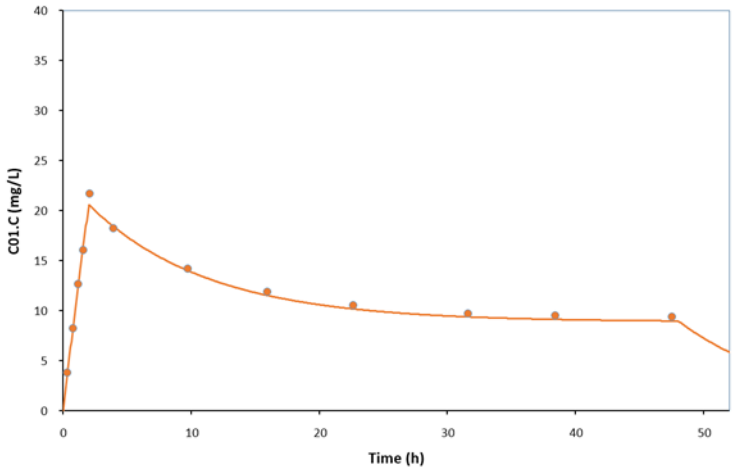


FIG. 3. The effect of creatinine clearance on vancomycin concentrations administered by continuous infusion (35 mg/kg per day after 35-mg/kg loading dose).

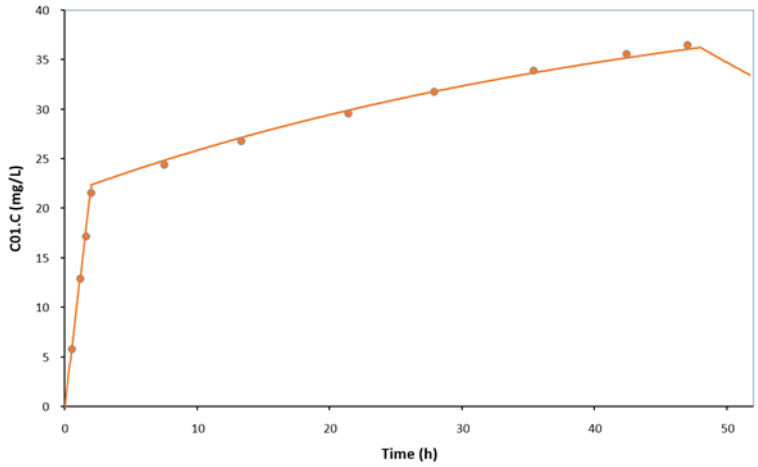
Note:

We inferred that the loading was infused in 2.0 hours (not 3.0 hours)



250 mL/min/1.73m²

(25.488 µmol/L)



50 mL/min/1.73m²

(122.838 µmol/L)

3.3 Roberts et al. Figure 4

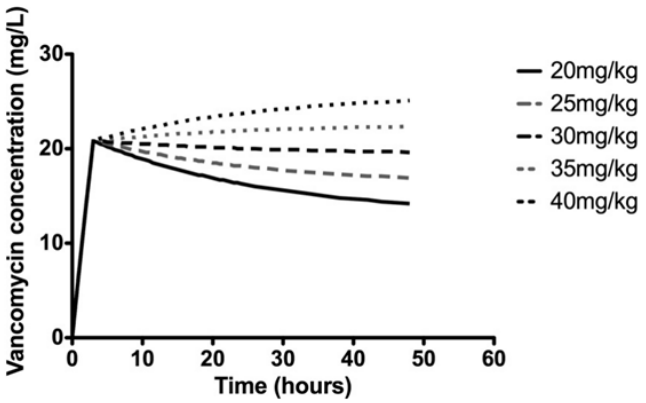
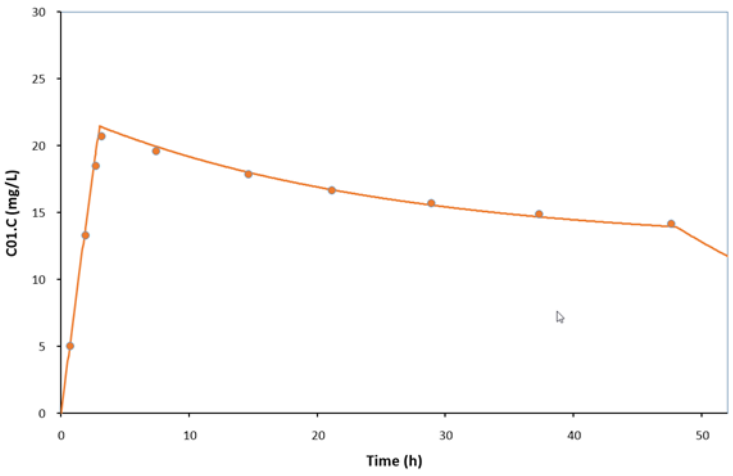


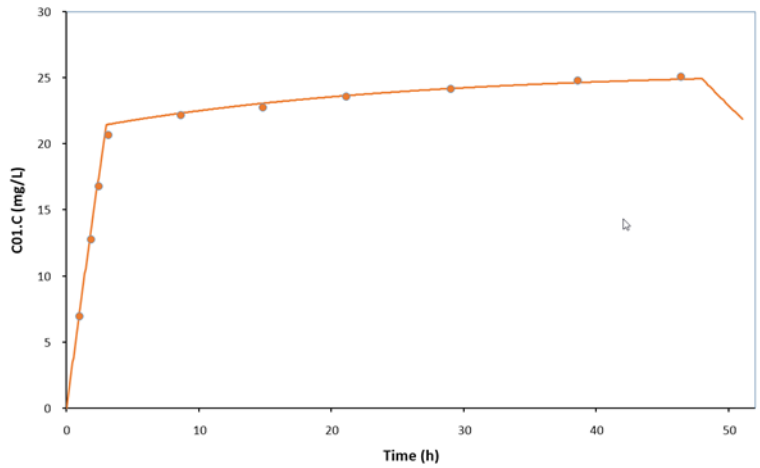
FIG. 4. The effect of different doses (mg/kg) on vancomycin concentrations administered by continuous infusion after a 35-mg/kg loading dose in a patient with a creatinine clearance of 100 ml/min/1.73 m^2.

Note:

Loading was infused in 3.0 hours



20 mg/kg/day

 C01.C (mg/L) Time (h) 0 5 10 15 20 25 30 0 10 20 30 40 50	**40 mg/kg/day**

4 VANCOMYCIN DOSE CALCULATION IN MWPHARM ONLINE

4.1 Model Selection

After the model has been imported, it can be selected in the Case screen (Figure 8).

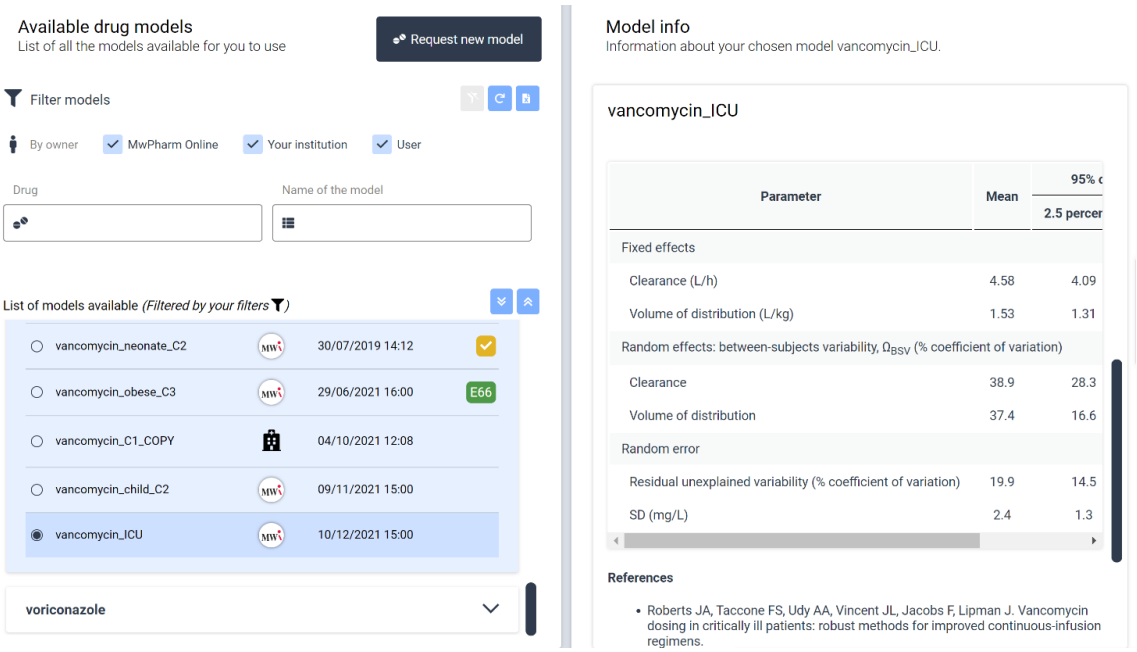


Figure 8. Model selection.

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4.2 Dose Calculation

The Roberts vancomycin-ICU model has been configured for continuous infusions by default using an AUC24 target of 400 mg.h/L.

Figure 9. Dose calculation.

Set the Load setting to "None" if you do not want to use a loading dose (

Figure 10).

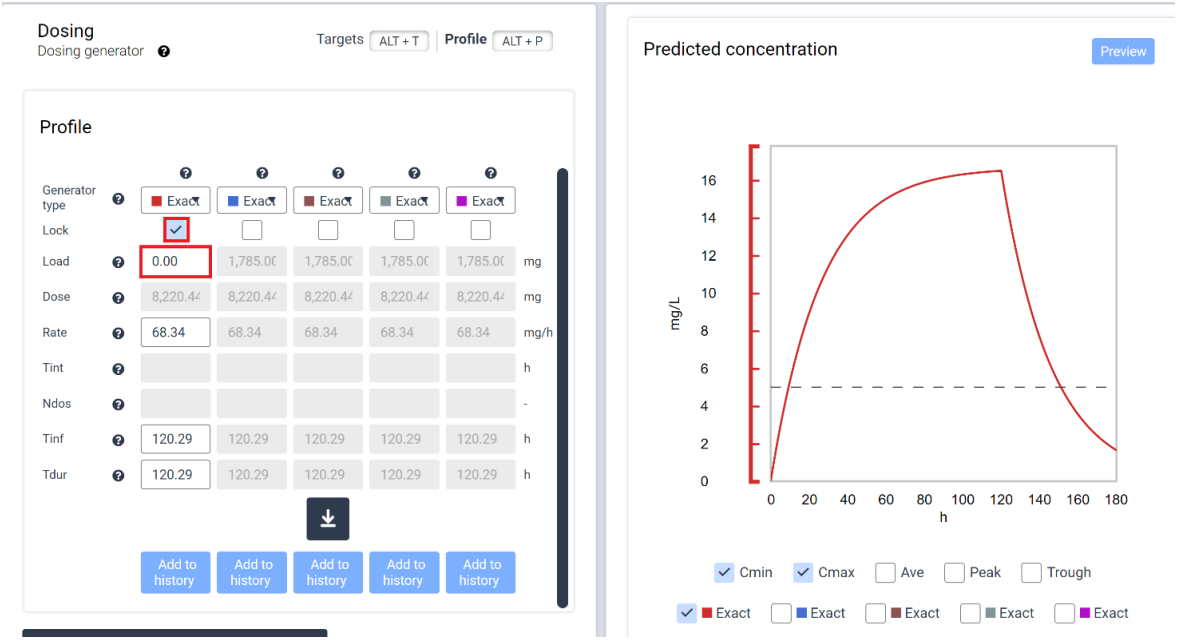

Figure 10. Continuous infusion without a loading dose.

However, this will cause the AUC24 to be suboptimal which may be associated with therapy failure. The infusion duration calculated by MwPharm for reaching 99% steady state is 120 hours. If you reduce this to 24 hours, you can see that the AUC24 without a loading dose at 24 hours is only 240 mg.h/L instead of the recommended 400 mg.h/L (Figure 11).

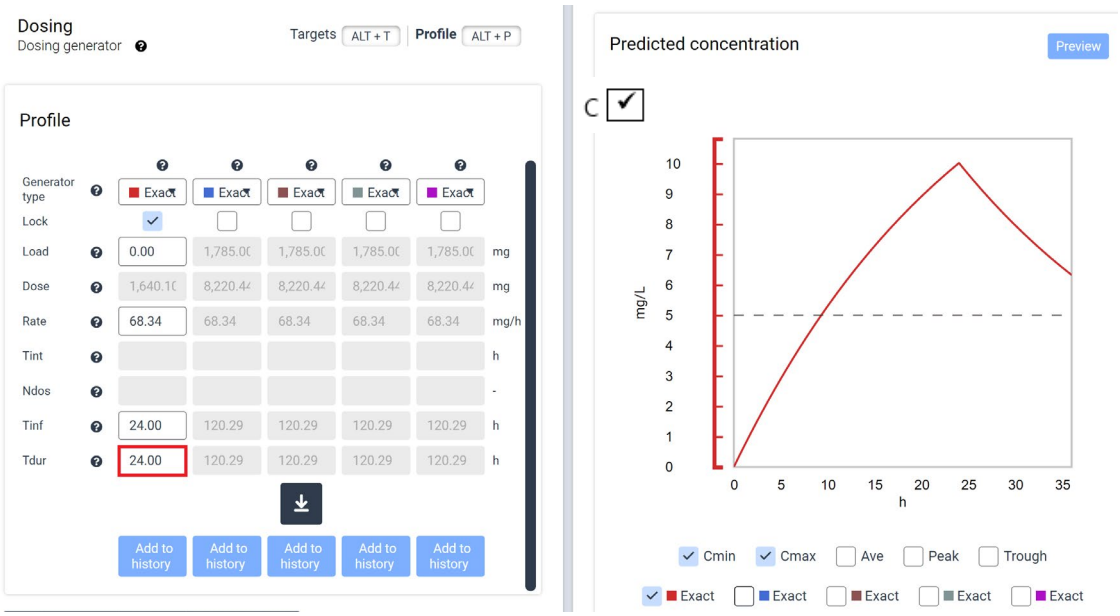

Figure 11. AUC during first 24 hours of therapy.

4.3 Dose Insertion

Click the [Add to History] button for inserting the current user regimen into an existing medication history. Two lines will be added. One for the loading dose and one for the maintenance regimen (Figure 12).

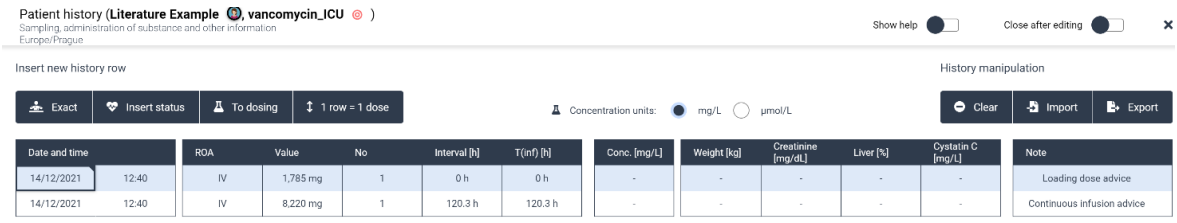

Figure 12. Inserted vancomycin continuous infusion regimen.

Please note that MwPharm will always calculate a bolus loading dose. However, for many drugs this is not recommend. E.g., administering a high dose of vancomycin too rapidly may result in the so-called red man-syndrome, which typically consists of pruritus, an erythematous rash that involves the face, neck, and upper torso. Less frequently, hypotension and angioedema can occur. Roberts et al. (4) therefore recommend the infusion times as shown in Table 2 for a vancomycin loading dose.

Load (mg/kg)	Tinf (h)	Dose mg/70kg
5	1.0	350
15	1.0	1050
20	1.5	1400
25	2.0	1750
30	3.0	2100
35	3.0	2450
40	3.0	2800

Table 2. Recommended vancomycin loading dose infusion times (Roberts et al., 4).

Simply set a safe loading dose infusion time in the MwPharm Online medication history. Shift the start of the continuous infusion accordingly.

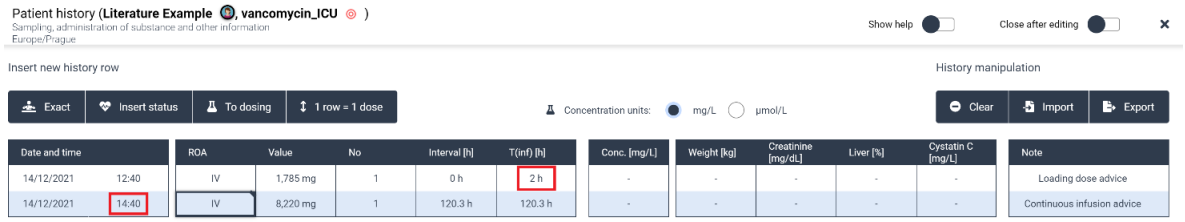

Figure 13. Changing a bolus loading dose into a short infusion loading dose.

The resulting plasma concentration profile is shown in Figure 14.

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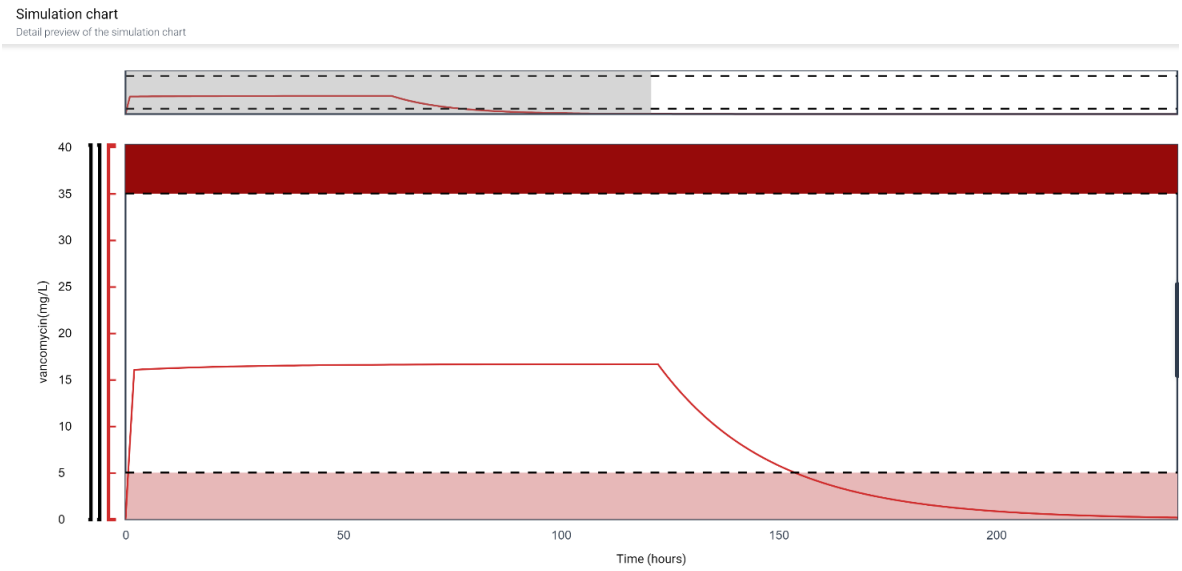

Figure 14. Short loading dose infusion directly followed by a continuous infusion.

5 REFERENCES

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2. **Póvoa P, Moniz P, Pereira JG, Coelho L**. *Optimizing Antimicrobial Drug Dosing in Critically Ill Patients*. Microorganisms. 2021 Jun 28;9(7):1401.

3. **Guo T, van Hest RM, Roggeveen LF, Fleuren LM, Thoral PJ, Bosman RJ, van der Voort PHJ, Girbes ARJ, Mathot RAA, Elbers PWG**. *External Evaluation of Population Pharmacokinetic Models of Vancomycin in Large Cohorts of Intensive Care Unit Patients*. Antimicrob Agents Chemother. 2019 Apr 25;63(5):e02543-18.

4. **Roberts JA, Taccone FS, Udy AA, Vincent JL, Jacobs F, Lipman J**. *Vancomycin dosing in critically ill patients: robust methods for improved continuous-infusion regimens*. Antimicrob Agents Chemother. 2011 Jun;55(6):2704-9.