FOSFOMYCIN DOSING REGIMENS FOR THE TREATMENT OF CARBAPENEM-RESISTANT ENTEROBACTERIACEAE INFECTIONS IN PATIENTS RECEIVING CONTINUOUS RENAL REPLACEMENT THERAPY: A MONTE CARLO SIMULATION

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Background:

To predict the appropriate dosing of intravenous fosfomycin for treatment of carbapenem-resistant Enterobacteriaceae (CRE) infection in continuous renal replacement therapy (CRRT) patients.

Methods:

Minimum inhibitory concentration (MIC) values of all isolates were determined by E-test method. Population pharmacokinetic parameters were obtained from a previously published study. The percentages of a 24-hour period in which the drug concentration exceeded the MIC (%T>MIC) were defined to be 70% T>MIC and 100% T>MIC, respectively. In addition, the 24-hour area under the unbound concentration-time curve over the MIC (AUC_{0-24} /MIC) of 45 mg·h/L was used as a target value. All dosing regimens were estimated for the probability of target attainment (PTA) using a Monte Carlo simulation.

Results:

For the effluent rate of 20 mL/kg/h, the PTA for reaching 70% T>MIC, 100% T>MIC, and AUC_{0-24}/MIC of 45 mg·h/L was achieved in pathogens with a MIC of 24 mg/L, 12 mg/L, and 24 mg/L in all regimens, respectively. Meanwhile for the effluent rate of 25 mL/kg/h, the PTA for reaching 70% T>MIC, 100% T>MIC, and AUC /MIC of 45 mg·h/L was achieved in organisms with a MIC of 16 mg/L, 12 mg/L and 24 mg/L in all regimens, respectively.

Probability of Target Attainment of all fosfomycin dosing regimens for Carbapenem-resistant Enterobacteriaceae infections in continuous venovenous hemofiltration modality with 20 mL/kg/h effluent rates.

Effluent rate (mL/kg/h)	Fosfomycin dosing regimen		PTA to achieving 70% T>MIC					PTA to achieving 100% T>MIC					PTA to achieving AUC_{0-24}/MIC of 45 mg·h/L				
	Loading[a]	Maintenance[b]	MIC (mg/L)					MIC (mg/L)					MIC (mg/L)				
			8	16	32	64	96	8	16	32	64	96	8	16	32	64	96
20	Short infusion[c]																
	4 g	4 g q 8 h	100	99.98	93.01	33.88	6.46	100	99.03	66.43	7.22	0.56	100	99.71	82.37	16.81	1.93
		6 g q 12 h	100	99.65	77.51	12.41	1.19	99.75	80.42	14.68	0.18	0.02	100	99.77	81.86	15.70	1.68
		4 g q 6 h	100	100	99.62	75.37	34.28	100	99.99	96.79	46.07	10.78	100	99.99	95.98	42.42	9.01
		8 g q 12 h	100	99.97	93.90	35.76	7.16	99.97	94.63	38.05	1.28	0.04	100	100	95.56	41.52	9.58
		6 g q 6 h	100	100	99.99	96.53	75.74	100	100	99.88	84.09	45.72	100	100	99.82	82.02	43.00
		8 g q 8 h	100	100	99.97	92.48	63.19	100	100	98.69	63.45	22.47	100	100	99.71	82.07	42.81
	Prolong infusion[d]																
	4 g	4 g q 8 h	100	99.99	98.08	57.32	17.72	100	99.94	91.56	30.43	4.95	100	99.7	81.97	15.84	1.77
		6 g q 12 h	100	99.98	92.89	33.11	6.15	99.99	96.39	45.09	2.30	0.09	100	99.77	81.59	15.94	1.83
		4 g q 6 h	100	100	99.93	89.94	56.30	100	100	99.70	80.81	41.04	100	100	95.89	43.52	9.77
		8 g q 12 h	100	100	98.96	64.53	22.35	100	99.51	74.51	10.67	0.67	100	99.97	95.63	41.49	9.40
		6 g q 6 h	100	100	100	99.01	90.22	100	100	99.99	97.48	81.38	100	100	99.68	83.25	42.03
		8 g q 8 h	100	100	99.99	97.73	81.96	100	100	99.95	89.82	57.21	100	100	99.77	81.65	41.18
	Continuous infusion[e]																
	4 g	12 g	100	100	99.64	78.18	36.23	100	100	99.60	77.06	34.85	100	99.89	88.22	23.68	3.49
		16 g	100	100	99.99	93.93	66.57	100	100	99.99	93.83	66.29	100	100	96.34	45.05	10.77
		24 g	100	100	100	99.22	90.77	100	100	99.99	96.16	74.08	100	100	99.57	77.23	35.35
	Short infusion[c]																
	8 g	4 g q 8 h	100	99.98	93.72	33.63	6.22	100	99.07	67.22	7.10	0.44	100	99.81	82.42	16.66	1.99
		6 g q 12 h	100	99.62	77.90	12.71	1.26	99.79	83.37	17.45	0.25	0.00	100	99.78	82.22	16.15	1.81
		4 g q 6 h	100	100	99.52	77.24	35.13	100	100	96.67	48.32	11.9	100	100	95.72	43.76	9.91
		8 g q 12 h	100	99.99	93.94	35.93	6.94	100	95.91	43.21	2.05	0.11	100	100	95.66	42.19	9.53
		6 g q 6 h	100	100	99.98	96.49	76.49	100	100	99.8	84.88	47.27	100	100	99.72	82.35	43.05
		8 g q 8 h	100	100	99.94	92.75	63.33	100	100	98.85	65.08	22.88	100	100	99.76	81.99	42.52
	Prolong infusion[d]																
	8 g	4 g q 8 h	100	100	98.47	59.78	19.46	100	99.94	92.36	31.72	5.25	100	99.80	82.22	16.61	2.02
		6 g q 12 h	100	99.97	92.79	33.58	6.40	100	97.15	50.02	3.11	0.13	100	99.77	81.76	16.68	1.92
		4 g q 6 h	100	100	99.94	90.38	57.48	100	100	99.74	82.21	42.49	100	99.98	96.06	43.95	10.51
		8 g q 12 h	100	100	98.96	64.53	22.35	100	99.51	74.51	10.67	0.67	100	99.99	95.84	42.41	9.25
		6 g q 6 h	100	100	100	99.12	90.35	100	100	100	97.85	81.57	100	100	99.77	81.70	42.91
		8 g q 8 h	100	100	100	97.96	82.43	100	100	99.95	91.06	58.48	100	100	99.84	82.04	41.96
	Continuous infusion[e]																
	8 g	12 g	100	100	99.83	82.62	43.50	100	100	99.71	78.30	37.22	100	100	97.02	49.59	12.88
		16 g	100	100	99.98	94.86	70.64	100	100	99.98	93.82	67.53	100	100	98.94	67.56	25.29
		24 g	100	100	100	99.60	94.09	100	100	100	99.56	93.63	100	100	99.88	87.91	52.92

g, gram; %T>MIC, the percentage of time above MIC; MIC, minimum inhibitory concentration; a, loading dose infused for 30 minutes; b, maintenance dose was started after loading dose depend on intervals of each regimen. On the other hand, continuous infusion scenarios contained the loading dose, followed by the maintenance dose immediately after the loading dose.; c, intravenous drip in 30 minutes; d, intravenous drip in 4 hours; e, intravenous drip over 24 hours

Probability of Target Attainment of all fosfomycin dosing regimens for Carbapenem-resistant Enterobacteriaceae infections in continuous venovenous hemofiltration modality with 25 mL/kg/h effluent rates.

Effluent rate (mL/kg/h)	Fosfomycin dosing regimen		PTA to achieving 70% T>MIC					PTA to achieving 100% T>MIC					PTA to achieving AUC_{0-24}/MIC of 45 mg·h/L				
	Loading[a]	Maintenance[b]	MIC (mg/L)					MIC (mg/L)					MIC (mg/L)				
			8	16	32	64	96	8	16	32	64	96	8	16	32	64	96
25	Short infusion[c]																
	4 g	4 g q 8 h	100	99.89	89.00	24.79	3.43	100	97.83	54.52	3.40	0.15	100	99.58	78.07	12.31	1.14
		6 g q 12 h	100	99.09	68.12	7.46	0.58	99.19	69.18	7.76	0.03	0.00	100	99.55	77.40	12.12	1.22
		4 g q 6 h	100	100	99.25	70.76	28.56	100	99.96	94.77	37.97	8.15	100	99.96	94.71	37.57	8.00
		8 g q 12 h	100	99.87	89.70	25.72	3.69	99.87	89.53	25.44	0.50	0.00	100	99.92	93.97	36.39	6.68
		6 g q 6 h	100	100	99.99	94.65	69.73	100	100	99.62	78.41	36.82	100	100	99.63	78.59	37.00
		8 g q 8 h	100	100	99.94	89.68	55.70	100	100	97.78	54.17	15.41	100	100	99.68	78.77	37.28
	Prolong infusion[d]																
	4 g	4 g q 8 h	100	100	97.01	48.97	12.63	100	99.83	87.11	21.32	2.89	100	99.61	77.99	12.69	1.17
		6 g q 12 h	100	99.91	89.07	25.51	3.94	99.96	93.24	34.32	1.14	0.03	100	99.61	77.50	12.83	1.33
		4 g q 6 h	100	100	99.88	87.27	51.05	100	100	99.50	76.09	34.73	100	99.98	94.79	38.31	7.51
		8 g q 12 h	100	99.99	97.81	55.23	16.10	99.99	98.81	64.13	5.75	0.29	100	99.97	93.80	35.69	6.73
		6 g q 6 h	100	100	100	98.61	86.71	100	100	99.99	96.31	75.60	100	100	99.62	78.62	36.90
		8 g q 8 h	100	100	99.99	96.60	76.67	100	100	99.81	85.72	48.63	100	100	99.62	77.03	36.11
	Continuous infusion[e]																
	4 g	12 g	100	100	99.50	74.13	31.83	100	100	99.42	73.01	30.29	100	99.89	85.99	19.96	2.65
		16 g	100	100	99.97	92.44	61.40	100	100	99.96	92.32	61.05	100	99.98	95.49	39.88	8.80
		24 g	100	100	99.99	98.79	88.95	100	100	99.94	95.89	73.61	100	100	99.33	73.88	32.31
	Short infusion[c]																
	8 g	4 g q 8 h	100	99.92	89.25	25.73	3.65	100	97.82	55.75	3.75	0.17	100	99.59	78.22	13.06	1.07
		6 g q 12 h	100	99.67	77.66	13.04	1.14	99.83	83.16	17.93	0.21	0.00	100	99.80	81.99	16.46	1.65
		4 g q 6 h	100	99.99	99.25	70.49	28.08	100	99.94	94.64	38.41	7.79	100	99.93	94.38	37.63	7.42
		8 g q 12 h	100	99.95	89.97	26.81	4.01	99.96	91.55	30.08	0.65	0.03	100	99.98	93.79	36.64	7.40
		6 g q 6 h	100	100	99.98	95.02	69.96	100	100	99.69	79.46	38.35	100	100	99.65	78.85	37.57
		8 g q 8 h	100	100	99.91	89.33	54.03	100	100	98.13	53.92	16.20	100	100	99.71	78.51	36.51
	Prolong infusion[d]																
	8 g	4 g q 8 h	100	100	97.12	50.81	13.89	100	99.81	87.88	23.51	3.09	100	99.53	78.90	13.46	1.11
		6 g q 12 h	100	99.93	88.86	24.77	3.65	99.99	94.20	37.17	1.19	0.05	100	99.68	77.59	12.30	1.07
		4 g q 6 h	100	100	99.89	87.62	50.65	100	100	99.61	76.50	34.50	100	99.96	94.58	37.06	7.76
		8 g q 12 h	100	99.98	97.88	55.19	15.95	99.99	99.04	66.78	6.90	0.43	100	99.98	94.51	36.35	6.97
		6 g q 6 h	100	100	100	98.85	87.57	100	100	100	96.79	76.38	100	100	99.67	79.09	38.12
		8 g q 8 h	100	100	100	97.24	78.14	100	100	99.90	86.99	50.43	100	100	99.67	78.23	36.28
	Continuous infusion[e]																
	8 g	12 g	100	99.99	99.54	78.00	36.77	100	99.99	99.39	73.72	31.49	100	99.99	96.09	44.47	9.92
		16 g	100	100	99.96	93.23	64.33	100	100	99.93	91.79	61.00	100	100	98.61	62.08	21.01
		24 g	100	100	100	99.40	91.89	100	100	99.34	91.26	48.24	100	100	99.82	85.48	48.24

g, gram; %T>MIC, the percentage of time above MIC; MIC, minimum inhibitory concentration; a, loading dose infused for 30 minutes; b, maintenance dose was started after loading dose depend on intervals of each regimen. On the other hand, continuous infusion scenarios contained the loading dose, followed by the maintenance dose immediately after the loading dose.; c, intravenous drip in 30 minutes; d, intravenous drip in 4 hours; e, intravenous drip over 24 hours

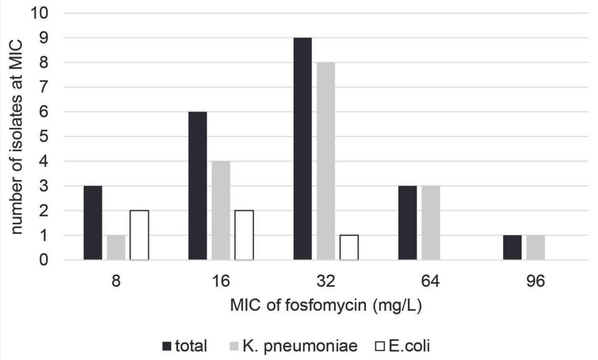
Recommendations of fosfomycin dosing regimens for treating CRE infections in patients with CVVH modality, according to EUCAST breakpoints.

Effluent flow rates	Dosing regimens suggestion according to EUCAST breakpoint [a]		
	70% T>MIC	100% T>MIC	AUC_{0-24}/MIC of 45 mg·h/L
20 ml/kg/h	4 g LD, followed by MD of 4 g infused over 4 hours every 8 hours	4 g LD, followed by MD of 4 g infused over 4 hours every 8 hours	8 g LD, followed by MD of 12 g infused over 24 hours
25 ml/kg/h	4 g LD, followed by MD of 4 g infused over 4 hours every 8 hours	4 g LD, followed by MD of 12 g infused over 24 hours	8 g LD, followed by MD of 12 g infused over 24 hours

g, gram; %T>MIC, the percentage of time above MIC; MIC, minimum inhibitory concentration; AUC_{0-24}/MIC, the 24-hour area under the unbound concentration-time curve over the MIC; LD, loading dose; MD, maintenance dose

[a] EUCAST breakpoints for Enterobacteriaceae spp. Isolates, MIC ≤ 32 mg/L as susceptible.

Minimum inhibitory concentrations distribution of fosfomycin against Carbapenem-resistant Enterobacteriaceae isolates.



Conclusions:

The appropriate fosfomycin dosing regimens for CRE infections in critically ill patients receiving CRRT were suggested based on pharmacokinetic/pharmacodynamic targets, MIC values, and effluent rates. Clinical validation is warranted.