

Evaluation of Empirical Dosing Regimens for Meropenem in ICU Patients Using Population Pharmacokinetic Modeling and Target Attainment Analysis

Guohua An^{1*}, C. Buddy Creech², Nan Wu¹, Roger L. Nation³, Kenan Gu⁴, Demet Nalbant¹, Natalia Jimenez-Truque², William Fissell⁵, Stephanie Rolsma², Pratish C. Patel⁶, Amy Watanabe⁷, Nicholas Fishbane⁷, Carl M.J. Kirkpatrick³, Cornelia B. Landersdorfer³, and Patricia Winokur^{8,*}

¹Department of Pharmaceutical Sciences and Experimental Therapeutics, College of Pharmacy, University of Iowa, USA

²Division of Pediatric Infectious Diseases, Vanderbilt University Medical Center, Nashville, TN, USA

³Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia

⁴Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, USA

⁵Division of Nephrology and Hypertension, Vanderbilt University Medical Center, Nashville, TN, United States of America

⁶ Department of Pharmaceutical Services, Vanderbilt University Medical Center, Nashville, TN, USA

⁷ The Emmes Company, LLC, Rockville, MD, USA

⁸Division of Infectious Diseases, Carver College of Medicine, University of Iowa, USA

SUPPLEMENTARY MATERIALS

Table S1. Predicted meropenem breakpoints following different dosing regimens in all subjects as well as subjects with different renal functions with targets 100% $fT_{>MIC}$ or 40% $fT_{>MIC}$.

Table S2. Estimated percentage of subjects with C_{trough} exceeding predefined thresholds and Predicted probability of meropenem-induced nephrotoxicity and neurotoxicity.

Figure S1. Goodness-of-fit plots for the population PK model of meropenem. (A) Observed versus population-predicted meropenem concentrations, (B) observed versus individual-predicted meropenem concentrations, (C) conditional weighted residuals versus time since the last dose, (D) conditional weighted residuals versus population-predicted meropenem concentrations. Solid black lines represent lines of identity in (A) and (B) and zero residuals in (C) and (D). Trend lines are shown in red.

Figure S2. PTA of meropenem versus MIC following different dosing regimens with the target of 40% $fT_{>MIC}$ (upper panel), 100% $fT_{>MIC}$ (middle panel) and 100% $fT_{>4x MIC}$ (lower panel).

Figure S3. Heatmap of PTA of meropenem at different MIC values following different dosing regimens in all subjects as well as subjects with different renal functions, with the PK/PD targets of 40% $fT_{>MIC}$, 100% $fT_{>MIC}$, and 100% $fT_{>4x MIC}$. Color coding: green, PTA $\geq 90\%$; yellow, PTA 80% - 89%; orange, PTA 50% - 79%; red, PTA $< 50\%$

Table S1. Predicted meropenem breakpoints following different dosing regimens in all subjects as well as subjects with different renal functions with targets 100% $fT>MIC$ or 40% $fT>MIC$.

Dosing Regimen	CrCL	Meropenem breakpoints (mg/L) (i.e. the highest MIC at which ≥ 90 % of the subjects achieve targets)	
		Target 100 % $fT>MIC$	Target 40 % $fT>MIC$
0.5g Q6h 30-min infusion	all	2	4
	less than 60 mL/min	4	8
	60 to 129 mL/min	2	8
	130 mL/min and above	0.5	4
0.5g Q8h 30-min infusion	all	1	4
	less than 60 mL/min	4	8
	60 to 129 mL/min	1	4
	130 mL/min and above	0.25	2
1g Q8h 30-min infusion	all	2	8
	less than 60 mL/min	8	16
	60 to 129 mL/min	2	8
	130 mL/min and above	0.5	4
1g Q12h 30-min infusion	all	0.5	4
	less than 60 mL/min	2	8
	60 to 129 mL/min	0.5	4
	130 mL/min and above	<0.125	2
2g Q8h 30-min infusion	all	4	16
	less than 60 mL/min	16	32
	60 to 129 mL/min	4	16
	130 mL/min and above	1	8
2g Q12h 30-min infusion	all	1	8
	less than 60 mL/min	4	16
	60 to 129 mL/min	1	8
	130 mL/min and above	0.125	4
0.5g Q6h 3-h infusion	all	2	4
	less than 60 mL/min	8	8
	60 to 129 mL/min	4	8
	130 mL/min and above	1	4
0.5g Q8h 3-h infusion	all	1	4
	less than 60 mL/min	4	8
	60 to 129 mL/min	2	4
	130 mL/min and above	0.5	2
1g Q8h 3-h infusion	all	2	8
	less than 60 mL/min	8	16
	60 to 129 mL/min	4	8
	130 mL/min and above	1	4
1g Q12h 3-h infusion	all	0.5	8
	less than 60 mL/min	4	16
	60 to 129 mL/min	1	8
	130 mL/min and above	0.125	4
2g Q8h 3-h infusion	all	4	16
	less than 60 mL/min	16	32
	60 to 129 mL/min	8	16
	130 mL/min and above	2	8
2g Q12h 3-h infusion	all	1	16
	less than 60 mL/min	8	32
	60 to 129 mL/min	4	16
	130 mL/min and above	0.25	8
2g daily continuous infusion	all	4	4
	less than 60 mL/min	8	8
	60 to 129 mL/min	4	4
	130 mL/min and above	4	4
4g daily continuous infusion	all	8	8

	less than 60 mL/min	16	16
	60 to 129 mL/min	8	8
	130 mL/min and above	8	8
6g daily continuous infusion	all	16	16
	less than 60 mL/min	32	32
	60 to 129 mL/min	16	16
	130 mL/min and above	8	8
8g daily continuous infusion	all	16	16
	less than 60 mL/min	32	32
	60 to 129 mL/min	16	16
	130 mL/min and above	16	16

Table S2. Estimated percentage of subjects with Ctrough exceeding predefined thresholds and Predicted probability of meropenem-induced nephrotoxicity and neurotoxicity.

Meropenem dosing regimen	CL _{CR}	Estimated % of subjects with Ctrough > 44.5 mg/L	Predicted possibility of nephrotoxicity (%)	Estimated % of subjects with Ctrough > 64.2 mg/L	Predicted possibility of neurotoxicity (%)
0.5g Q6h 30-min infusion	all	1.60	0.80	0.28	0.14
	less than 60 mL/min	4.51	2.26	0.74	0.37
	60 to 129 mL/min	0.37	0.19	0.07	0.04
	130 mL/min and above	0.16	0.08	0.08	0.04
0.5g Q8h 30-min infusion	all	0.21	0.11	0.04	0.02
	less than 60 mL/min	0.63	0.32	0.06	0.03
	60 to 129 mL/min	0.04	0.02	0.04	0.02
	130 mL/min and above	0.00	0.00	0.00	0.00
1g Q8h 30-min infusion	all	4.84	2.42	1.30	0.65
	less than 60 mL/min	12.80	6.40	3.66	1.83
	60 to 129 mL/min	1.52	0.76	0.26	0.13
	130 mL/min and above	0.88	0.44	0.24	0.12
1g Q12h 30-min infusion	all	0.68	0.34	0.11	0.06
	less than 60 mL/min	1.89	0.95	0.34	0.17
	60 to 129 mL/min	0.22	0.11	0.00	0.00
	130 mL/min and above	0.00	0.00	0.00	0.00
2g Q8h 30-min infusion	all	23.21	11.61	10.75	5.38
	less than 60 mL/min	48.40	24.20	25.43	12.72
	60 to 129 mL/min	15.26	7.63	5.30	2.65
	130 mL/min and above	5.12	2.56	2.00	1.00
2g Q12h 30-min infusion	all	6.65	3.33	2.32	1.16
	less than 60 mL/min	18.06	9.03	6.80	3.40
	60 to 129 mL/min	1.78	0.89	0.30	0.15
	130 mL/min and above	1.20	0.60	0.40	0.20
0.5g Q6h 3-h infusion	all	2.19	1.10	0.37	0.19
	less than 60 mL/min	6.34	3.17	1.20	0.60
	60 to 129 mL/min	0.41	0.21	0.00	0.00
	130 mL/min and above	0.24	0.12	0.00	0.00

0.5g Q8h 3-h infusion	all	0.33	0.17	0.04	0.02
	less than 60 mL/min	1.03	0.52	0.11	0.06
	60 to 129 mL/min	0.04	0.02	0.00	0.00
	130 mL/min and above	0.00	0.00	0.00	0.00
1g Q8h 3-h infusion	all	6.49	3.25	1.95	0.98
	less than 60 mL/min	17.43	8.72	5.43	2.72
	60 to 129 mL/min	2.07	1.04	0.44	0.22
	130 mL/min and above	0.72	0.36	0.32	0.16
1g Q12h 3-h infusion	all	0.81	0.41	0.16	0.08
	less than 60 mL/min	2.23	1.12	0.40	0.20
	60 to 129 mL/min	0.19	0.10	0.04	0.02
	130 mL/min and above	0.16	0.08	0.08	0.04
2g Q8h 3-h infusion	all	29.09	14.55	15.21	7.61
	less than 60 mL/min	58.97	29.49	35.26	17.63
	60 to 129 mL/min	20.48	10.24	8.07	4.04
	130 mL/min and above	5.84	2.92	2.56	1.28
2g Q12h 3-h infusion	all	8.63	4.32	3.11	1.56
	less than 60 mL/min	22.86	11.43	8.80	4.40
	60 to 129 mL/min	2.89	1.45	0.81	0.41
	130 mL/min and above	1.12	0.56	0.08	0.04
2g daily continuous infusion	all	4.44	2.22	0.93	0.47
	less than 60 mL/min	11.94	5.97	2.74	1.37
	60 to 129 mL/min	1.48	0.74	0.15	0.08
	130 mL/min and above	0.32	0.16	0.08	0.04
4g daily continuous infusion	all	28.68	14.34	11.77	5.89
	less than 60 mL/min	55.77	27.89	27.66	13.83
	60 to 129 mL/min	21.78	10.89	6.26	3.13
	130 mL/min and above	5.68	2.84	1.44	0.72
6g daily continuous infusion	all	52.32	26.16	30.63	15.32
	less than 60 mL/min	83.03	41.52	60.06	30.03
	60 to 129 mL/min	48.63	24.32	23.04	11.52
	130 mL/min and above	17.28	8.64	5.84	2.92
8g daily continuous infusion	all	69.91	34.95	48.82	24.41
	less than 60 mL/min	93.60	46.80	79.14	39.57

60 to 129 mL/min	72.11	36.06	44.78	22.39
130 mL/min and above	32.00	16.00	15.12	7.56

Figure S1. Goodness-of-fit plots for the population PK model of meropenem. (A) Observed versus population-predicted meropenem concentrations, (B) observed versus individual-predicted meropenem concentrations, (C) conditional weighted residuals versus time since the last dose, (D) conditional weighted residuals versus population-predicted meropenem concentrations. Solid black lines represent lines of identity in (A) and (B) and zero residuals in (C) and (D). Trend lines are shown in red.

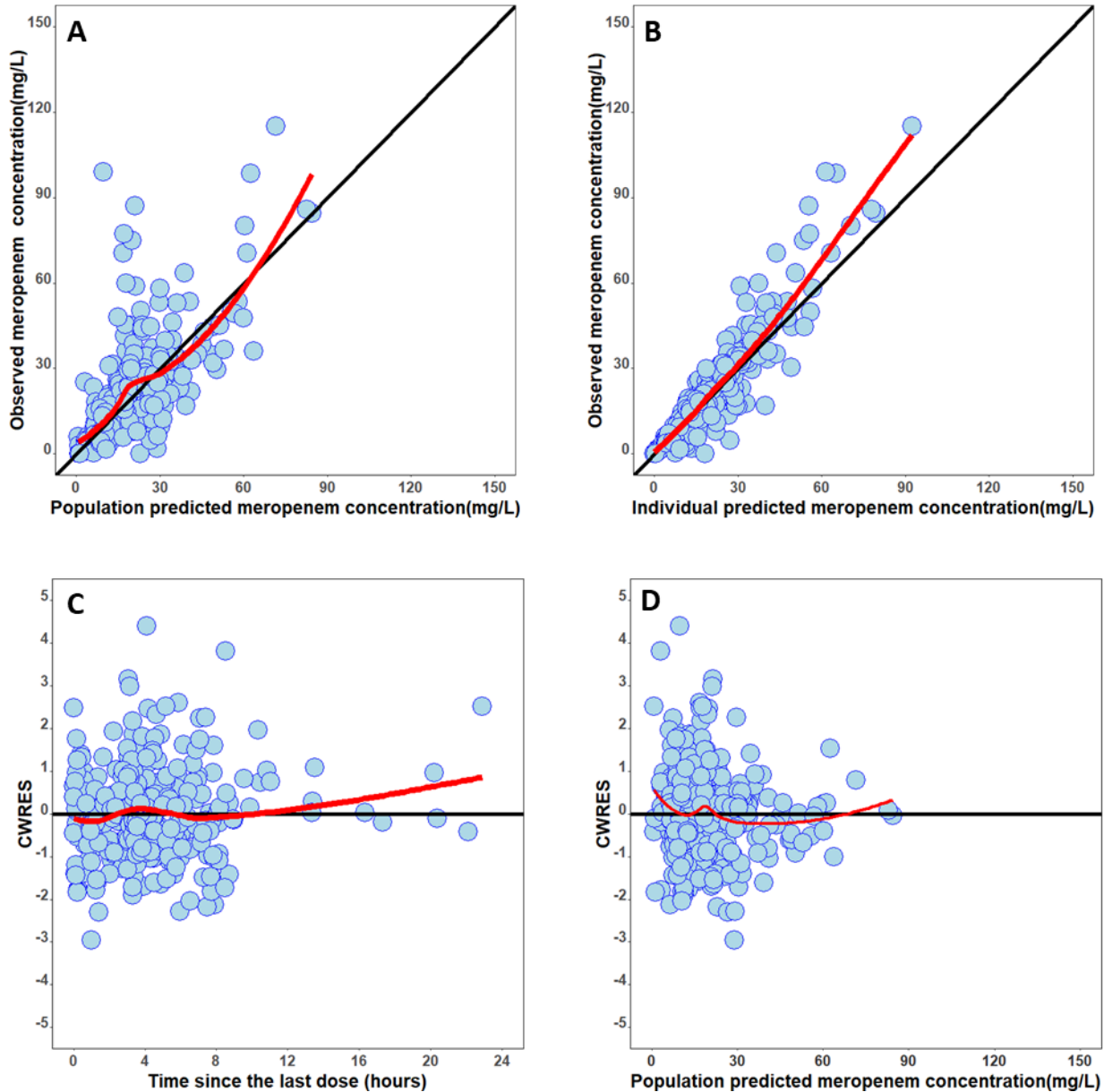


Figure S2. PTA of meropenem versus MIC following different dosing regimens with the target of 40% $fT_{>MIC}$ (upper panel), 100% $fT_{>MIC}$ (middle panel) and 100% $fT_{>4\times MIC}$ (lower panel).

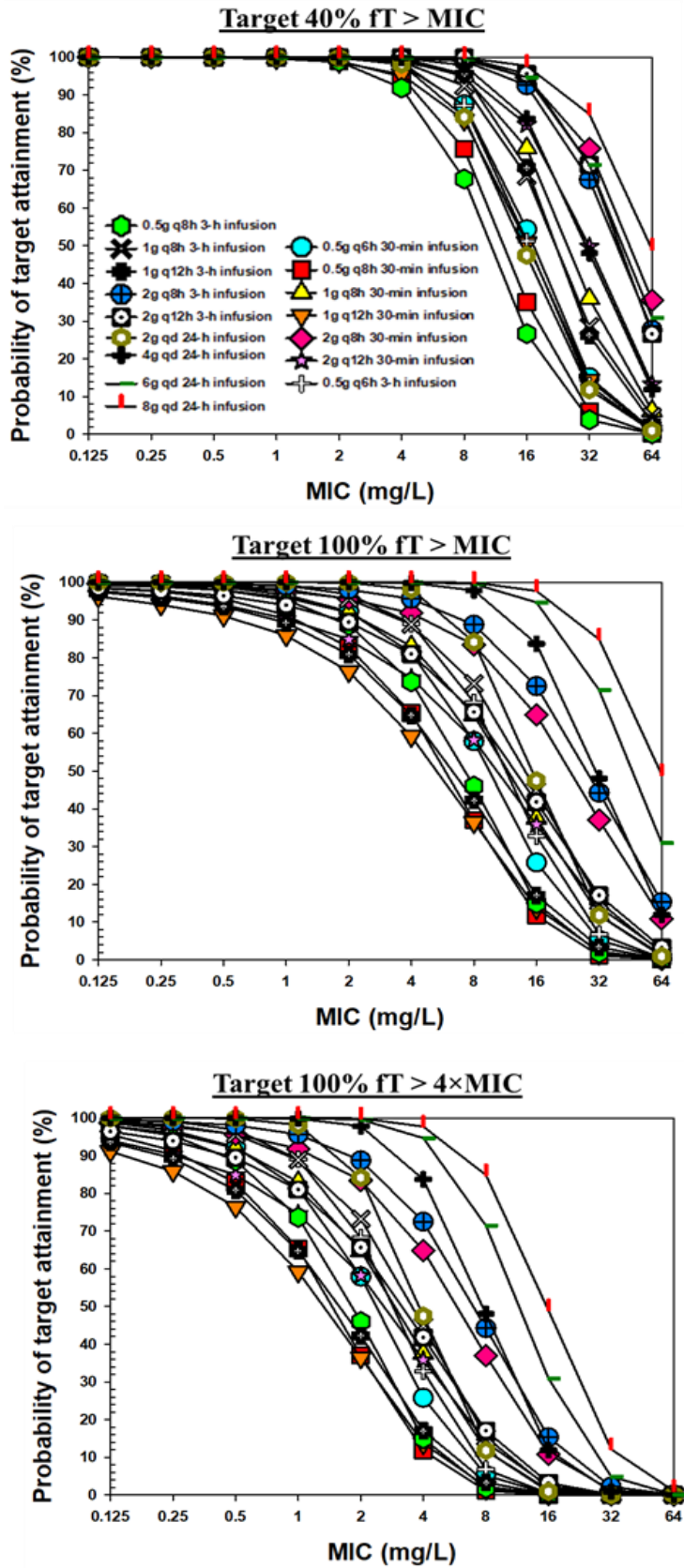


Figure S3. Heatmap of PTA of meropenem at different MIC values following different dosing regimens in all subjects as well as subjects with different renal functions with the PK/PD targets of 40% $fT_{>MIC}$, 100% $fT_{>MIC}$, and 100% $fT_{>4\times MIC}$. Color coding: green, PTA $\geq 90\%$; yellow, PTA 80% - 89%; orange, PTA 50% - 79%; red, PTA $< 50\%$

DosingRegimen	CrCL	Target 40% $fT_{>MIC}$										Target 100% $fT_{>MIC}$										Target 100% $fT_{>4\times MIC}$									
		MIC (mg/L)										MIC (mg/L)										MIC (mg/L)									
		0.125	0.25	0.5	1	2	4	8	16	32	64	0.125	0.25	0.5	1	2	4	8	16	32	64	0.125	0.25	0.5	1	2	4	8	16	32	64
0.5g q6h 30-min infusion	all	100.00	99.98	99.98	99.96	99.86	98.14	87.53	54.35	15.09	1.23	99.68	99.32	98.77	96.68	92.28	81.26	57.93	25.75	5.21	0.28	98.77	96.68	92.28	81.26	57.93	25.75	5.21	0.28	0.00	
	less than 60 mL/min	100.00	100.00	100.00	100.00	100.00	100.00	99.37	83.20	32.69	3.31	100.00	100.00	100.00	99.89	99.60	97.77	89.14	53.20	13.37	0.74	100.00	99.89	99.60	97.77	89.14	53.20	13.37	0.74	0.00	
	130 mL/min and above	100.00	99.92	99.92	99.92	99.44	92.08	59.20	18.24	2.96	0.08	98.64	97.20	95.04	87.20	72.96	48.40	19.60	5.60	0.96	0.08	95.04	87.20	72.96	48.40	19.60	5.60	0.96	0.08	0.00	
0.5g q8h 30-min infusion	all	100.00	99.98	99.93	99.77	98.98	94.91	75.67	35.05	6.05	0.23	98.46	97.54	95.61	91.35	82.81	65.39	37.00	11.70	1.12	0.04	95.61	91.35	82.81	65.39	37.00	11.70	1.12	0.04	0.00	
	less than 60 mL/min	100.00	100.00	100.00	100.00	100.00	99.83	96.46	61.94	15.49	0.63	100.00	99.94	99.77	97.66	93.03	69.14	27.77	3.31	0.06	99.77	99.31	97.66	93.03	69.14	27.77	3.31	0.06	0.00		
	130 mL/min and above	100.00	99.96	99.96	99.96	99.96	98.59	80.04	30.11	2.33	0.07	99.56	99.19	95.41	87.19	65.63	28.85	5.59	0.11	0.04	98.19	95.41	87.19	65.63	28.85	5.59	0.11	0.04	0.00		
1g q8h 30-min infusion	all	100.00	100.00	99.98	99.88	99.26	94.98	75.89	35.95	6.21	99.28	98.84	97.89	95.98	92.02	83.04	64.81	37.47	11.79	1.32	97.89	95.98	92.02	83.04	64.81	37.47	11.79	1.32	0.00		
	less than 60 mL/min	100.00	100.00	100.00	100.00	100.00	100.00	100.00	96.34	65.49	15.60	100.00	99.94	99.77	96.66	92.26	79.94	91.37	71.26	28.91	3.66	99.77	96.66	92.26	79.94	91.37	71.26	28.91	3.66	0.23	
	130 mL/min and above	100.00	100.00	100.00	100.00	100.00	99.96	97.96	79.04	29.59	2.63	99.93	99.78	99.26	97.96	95.15	87.04	64.96	28.37	5.04	0.26	99.26	97.96	95.15	87.04	64.96	28.37	5.04	0.26	0.00	
1g q12h 30-min infusion	all	100.00	100.00	100.00	100.00	100.00	100.00	99.96	97.96	79.04	29.59	2.63	99.93	99.78	99.26	97.96	95.15	87.04	64.96	28.37	5.04	0.26	99.26	97.96	95.15	87.04	64.96	28.37	5.04	0.26	0.00
	less than 60 mL/min	100.00	100.00	100.00	100.00	100.00	100.00	99.96	97.96	79.04	29.59	2.63	99.93	99.78	99.26	97.96	95.15	87.04	64.96	28.37	5.04	0.26	99.26	97.96	95.15	87.04	64.96	28.37	5.04	0.26	0.00
	130 mL/min and above	99.96	99.93	99.84	99.65	98.72	95.44	83.35	50.77	14.32	0.86	96.25	94.07	91.14	85.91	76.39	59.21	36.39	13.67	2.23	0.11	91.14	85.91	76.39	59.21	36.39	13.67	2.23	0.11	0.00	
2g q8h 30-min infusion	all	100.00	100.00	100.00	100.00	100.00	100.00	99.94	98.17	81.03	30.23	99.54	99.26	99.03	98.34	97.77	94.63	86.97	69.31	33.71	6.91	99.03	98.34	97.77	94.63	86.97	69.31	33.71	6.91	0.29	
	less than 60 mL/min	100.00	99.96	99.96	99.96	99.93	99.89	98.70	87.52	45.89	7.26	99.15	98.33	96.30	93.48	88.41	77.89	56.26	26.07	6.07	0.33	96.30	93.48	88.41	77.89	56.26	26.07	6.07	0.33	0.04	
	130 mL/min and above	99.92	99.92	99.76	99.44	98.72	95.12	82.32	48.16	14.64	2.40	92.08	88.08	82.16	72.32	59.28	39.36	22.32	10.00	3.44	0.40	82.16	72.32	59.28	39.36	22.32	10.00	3.44	0.40	0.08	
0.5g q6h 3-h infusion	all	100.00	100.00	100.00	100.00	100.00	99.80	87.18	51.26	12.88	0.75	99.95	99.89	99.65	99.09	96.88	89.07	68.23	32.75	6.75	0.40	99.65	99.09	96.88	89.07	68.23	32.75	6.75	0.40	0.04	
	less than 60 mL/min	100.00	100.00	100.00	100.00	100.00	100.00	99.03	80.23	28.74	2.06	100.00	100.00	100.00	99.94	99.54	93.83	63.43	17.77	1.26	100.00	99.94	99.54	93.83	63.43	17.77	1.26	1.11	0.00		
	130 mL/min and above	100.00	100.00	100.00	100.00	100.00	99.63	91.78	49.07	7.96	0.26	100.00	100.00	100.00	99.93	99.07	94.59	69.48	24.59	2.33	0.04	100.00	99.93	99.07	94.59	69.48	24.59	2.33	0.04	0.00	
0.5g q8h 3-h infusion	all	100.00	100.00	100.00	100.00	100.00	99.92	94.40	60.64	15.44	1.28	0.00	99.76	95.52	98.40	96.08	87.92	62.48	29.68	7.44	0.88	0.00	98.40	96.08	87.92	62.48	29.68	7.44	0.88	0.00	0.00
	less than 60 mL/min	100.00	100.00	100.00	100.00	100.00	99.71	93.14	51.77	9.71	0.46	100.00	100.00	99.83	95.35	88.68	73.67	46.02	14.91	1.81	0.04	99.71	95.35	88.68	73.67	46.02	14.91	1.81	0.04	0.00	
	130 mL/min and above	100.00	100.00	100.00	100.00	100.00	99.89	96.26	70.07	20.33	1.56	0.00	99.89	99.78	99.41	98.04	93.22	76.96	41.00	7.93	0.37	0.00	99.41	98.04	93.22	76.96	41.00	7.93	0.37	0.00	0.00
1g q8h 3-h infusion	all	100.00	100.00	100.00	100.00	100.00	100.00	99.77	93.54	56.29	12.80	100.00	100.00	100.00	99.77	99.03	95.03	77.60	36.46	5.49	100.00	100.00	99.77	99.03	95.03	77.60	36.46	5.49	0.00		
	less than 60 mL/min	100.00	100.00	100.00	100.00	100.00	99.93	96.67	70.11	20.89	1.41	99.93	99.89	99.78	99.41	98.37	93.56	76.44	38.33	7.37	0.44	99.78	99.41	98.37	93.56	76.44	38.33	7.37	0.44	0.00	
	130 mL/min and above	100.00	100.00	100.00	100.00	100.00	99.81	95.47	70.65	26.21	2.98	97.44	95.93	93.58	89.30	80.86	64.77	42.23	17.04	3.35	0.16	93.58	89.30	80.86	64.77	42.23	17.04	3.35	0.16	0.00	
2g qd 24-h infusion	all	100.00	100.00	100.00	100.00	100.00	100.00	99.71	92.46	48.23	7.71	99.66	99.26	99.09	98.23	96.86	91.14	74.91	39.09	9.26	0.40	99.09	98.23	96.86	91.14	74.91	39.09	9.26	0.40	0.00	
	less than 60 mL/min	100.00	100.00	100.00	100.00	100.00	100.00	99.78	71.85	21.33	1.26	99.04	98.15	96.48	92.70	84.30	64.74	35.11	9.22	0.96	0.04	96.48	92.70	84.30	64.74	35.11	9.22	0.96	0.04	0.00	
	130 mL/min and above	100.00	100.00	100.00	100.00	100.00	99.12	84.56	37.52	5.92	0.08	90.88	86.48	79.60	69.44	51.04	27.92	11.84	3.04	0.24	0.00	79.60	69.44	51.04	27.92	11.84	3.04	0.24	0.00	0.00	
4g qd 24-h infusion	all	100.00	100.00	100.00	100.00	100.00	100.00	99.85	96.83	68.11	21.04	99.93	99.93	99.93	99.78	99.37	98.00	93.26	75.89	37.48	8.11	99.93	99.78	99.37	98.00	93.26	75.89	37.48	8.11	0.30	
	less than 60 mL/min	100.00	100.00	100.00	100.00	100.00	100.00	99.85	96.83	68.11	21.04	99.93	99.93	99.93	99.78	99.37	98.00	93.26	75.89	37.48	8.11	99.93	99.78	99.37	98.00	93.26	75.89	37.48	8.11	0.30	
	130 mL/min and above	100.00	100.00	100.00	100.00	100.00	100.00	99.86	95.60	71.42	26.58	98.60	97.77	96.46	93.93	89.46	81.02	65.65	41.79	17.04	3.18	96.46	93.93	89.46	81.02	65.65	41.79	17.04	3.18	0.12	
6g qd 24-h infusion	all	100.00	100.00	100.00	100.00	100.00	100.00	99.89	90.74	49.77	99.83	99.83	99.66	99.20	98.57	96.29	90.97	74.11	40.57	8.91	99.66	99.20	98.57	96.29	90.97	74.11	40.57	8.91	0.40		
	less than 60 mL/min	100.00	100.00	100.00	100.00	100.00	100.00	100.00	99.74	73.89	21.44	99.70	99.11	98.33	96.30	92.52	84.44	65.67	34.74	8.11	0.85	98.33	96.30	92.52	84.44	65.67	34.74	8.11	0.85	0.00	
	130 mL/min and above	100.00	100.00	100.00	100.00	100.00	99.36	84.96	39.04	5.20	94.48	92.00	87.92	81.44	70.08	52.24	30.16	11.76	3.36	0.16	87.92	81.44	70.08	52.24	30.16	11.76	3.36	0.16	0.00		
8g qd 24-h infusion	all	100.00	100.00	100.00	100.00	100.00	100.00	98.63	77.60	27.94	2.74	100.00	100.00	100.00	100.00	100.00	98.63	77.60	27.94	2.74	100.00	100.00	100.00	100.00	100.00	98.63	77.60	27.94	2.74		
	less than 60 mL/min	100.00	100.00	100.00	100.00	100.00	99.56	89.81	43.59	5.96	0.15	100.00	100.00	100.00	100.00	100.00	99.56	89.81	43.59	5.96	0.15	100.00	100.00	100.00	100.00	100.00	99.56	89.81	43.59	5.96	0.15
	130 mL/min and above	100.00	100.00	100.00	100.00	100.00	99.60	92.56	51.76	13.68	1.68	0.08	100.00	100.00	100.00	100.00	99.60	92.56	51.76	13.68	1.68	0.08	100.00	100.00	99.60	92.56	51.76	13.68	1.68	0.08	0.00
8g qd 24-h infusion	all	100.00	100.00	100.00	100.00	100.00	99.84	97.88	83.74	48.04	11.89	100.00	100.00	100.00	100.00	100.00	99.84	97.88	83.74	48.04	11.89	100.00	100.00	100.00	100.00	100.00	99.84	97.88	83.74	48.04	11.89