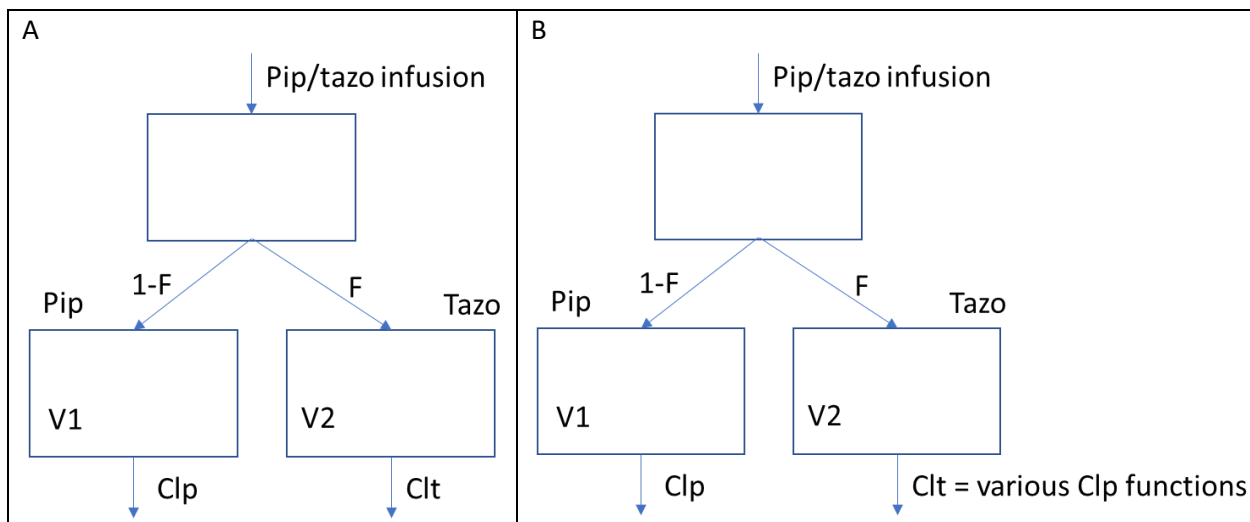


**Balancing the Scales: Achieving the Optimal Beta-Lactamase Inhibitor to Beta-Lactam  
Ratio in Piperacillin/Tazobactam Against *Enterobacterales***

**Supplemental Materials**

**Figure S1.** Modeling Strategy to comodel both piperacillin (Pip) / tazobactam (tazo) infusion using a fractionation function for the dose and independent compartments for each compound.



F, fraction of infusion representative of each compound. Since piperacillin : tazobactam is formulated 8:1 , the value for F was fixed to  $1/9 = 0.11$

V1, represents the volume of the central compartment for piperacillin

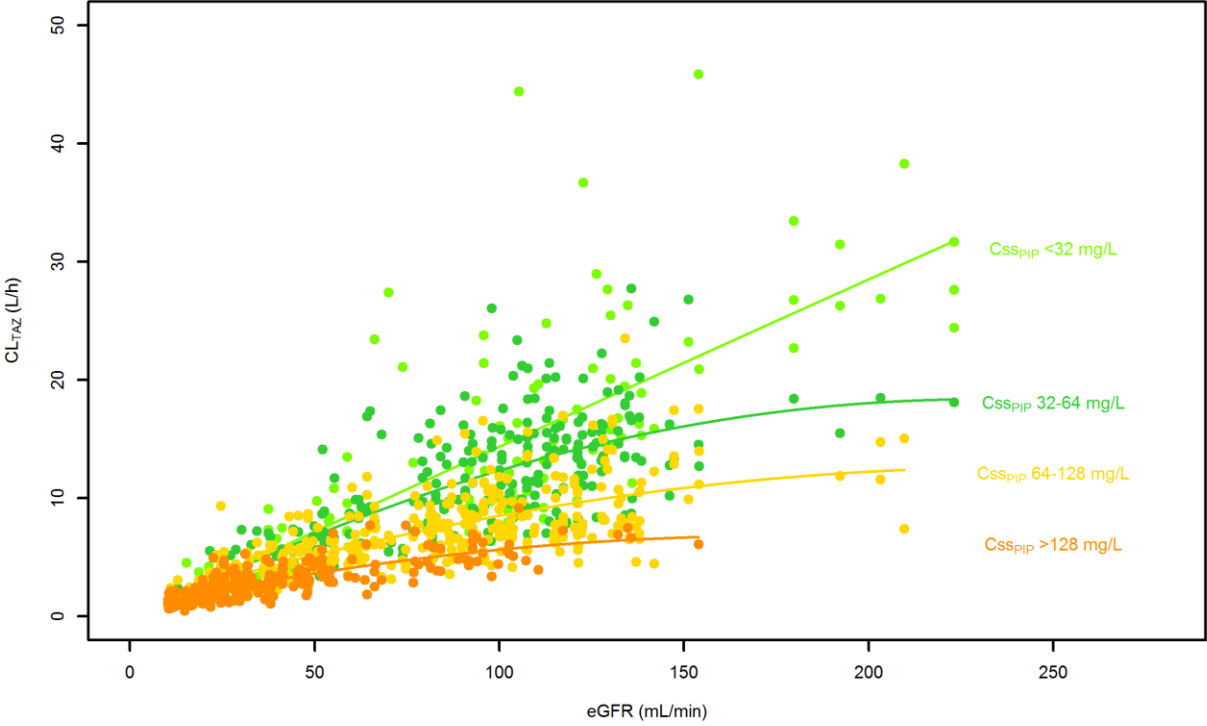
V2, represents the volume of the central compartment for tazobactam

Clp, piperacillin clearance

Clt, tazobactam clearance

Clt = various functions of Clp is provided in Table 1 that includes linear, power, and saturable models of Clt as a function of Clp. This is based on the known renal tubular inhibition of tazobactam clearance by piperacillin

**Figure S2.** Exploratory analysis illustrating the potential impact of increasing piperacillin concentrations on reductions in tazobactam clearance



**Table S1.** Structural model number, name, description, and structural equations used in Monolix 2023R1.

Number	Model name & description	Structure
1	<p>PipTazoIndependent</p> <p>A model that reflects independent modeling of piperacillin clearance (Clp) and tazobactam clearance (Clt), illustrated in Figure S1 A</p>	<p>input = {V1, Clp, Clt, V2, F}</p> <p>PK: ; PK model definition depot(target = A1)</p> <p>Equation: t_0 = 0 A1_0 = 0 A2_0 = 0 A3_0 = 0</p> <p>ddt_A1 = -F*A1 - (1-F)*A1 ddt_A2 = (1-F)*A1 - Clp/V1*A2 ddt_A3 = (F)*A1 - Clt/V2*A3</p> <p>C1 = A2/V1 C2 = A3/V2</p> <p>OUTPUT: output = {C1, C2}</p>
2	<p>PipTazoComod-Linear(Slope)</p> <p>A model that reflects independent modeling of piperacillin clearance (Clp) and tazobactam clearance (Clt) that is a slope only model of piperacillin clearance (Clp), illustrated in Figure S1 B</p>	<p>input = {V1, Clp, V2, F, S}</p> <p>PK: ; PK model definition depot(target = A1)</p> <p>Equation: t_0 = 0 A1_0 = 0 A2_0 = 0 A3_0 = 0</p> <p>ddt_A1 = -F*A1 - (1-F)*A1 ddt_A2 = (1-F)*A1 - Clp/V1*A2 ddt_A3 = (F)*A1 - (Clp*S)/V2*A3</p> <p>C1 = A2/V1 C2 = A3/V2</p> <p>OUTPUT: output = {C1, C2}</p>
3	<p>PipTazoComod-Power(Int+Slope)</p>	<p>input = {V1, Clp, V2, F, S, Int}</p>

	<p>A model that reflects independent modeling of piperacillin clearance (Clp) and tazobactam clearance (Clt) that is a slope and intercept model of piperacillin clearance (Clp), illustrated in Figure S1 B</p>	<p>PK: ; PK model definition depot(target = A1)</p> <p>Equation: t_0 = 0 A1_0 = 0 A2_0 = 0 A3_0 = 0</p> <p>ddt_A1 = -F*A1 - (1-F)*A1 ddt_A2 = (1-F)*A1 - Clp/V1*A2 ddt_A3 = (F)*A1 - (Int + (Clp)*S/V2)*A3</p> <p>C1 = A2/V1 C2 = A3/V2</p> <p>OUTPUT: output = {C1, C2}</p>
4	<p>PipTazoComod-Power(Slope)</p> <p>A model that reflects independent modeling of piperacillin clearance (Clp) and tazobactam clearance (Clt) that is a power model of piperacillin clearance (Clp), illustrated in Figure S1 B</p>	<p>input = {V1, Clp, V2, F, S}</p> <p>PK: ; PK model definition depot(target = A1)</p> <p>Equation: t_0 = 0 A1_0 = 0 A2_0 = 0 A3_0 = 0</p> <p>ddt_A1 = -F*A1 - (1-F)*A1 ddt_A2 = (1-F)*A1 - Clp/V1*A2 ddt_A3 = (F)*A1 - (Clp^S)/V2*A3</p> <p>C1 = A2/V1 C2 = A3/V2</p> <p>OUTPUT: output = {C1, C2}</p>
5	<p>5PipTazoComod-Power(Int+Slope)</p> <p>A model that reflects independent modeling of piperacillin clearance (Clp) and tazobactam clearance (Clt) that is a power model with a</p>	<p>[LONGITUDINAL] input = {V1, Clp, V2, F, S, Int}</p> <p>PK: ; PK model definition depot(target = A1)</p> <p>Equation:</p>

	<p>coefficient of piperacillin clearance (Clp), illustrated in Figure S1 B</p>	<p> <math>t_0 = 0</math>  <math>A1_0 = 0</math>  <math>A2_0 = 0</math>  <math>A3_0 = 0</math> </p> <p> <math>ddt\_A1 = -F*A1 - (1-F)*A1</math>  <math>ddt\_A2 = (1-F)*A1 - Clp/V1*A2</math>  <math>ddt\_A3 = (F)*A1 - (Int*(Clp)^S/V2)*A3</math> </p> <p> <math>C1 = A2/V1</math>  <math>C2 = A3/V2</math> </p> <p>OUTPUT: output = {C1, C2}</p>
6	<p>PipTazoComod-Saturable(Emax)</p> <p>A model that reflects independent modeling of piperacillin clearance (Clp) and tazobactam clearance (Clt) that is an Emax model (inhibitory) of piperacillin clearance (Clp), illustrated in Figure S1 B</p>	<p>[LONGITUDINAL] input = {V1, Clp, V2, F, lmax, IC50}</p> <p>PK: ; PK model definition depot(target = A1)</p> <p>Equation:  <math>t_0 = 0</math>  <math>A1_0 = 0</math>  <math>A2_0 = 0</math>  <math>A3_0 = 0</math> </p> <p> <math>ddt\_A1 = -F*A1 - (1-F)*A1</math>  <math>ddt\_A2 = (1-F)*A1 - Clp/V1*A2</math>  <math>C1 = A2/V1</math>  <math>ddt\_A3 = (F)*A1 - (Clp*(1 - (lmax*C1)/(IC50+C1)))/V2*A3</math>  <math>C2 = A3/V2</math> </p> <p>OUTPUT: output = {C1, C2}</p>
7	<p>PipTazoComod-Saturable(Sigmoidal)</p> <p>A model that reflects independent modeling of piperacillin clearance (Clp) and tazobactam clearance (Clt) that is an Emax model (inhibitory) with sigmoidicity parameter Gamma of piperacillin clearance (Clp), illustrated in Figure S1 B</p>	<p>[LONGITUDINAL] input = {V1, Clp, V2, F, lmax, IC50, Gamma}</p> <p>PK: ; PK model definition depot(target = A1)</p> <p>Equation:  <math>t_0 = 0</math>  <math>A1_0 = 0</math>  <math>A2_0 = 0</math>  <math>A3_0 = 0</math> </p>

		$\text{ddt\_A1} = -F \cdot A1 - (1-F) \cdot A1$ $\text{ddt\_A2} = (1-F) \cdot A1 - \text{Clp}/V1 \cdot A2$ $C1 = A2/V1$ $\text{ddt\_A3} = (F) \cdot A1 - (\text{Clp} \cdot (1 - (\text{Imax} \cdot C1^\gamma) / (\text{IC50} + C1^\gamma)) / V2) \cdot A3$ $C2 = A3/V2$ OUTPUT: output = {C1, C2}
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**Table S2.** Model Log (Proportional/normal error), V1, V2, F fixed

Model Number	Parameters	AIC	Proposal offered by statistical testing and incorporated in the covariate (Covar) model
1 (Base)	CLp, CLt	8562.42	
1 (Covar)	CLp, CLt	7771.89	Correlation CLp+CLt , CKDEPI2021mlmin for both
2 (Base)	CLp, S -linear	8047.99	
2 (Covar)	CLp, S - linear	7783.47	CKDEPI2021mlmin for CLp
3 (Base)	CLp, S, Int - linear	8060.56	
3 (Covar)	CLp, S, Int - linear	7779.36	CKDEPI2021mlmin for CLp & S
4 (Base)	CLp, S - power	8072.28	
4 (Covar)	CLp, S - power	7805.01	CKDEPI2021mlmin for CLp
5 (Base)	CLp, S, Int - power	8043.7	
5 (Covar)	CLp, S, Int - power	7779.6	CKDEPI2021mlmin for CLp
6 (Base)	CLp, Imax, IC50 - Emax	8042.92	
6 (Covar)	CLp, Imax, IC50 - Emax	7777.5	CKDEPI2021mlmin for CLp
7 (Base)	CLp, Imax, IC50, $\gamma$ - Sig	8050.83	
7 (Covar)	CLp, Imax, IC50, $\gamma$ - Sig	7788.15	Correlation CLp, IC50, $\gamma$ & CKDEPI2021mlmin for CLp

\* CKDEPI2021mlmin benchmarked to 60 ml/min

**Table S3.** Comparison of independent clearance structured model (Model 1) for piperacillin and tazobactam compared to dependent model (Model 6)

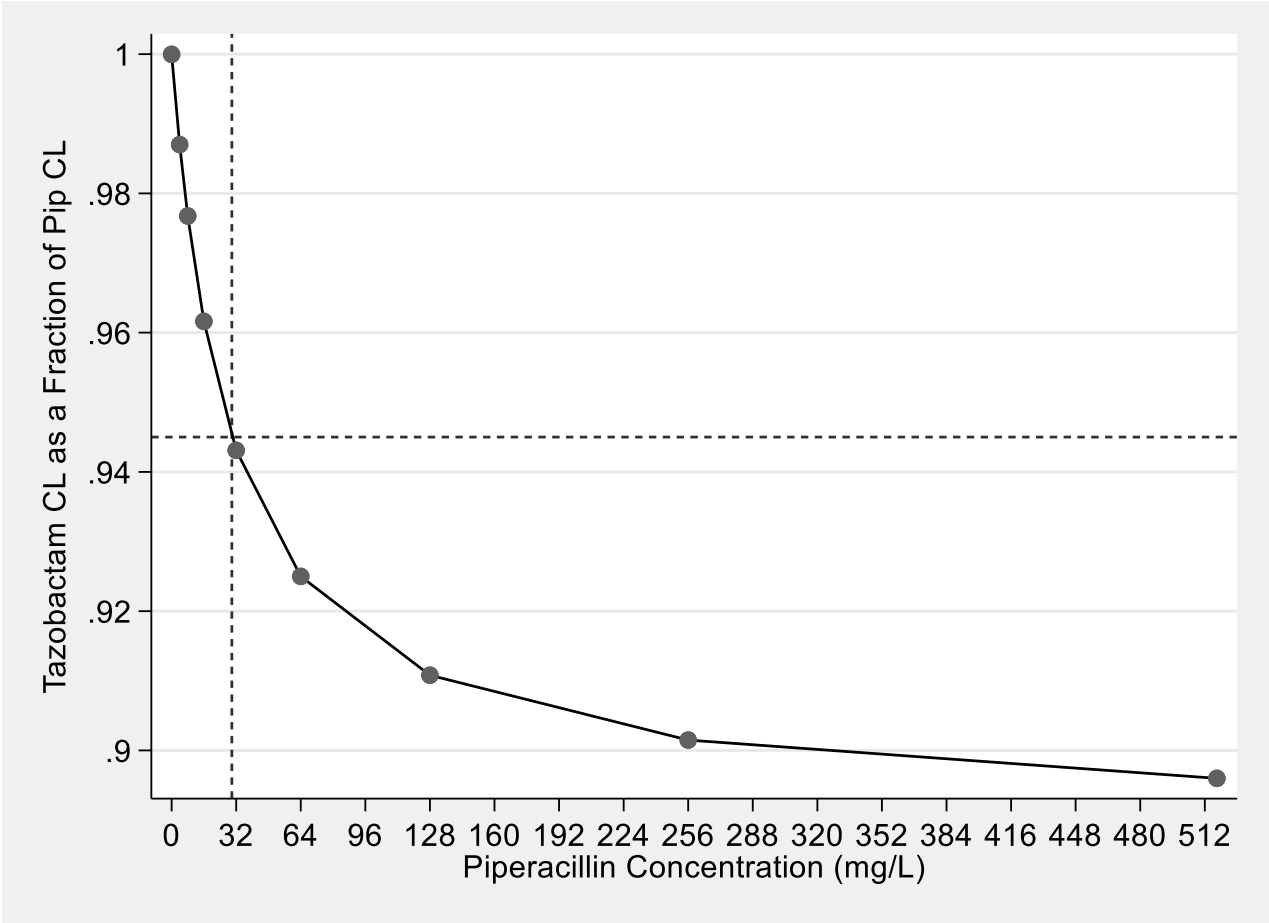
Model 1	VALUE		STOCH. APPROX.	
AIC= 7771.89			S.E.	R.S.E.(%)
Fixed Effects				
V1_pop	15			
Clp_pop	6.36		0.19	3
beta_Clp_logtCKDEPI2021mlmin	0.77		0.044	5.65
Clt_pop	5.88		0.17	2.96
beta_Clt_logtCKDEPI2021mlmin	0.93		0.042	4.47
V2_pop	15			
F_pop	0.11			
Standard Deviation of the Random Effects				
	Value	C.V.(%)		
omega_Clp	0.41	43.3	0.13	31.7
omega_Clt	0.42	43.64	0.14	33.5
Correlations				
corr_Clt_Clp	0.92		0.31	34
Error Model Parameters				
b1	0.28		0.013	4.71
b2	0.29		0.011	3.91

Model 6	VALUE		STOCH. APPROX.	
AIC= 7777.50			S.E.	R.S.E.(%)
Fixed Effects				
V1_pop	15			
Clp_pop	6.38		0.18	2.78
beta_Clp_logtCKDEPI2021mlmin	0.84		0.039	4.69
V2_pop	15			
F_pop	0.11			
Imax_pop	0.11		0.015	13.8
IC50_pop	29.86		14.51	48.6
Standard Deviation of the Random Effects				
	Value	C.V.(%)		
omega_Clp	0.4	41.94	0.021	5.16
omega_Imax	0.49	52.64	0.097	19.6
omega_IC50	1.42	254.94	0.52	36.8
Error Model Parameters				
b1	0.29		0.011	3.75
b2	0.29		0.011	3.83



**Figure S3.** Illustration of the expected reduction in tazobactam clearance (CL) as a function of piperacillin concentrations where the maximum reduction approaches 11% ( $I_{max}$ ) at high piperacillin concentrations with half of this maximal effect at 29.9 mg/L

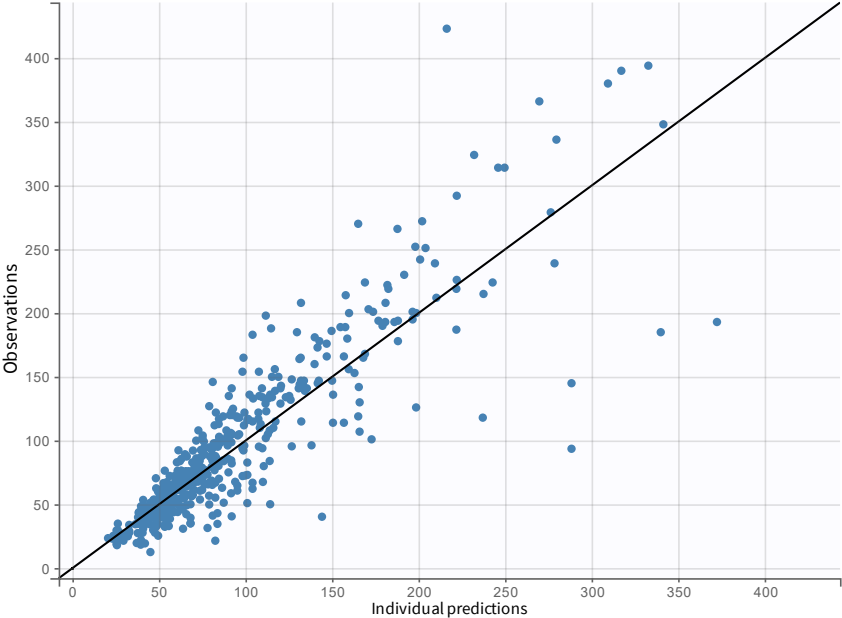


**Table S4.** Comparison of alternate kidney function estimation equations in standard and body surface area normalized units based on Model 1 to illustrate the rationale for selection of

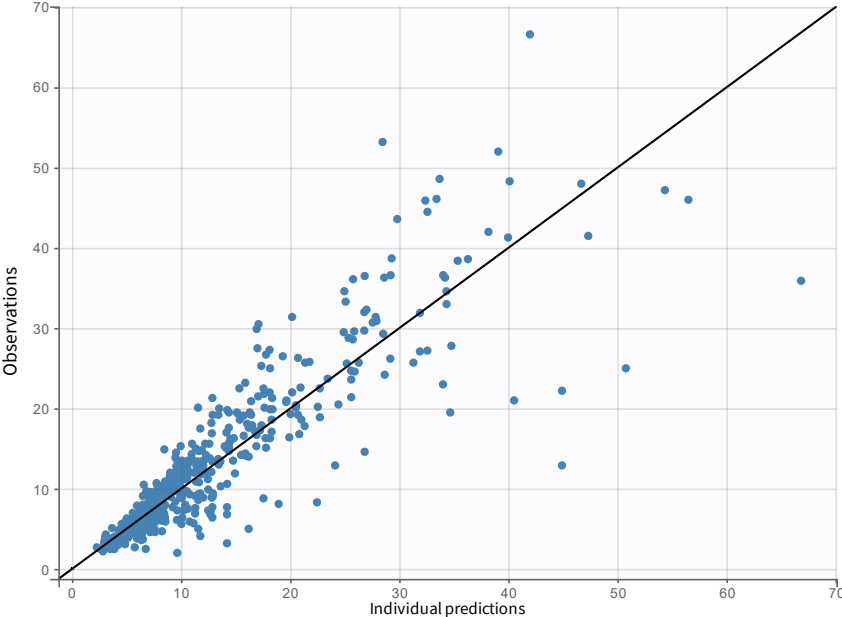
Parameter	Base						Final	
	No Covar.	CG	2009CKDEPI	2009CKDEPI	2021CKDEPI	CG_adjBW	CG_DW	2021CKDEPI
		mL/min	mL/min/1.73 m2	mL/min	mL/min/1.73 m2	mL/min	mL/min	mL/min
AIC	8562.65	8066.53	8130.03	8098.49	8142.89	8068.47	7839.32	7771.89
Delta AIC	0	-496.12	-432.62	-464.16	-419.76	-494.18	-723.33	-790.76
Stochastic approximation								
V1_pop	15	15	15	15	15	15	15	15
Clp_pop	6.35	6.91	7.02	6.68	6.72	6.32	3.24	6.39
	4.42%	2.91%	3.11%	2.94%	3.12%	2.94%	5.40%	2.92%
Clt_pop	5.89	6.49	6.7	6.23	6.31	5.84	2.61	5.89
	4.96%	2.89%	3.06%	2.83%	3.11%	2.86%	5.64%	2.95%
V2_pop	15	15	15	15	15	15	15	15
F_pop	0.111	0.111	0.111	0.111	0.111	0.111	0.111	0.111
$\beta_{Clp}$ (kidney function)		0.71	0.71	0.72	0.73	0.76	0.0098	0.77
		5.40%	6.28%	5.72%	6.25%	5.53%	6.34%	5.43%
$\beta_{Clt}$ (kidney function)		0.86	0.89	0.88	0.91	0.93	0.012	0.92
		4.38%	5%	4.60%	4.98%	4.38%	5.39%	4.47%
Standard deviation								
$\Omega_{Clp}$	0.66	0.39	0.42	0.4	0.43	0.4	0.46	0.41
	5.06%	5.71%	5.72%	6.34%	5.66%	5.96%	30.11%	11.64%
$\Omega_{Clt}$	0.74	0.39	0.41	0.37	0.43	0.39	0.48	0.41
	4.96%	5.56%	5.71%	6.04%	5.56%	5.56%	28.14%	12.01%
Correlation parameters								
corr_Clt_Clp							0.94	0.93
Residual error parameters								
piperacillin_prop	0.31	0.3	0.31	0.31	0.3	0.3	0.28	0.28
	4.45%	4.22%	4.17%	4.28%	4.19%	4.22%	3.79%	3.98%
tazobactam_prop	0.32	0.32	0.33	0.32	0.32	0.31	0.29	0.29
	4.24%	4.03%	4.17%	4.09%	4.12%	4.01%	4.15%	3.78%

CG, Cockcroft-Gault equation relying on actual or total body weight, 2009CKDEPI, the original 2009 Chronic Kidney Disease Epidemiology equation, 2021CKDEPI, the revised 2021 Chronic Kidney Disease Epidemiology equation, CG\_adjBW, Cockcroft-Gault equation relying on adjusted body weight, CG\_DW, Cockcroft-Gault equation relying on dosing weight where dosing weight is selection of actual weight when less than ideal body weight, adjusted body weight when actual weight is  $\geq 1.25$  fold higher than ideal body weight or ideal body weight when neither condition is met.

**Figure S4.** Observed and Individual prediction (mg/L) plots for observations (mg/L) with piperacillin (A) and tazobctam (B).

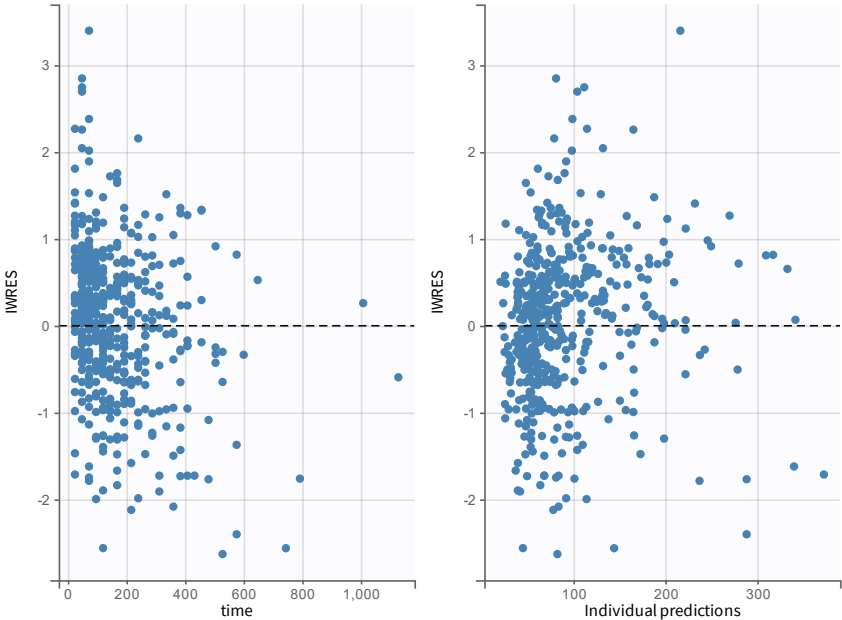


A

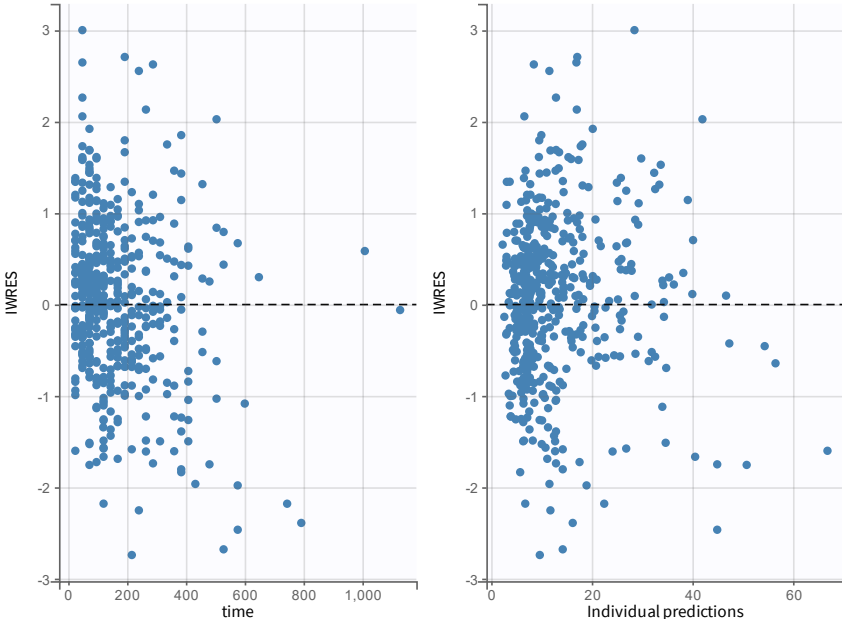


B

**Figure S5.** Individual weighted residuals versus time and individual predictions (mg/L) with piperacillin (A) and tazobactam (B).

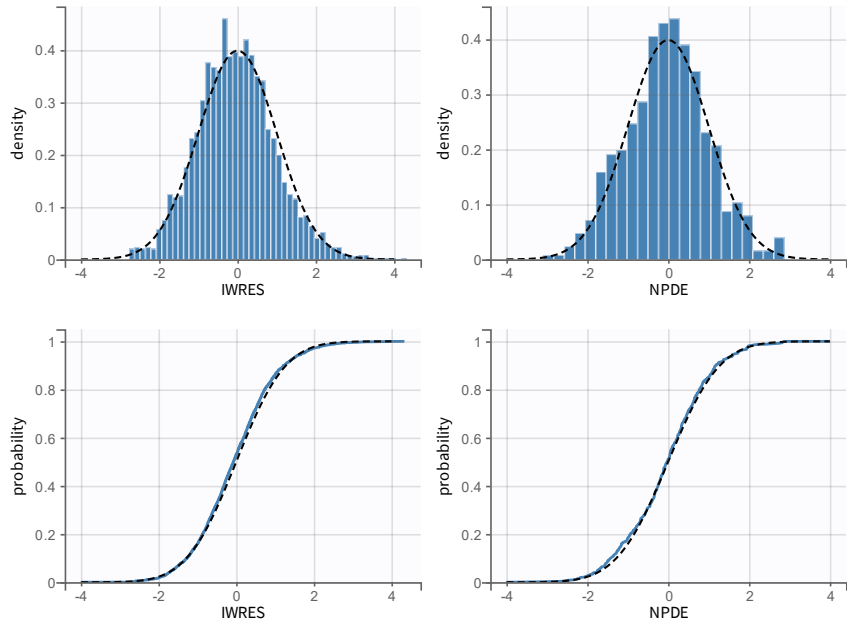


A

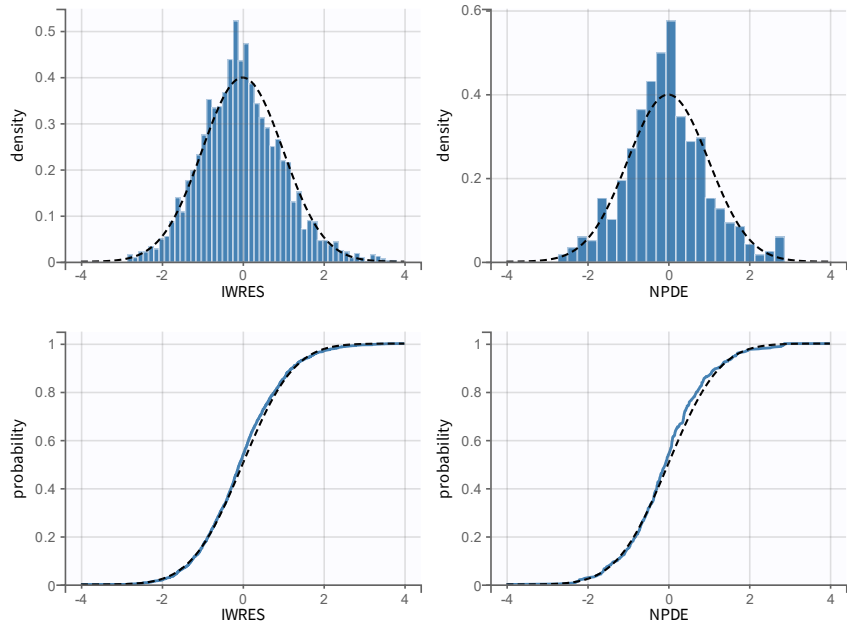


B

**Figure S6.** Histogram and cumulative probability distribution plots of the individual weighted residuals and normalized prediction distribution errors for piperacillin (A) and tazobactam (B).

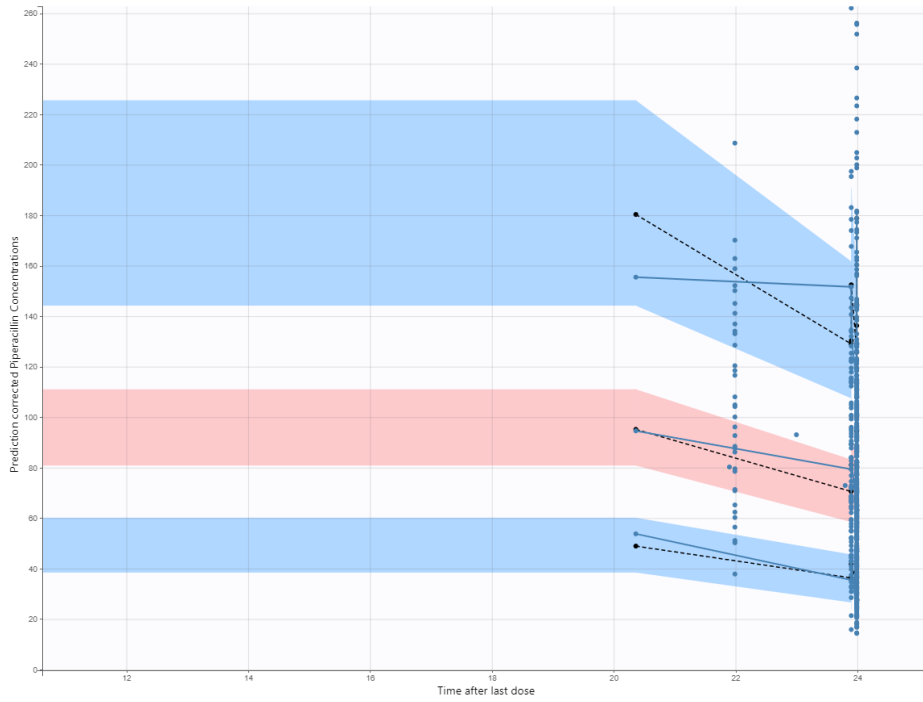


A

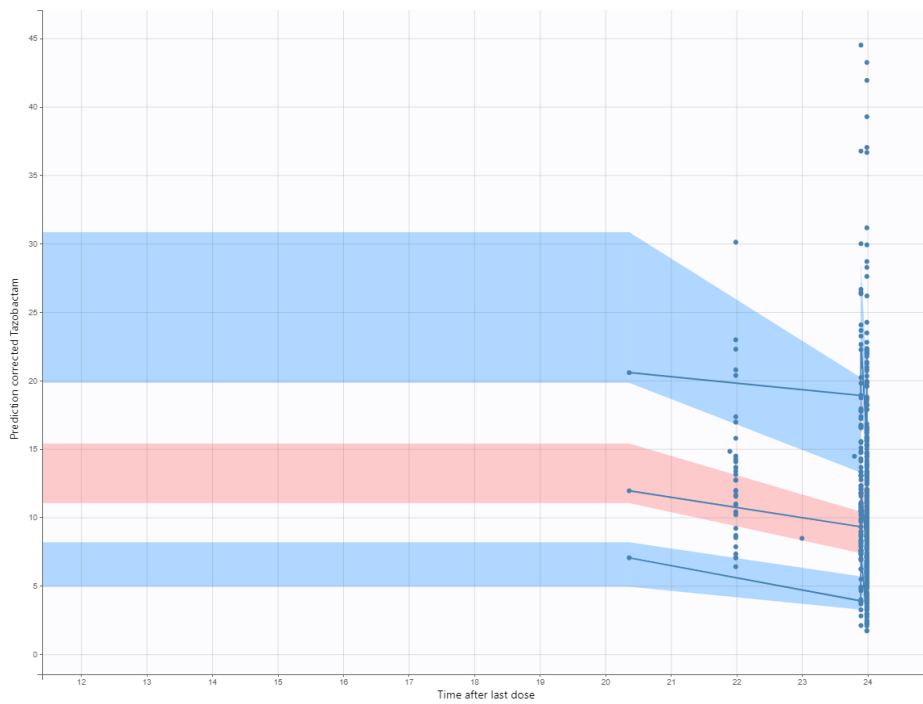


B

**Figure S7.** Visual predictive check plots with prediction corrected observed concentrations of piperacillin (A) and tazobactam (B) over time since last dose.



A



B

**Figure S8.** Scatter and linear fit plot (against the line of unity) of the analytical estimated (Rate of infusion/C<sub>ss</sub>) versus the final population PK model estimated individual clearance (CL) for piperacillin, R<sup>2</sup>= 0.95 (A) and Tazobactam, R<sup>2</sup>= 0.93 (B)

