Optimal dosing of Meropenem in a small cohort of critically ill children receiving continuous renal replacement therapy

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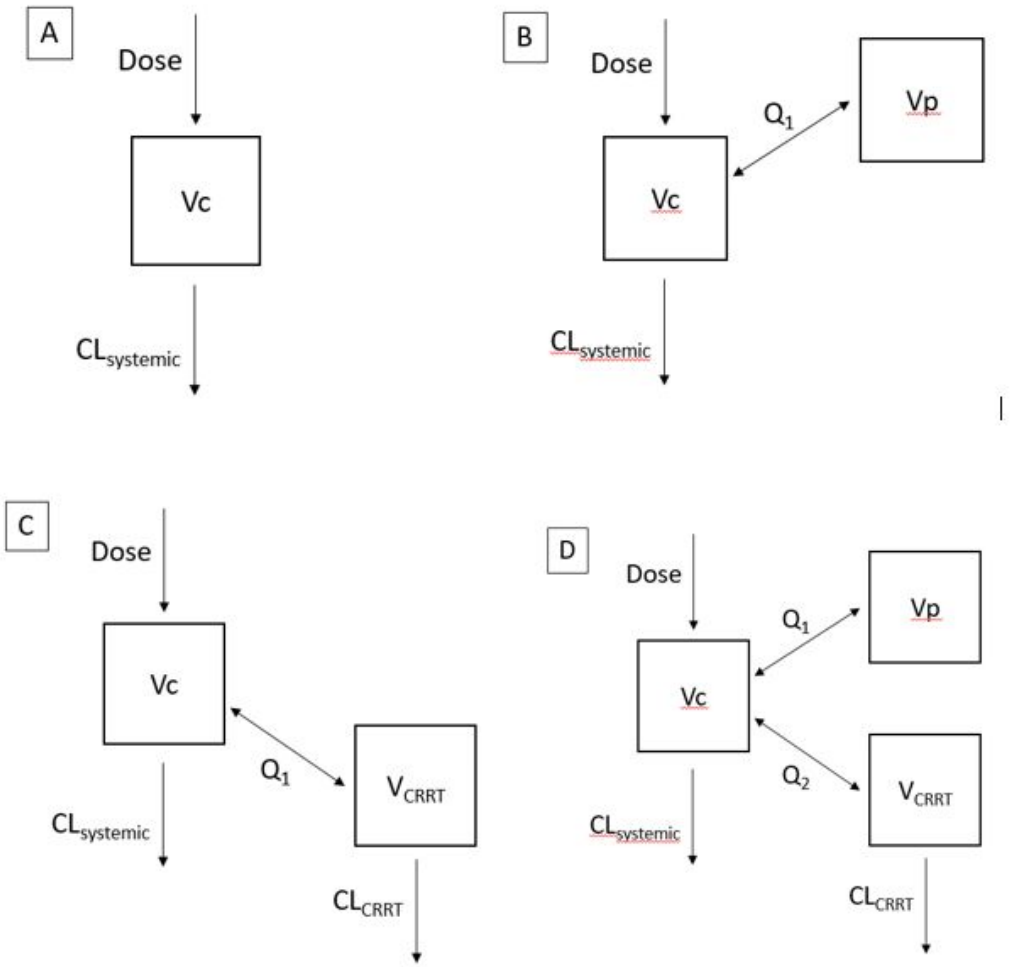
Supplementary Figure S1: Pharmacokinetic modeling using one-compartment model (A), two-compartment model (B), CRRT clearance model using plasma concentration only (C), and CRRT clearane mdoel using plasma and dialysate concentration (D)



Vc = Volume of distribution in the central compartment; Vp = volume of distribution in the peripheral compartment; $CL_{systemic}$ = systemic clearance; CL_{CRRT} = CRRT clearance; Q = intercompartment clearance

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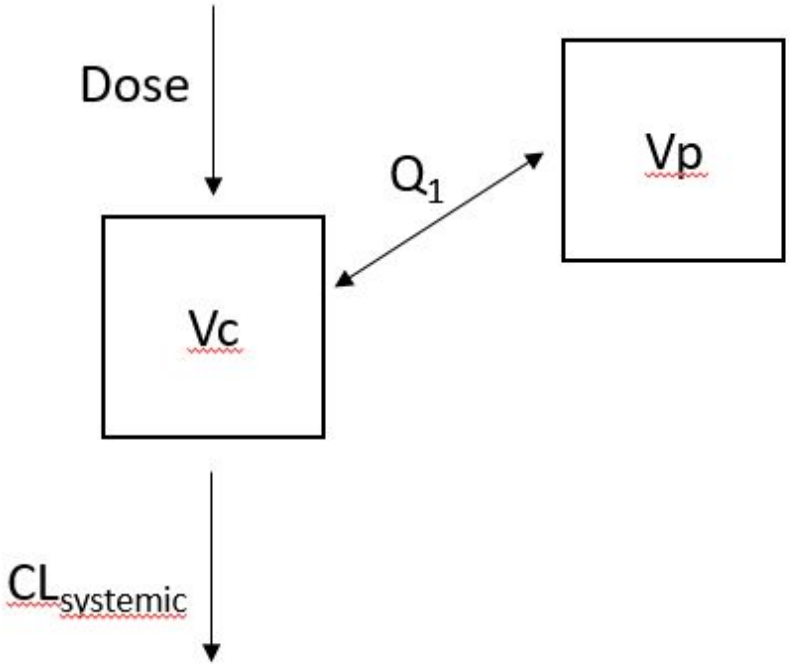
Supplementary Figure S2 : The Final Two-Compartment Pharmacokinetic Model



Vc = Volume of distribution in the central compartment; Vp = volume of distribution in the peripheral compartment; $CL_{systemic}$ = systemic clearance; Q = intercompartment clearance

The 2-compartment model provided the overall best fit for the data because it had a significant drop in the objective function value = -28.678 from the 1-compartment model and reliable estimates based on relative standard error and shrinkage values. When testing the CRRT clearance models, estimating the CL_{CRRT} using plasma concentration only resulted in a model converging without successful covariance step, and the estimated CL_{CRRT} was very small (towards 0). Estimating the CL_{CRRT} using plasma and dialysate concentration resulted in the model converging with successful covariance step. However, the precision of parameter estimates was poor with residual standard error >310% for both $CL_{Systemic}$ and CL_{CRRT}.

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Supplementary Table S3: Clinical laboratory and CRRT clearance parameters

ID	WBC (10^9/L)	Hb (g/dL)	Platelets (10^9/L)	Total Bilirubin (umol/l)	Direct Bilirubin (umol/l)	AST (U/L)	ALT (U/L)	Albumin (g/L)	Urea (mmol/L)	Creatinine (umol/L)	HF rate (ml/1.73 m^2/h)	DF rate (ml/1.73 m^2/h)
1	5.5	10.5	118.0	35.0	17.0	260.0	125.0	21.0	3.5	30.0	2141.9	2059.5
2	6.1	10.0	77.0	85.0	47.0	4110.0	2048.0	23.0	2.0	85.0	3040.6	0.0
3	13.1	10.4	30.0	219.0	198.0	52.0	29.0	24.0	3.4	37.0	1922.2	0.0
4	0.1	8.8	57.0	44.0	39.0	108.0	40.0	29.0	14.8	93.0	2000.7	2000.7
5	17.6	9.6	64.0	18.0	9.0	68.0	24.0	23.0	9.7	191.0	2039.4	0.0
6	11.7	10.1	39.0	112.0	78.0	527.0	638.0	52.0	9.1	70.0	1996.2	998.1
7	12.9	10.7	270.0	25.0	16.0	139.0	82.0	32.0	3.6	72.0	376.1	564.1
8	2.1	9.6	19.0	133.0	96.0	511.0	113.0	28.0	15.9	72.0	2022.1	0.0
9	21.6	11.6	81.0	219.0	195.0	92.0	31.0	37.0	15.7	152.0	2029.0	1014.5
MEAN	10.1	10.1	83.9	98.9	77.2	651.9	347.8	29.9	8.6	89.1	1952.0	737.4
SD	6.8	0.7	71.6	74.1	69.3	1234.7	628.2	9.2	5.4	48.9	643.6	795.4

HF: Hemofiltration; DF: Dialysate fluid

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Supplementary Figure S4: Final Population Pharmacokinetic Irreducible Model

$$CL_i = (\theta_{(1)}) * (WT_i / 70kg)^{0.75}$$

$$V_{ci} = (\theta_{(2)}) * (WT_i / 70kg)^{1}$$

$$Q_i = (\theta_{(3)}) * (WT_i / 70kg)^{0.75}$$

$$V_{pi} = (\theta_{(4)}) * (WT_i / 70kg)^{1}$$

Where $\theta_{(1)} = 4.1$L/hr, $\theta_{(2)} = 13.6$L , $\theta_{(3)} = 9.0$ L/hr, $\theta_{(4)} = 14.17$ L and WT is actual weight in kilograms; CL is total plasma clearance; Vc is the volume of distribution in the central compartment; Q is the inter-compartmental clearance; Vp is the volume of distribution in the peripheral compartment and i refers to the ith individual.

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Supplementary Table S5: Parameter Estimates for the Final Population Pharmacokinetics Model for Meropenem

Parameter	Estimate	RSE (%)	2.5th %ile	Bootstrap Median	97.5th %ile
Structural Model					
CL_{70KG} (L/h)	4.1	12.2	3.2	4.0	5.2
Vc_{70KG} (L)	13.6	10.4	9.6	13.6	21.0
Q_{70KG} (L)	9.0	17.6	1.5	8.8	16.7
Vp_{70KG} (L)	14.7	25.6	10.7	15.2	25.6
Inter-Individual Variability (CV%)					
CL	27.1	21.1	15.2	25.9	43.1
Residual Error					
Proportional error (%)	25.7	16.1	16.1	23.4	30.2

CL_{70KG}, population clearance estimate scaled to a 70-kg adult; CV, coefficient of variation; Q_{70KG}, population intercompartmental clearance estimate scaled to a 70-kg adult; RSE, relative standard error; Vc_{70KG}, population volume of distribution in the central compartment estimate scaled to a 70-kg adult; Vp_{70KG}, population volume of distribution in the peripheral compartment estimate scaled to a 70-kg adult

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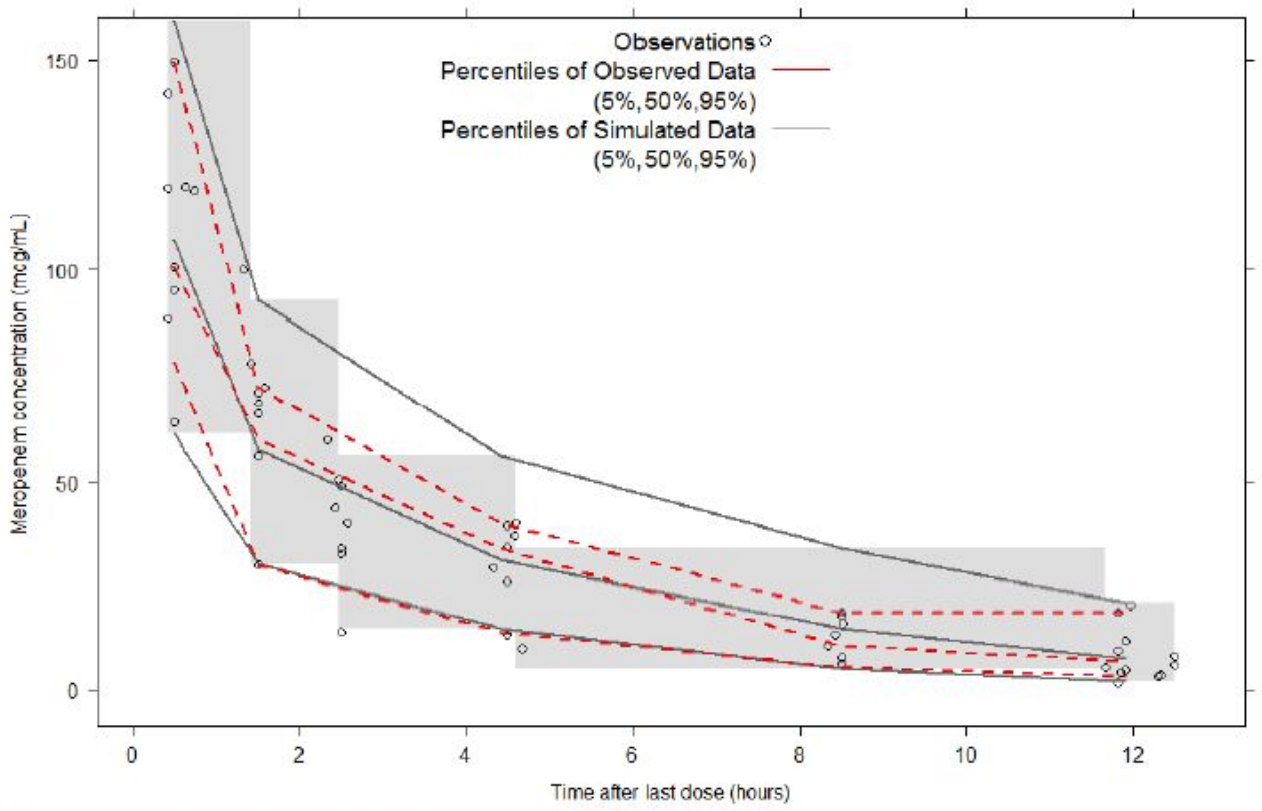
Supplementary Figure S6: Prediction Corrected Visual Predictive Check of Meropenem Observation vs Time after Last Dose



The shaded region denotes the 90% prediction interval of the simulated data.

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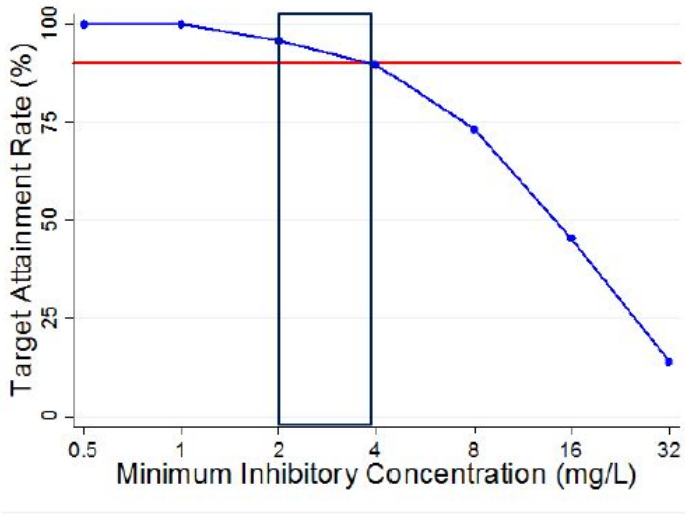
Supplementary Figure S7. Plots of Target Attainment Rates Based on Recommended Dose of 20 mg/kg (2-Hour Infusion) Every 8 Hours Based on Simulations Results in Children on Continuous Renal Replacement Therapy



The solid red line represents 90% target attainment rate, the blue dots connected by the blue lines represent the percent of simulated children reaching the target, and the blue boxes are markers for MIC 2 mg/L and 4 mg/L, respectively.