Table S1. Dosing Regimens Simulated

Piperacillin Amount (mg/kg/dose)	Infusion time (hours)	Dosing Interval (hours)
50	0.5, 2	4
75	0.5, 2, 3	6
75	0.5, 2	4
80	0.5, 2, 3	6
80	0.5, 2, 3, 4	8
90	0.5, 2, 3	6
90	0.5, 2, 3, 4	8
100	0.5, 2, 3, 4	8
100	0.5, 2	4
100	0.5, 2, 3	6
120	0.5, 2, 3	6
130	0.5, 2, 3, 4	8
150	0.5, 2, 3	6
300	Continuous infusion	24
320	Continuous infusion	24
350	Continuous infusion	24
400	Continuous infusion	24
450	Continuous infusion	24
480	Continuous infusion	24
600	Continuous infusion	24

Table S2. Clinical Adverse and Severe Adverse Events

	Adverse events N=89 (%)			Severe adverse events N=89 (%)		
	GP/GS	**H-O**	**PICU**	**GP/GS**	**H-O**	**PICU**
Drug Mediated						
Infusion site infiltration	2 (2%)	1 (1%)	-	-	-	-
Allergic reaction	-	-	1	-	1 (1%)	-
Injection site reaction	1 (1%)	-	-	-	-	-
Gastroenterology						
Intestinal discomfort	3 (3%)	5 (6%)	1 (1%)	-	-	-
Cardiology						
Prolonged QT interval	-	1 (1%)	-	-	-	-
1st Degree AV block	-	-	1 (1%)	-	-	-
Bradycardia	-	1 (1%)	1 (1%)	-	-	1 (1%)
Hypotension	-	-	1 (1%)	-	-	-
Infectious Disease						
Cellulitis	-	-	-	-	-	1 (1%)
Neurologic						
Delirium	-	-	-	-	-	1 (1%)
Hematology						
Thrombosis	-	-	-	-	-	1 (1%)
Neutropenia requiring G-CSF	-	-	-	-	1 (1%)	1 (1%)
Thrombocytopenia requiring transfusion	-	-	-	-	1 (1%)	-
Respiratory						
Upper airway obstruction	-	-	-	-	-	3 (3%)
Pleural effusion	-	-	1 (1%)	-	-	-
Respiratory failure	-	-	-	-	-	1 (1%)

AV: atrioventricular, G-CSF: Granulocyte-colony stimulating factor, GP/GS: general pediatrics/general surgery, H-O: hemato-oncology, PICU: pediatric intensive care unit

Table S3. Laboratory Adverse and Severe Adverse Events

	Adverse events N=89 (%)				Severe adverse events N=89 (%)			
		GP/GS	H-O	PICU		GP/GS	H-O	PICU
Electrolytes	**Definition**				**Definition**			
Hyponatremia (mmol/L)	*120-124*	-	-	2 (2%)	*< 120*	-	-	-
Hypernatremia (mmol/L)	*150-159*	-	-	3 (3%)	*> 159*	-	-	-
Elevated Bicarbonates (mmol/L)	*34-45*	-	-	1 (1%)	*> 45*	-	-	-
Liver								
Elevated AST (IU/L)	*200-1000*	-	1 (1%)	-	*> 1000*	-	-	-
Elevated ALT (IU/L)	*200-1000*	-	1 (1%)	-	*> 1000*	-	-	-
Elevated GGT (IU/L)	*100-125*	-	-	-	*> 125*	-	-	3 (3%)
Hematology								
Elevated Lactate (mmol/L)	*5-10*	-	-	1 (1%)	*> 10*	-	-	-
Eosinophilia	*>0.4*10^9/L*	1 (1%)	-		*N/A*	-	-	-
Neutropenia (x 10^9/ L)	*0.5-1.5*	-	-	3 (3%)	*< 0.5*	-	-	-
Thrombocytopenia (x 10^9/ L)	*50-100*	1 (1%)	-		*< 50*	-	-	-
Thrombocytosis (x 10^9/ L)	*450-1000*	6 (7%)	-	5 (6%)	*> 1000*	-	-	-
Anemia (x 10^9/ L)	*70-90*	-	2 (2%)	2 (2%)	*< 70*	-	-	-
Leucopenia (x 10^9/ L)	*0.5-2*	-	5 (6%)		*< 0.5*	-	-	-
Hyperleukocytosis (x 10^9/ L)	*30-50*	-	-	1 (1%)	*> 50*	-	-	-
Endocrinology								
Hyperglycemia (mmol/L)	*13.9-27.8*	-	-	2 (2%)	*> 27.8*	-	-	-

ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase, GP/GS: general pediatrics/general surgery, H-O: hemato-oncology, PICU: pediatric intensive care unit

Table S4. Piperacillin Model Progression

Description	Population Model	OFV	ΔOFV
Univariate Analysis			
Base Model	$CL=3.78*(WT/11.4)^{1.48}$; $Vc=4.99*(WT/11.4)^{1.31}$ $Q=0.27*(WT/11.4)^{1.48}$; $Vp=0.52*(WT/11.4)^{1.31}$	3226	.
Hospitalization Unit[1] on CL	$CL=3.77*(WT/11.4)^{1.42}$ if unit=1 $CL=3.77*(WT/11.4)^{1.42}*e^{0.15}$ if unit=2 $CL=3.77*(WT/11.4)^{1.42}*e^{-0.19}$ if unit=3 $Vc=4.93*(WT/11.4)^{1.35}$; $Q=0.21*(WT/11.4)^{1.42}$ $Vp=0.47*(WT/11.4)^{1.35}$	3222	-4
Furosemide on CL	$CL=3.92*(WT/11.4)^{1.40}*e^{-0.28}$ if furosemide $Vc=4.87*(WT/11.4)^{1.26}$; $Q=0.25*(WT/11.4)^{1.40}$ $Vp=0.49*(WT/11.4)^{1.26}$	3216	-10
Hospitalization Unit[1] on Vc	$CL=3.53*(WT/11.4)^{1.46}$ if unit=1 $CL=3.53*(WT/11.4)^{1.46}*e^{-0.7}$ if unit=2 $CL=3.53*(WT/11.4)^{1.46}*e^{0.4}$ if unit=3 $Vc=4.00*(WT/11.4)^{1.40}$; $Q=0.25*(WT/11.4)^{1.46}$ $Vp=0.48*(WT/11.4)^{1.40}$	3222	-4
Multivariate Analysis, Step 1			
Furosemide on CL and Albumin on Vc	$CL=3.76*(WT/11.4)^{1.39}*e^{-0.28}$ if furosemide $Vc=4.30*(WT/11.4)^{1.29}*(ALB/29)^{-1.52}$ $Q=0.43*(WT/11.4)^{1.39}$; $Vp=0.57*(WT/11.4)^{1.29}$	3212	-4
Backward Elimination, Step 1			
Albumin on Vc Backward Drop of Furosemide	$CL=3.64*(WT/11.4)^{1.46}$ $Vc=4.47*(WT/11.4)^{1.32}*(ALB/29)^{-1.31}$ $Q=0.36*(WT/11.4)^{1.46}$; $Vp=0.61*(WT/11.4)^{1.32}$	3223	+11
Furosemide on CL Backward Drop of Albumin	$CL=3.92*(WT/11.4)^{1.40}*e^{-0.28}$ if furosemide $Vc=4.87*(WT/11.4)^{1.26}$ $Q=0.25*(WT/11.4)^{1.40}$; $Vp=0.49*(WT/11.4)^{1.26}$	3216	+4
Backward Elimination, Step 2			
Backward Drop of Furosemide	$CL=3.78*(WT/11.4)^{1.48}$ $Vc=4.99*(WT/11.4)^{1.31}$ $Q=0.27*(WT/11.4)^{1.48}$; $Vp=0.52*(WT/11.4)^{1.31}$	3226	+10
Final Model			
Furosemide on CL	$CL=3.92*(WT/11.4)^{1.40}*e^{-0.28}$ if furosemide $Vc=4.87*(WT/11.4)^{1.26}$ $Q=0.25*(WT/11.4)^{1.40}$; $Vp=0.49*(WT/11.4)^{1.26}$	3216	.

[1]Hospitalization units: 1=general pediatrics/general surgery, 2=hemato-oncology, 3=pediatric intensive care unit

CL: clearance, OFV: objective function value, Q: intercompartmental clearance, Vc: volume of distribution of the central compartment, Vp: volume of distribution of peripheral compartment

Figure S1. Prediction-Corrected Visual Predictive Check for Final Piperacillin Model

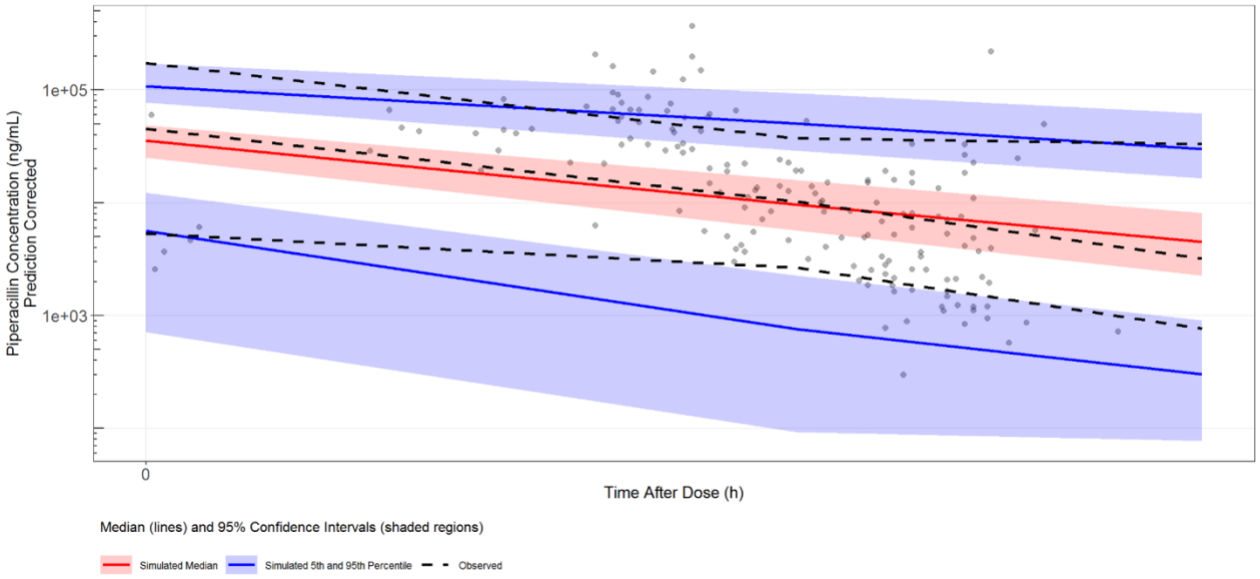

Table S5. Tazobactam Model Progression

Description	Population Model	OFV	ΔOFV
Univariate Analysis			
Base Model	$CL=3.0.6*(WT/11.4)^{1.31}$; $Vc=3.94*(WT/11.4)^{1.07}$ $Q=0.21*(WT/11.4)^{1.31}$; $Vp=3.74*(WT/11.4)^{1.07}$	2544	.
Sex on CL	$CL=3.37*(WT/11.4)^{1.27}*e^{-0.23}$ if female $Vc=3.90*(WT/11.4)^{1.05}$; $Q=0.21*(WT/11.4)^{1.27}$ $Vp=3.88*(WT/11.4)^{1.05}$	2539	5
Furosemide on CL	**$CL=3.15*(WT/11.4)^{1.24}*e^{-0.29}$ if furosemide $Vc=3.79*(WT/11.4)^{1.06}$; $Q=0.20*(WT/11.4)^{1.25}$ $Vp=3.65*(WT/11.4)^{1.06}$**	**2534**	**-10**
Sex on Vc	$CL=2.96*(WT/11.4)^{1.29}*e^{0.35}$ if female $Vc=3.15*(WT/11.4)^{1.05}$; $Q=0.21*(WT/11.4)^{1.29}$ $Vp=3.85*(WT/11.4)^{1.05}$	2540	-4
Multivariate Analysis, Step 1			
Furosemide and Sex on CL	**$CL=3.44*(WT/11.4)^{1.21}*e^{-0.2}$ if furosemide $CL=3.44*(WT/11.4)^{1.21}*e^{-0.28}$ if female $Vc=3.76*(WT/11.4)^{1.06}$ $Q=0.21*(WT/11.4)^{1.21}$; $Vp=3.75*(WT/11.4)^{1.06}$**	**2529**	**-5**
Backward Elimination, Step 1			
Drop Furosemide on CL	$CL=2.96*(WT/11.4)^{1.29}*e^{0.35}$ if female $Vc=3.15*(WT/11.4)^{1.05}$; $Q=0.21*(WT/11.4)^{1.29}$ $Vp=3.85*(WT/11.4)^{1.05}$	2540	+11
Drop Sex on CL	**$CL=3.15*(WT/11.4)^{1.06}*e^{-0.29}$ if furosemide $Vc=3.79*(WT/11.4)^{1.24}$; $Q=0.20*(WT/11.4)^{1.02}$ $Vp=3.65*(WT/11.4)^{1.24}$**	**2534**	**+5**
Backward Elimination, Step 2			
Drop Furosemide on CL	$CL=3.0.6*(WT/11.4)^{1.31}$; $Vc=3.94*(WT/11.4)^{1.07}$ $Q=0.21*(WT/11.4)^{1.31}$; $Vp=3.74*(WT/11.4)^{1.07}$	2544	+10
Final Model			
Furosemide on CL	$CL=3.15*(WT/11.4)^{1.24}*e^{-0.29}$ if furosemide $CL=3.15*(WT/11.4)^{1.24}$ otherwise $Vc=3.79*(WT/11.4)^{1.06}$ $Q=0.20*(WT/11.4)^{1.24}$ $Vp=3.65*(WT/11.4)^{1.06}$	2534	.

CL: clearance, OFV: objective function value, Q: intercompartmental clearance, Vc: volume of distribution of the central compartment, Vp: volume of distribution of peripheral compartment

Figure S2. Prediction-Corrected Visual Predictive Check for Final Tazobactam Model