Ceftazidime-avibactam plasma levels in critically ill patients, including those receiving continuous renal replacement therapy

NCT04358991

SIGNATURE PAGE

RESPONSIBLE STUDY AUTHORS

STUDY AUTHOR(S):

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Signature:_____ Date: _April 7, 2020_____

Ryan K. Shields

Principal Investigator

University of Pittsburgh

3550 Terrace Street, Room S805

Pittsburgh, PA 15621

412-864-3745

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List of Abbreviations.

AUC – area under curve
AVI – avibactam
CAZ – ceftazidime
CL – observed clearance at steady state
CLSI – Clinical and Laboratory Standards Institute
cm – centimeter
C_{max} – predicted maximum concentration
C_{min} – predicted minimum concentration
CrCl – creatinine clearance
CRRT – continuous renal replacement therapy
CVVHDF – continuous venovenous hemodiafiltration
EDTA – ethylenediaminetetraacetic acid
*f*T – time of free drug concentration
g – gram
HD – hemodialysis
IBW – ideal body weight
IQR – interquartile range
IV – intravenous(ly)
K_e – equilibrium constant
kg – kilogram
LCMS – liquid chromatography mass spectrometry
MIC – minimum inhibitory concentration
µg/mL – micrograms per millilter
PD – pharmacodynamics
PK – pharmacokinetic
RRT – renal replacement therapy
q 8/24/48h – every 8/24/48 hours
$t_{1/2}$ – half life
UHPLC – ultra high performance liquid chromatography
V_d – observed volume of distribution at steady state

Purpose.

Ceftazidime-avibactam is a β-lactam/β-lactamase inhibitor combination used to treat multidrug-resistant gram-negative infections. There are limited pharmacokinetic data among critically ill patients and no dosing recommendations for those receiving continuous renal replacement therapy (CRRT). The objective of this study is to describe the population pharmacokinetics of ceftazidime and avibactam among patients infected or being treated for multidrug-resistant gram-negative pathogens, including those on CRRT.

Methods.

Enrollment
Adult patients at UPMC Presbyterian hospital who received >24 hours of ceftazidime-avibactam were eligible for participation. Informed consent was obtained for each subject. The study protocol was approved by the University of Pittsburgh institutional review board (protocol number: PRO17060377).

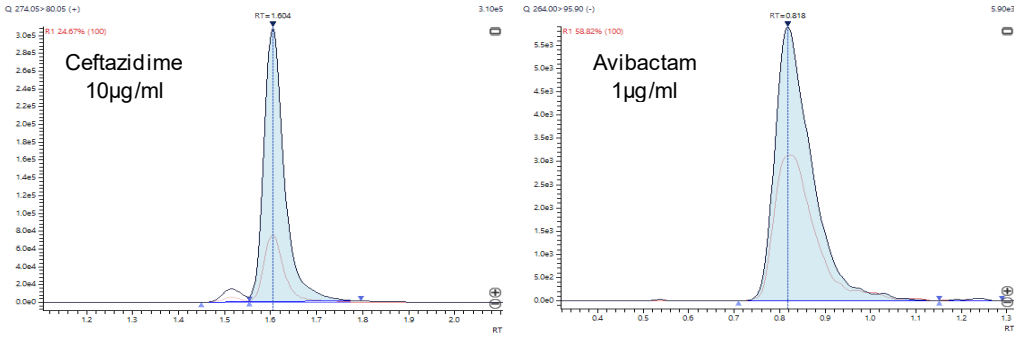
Clinical management
During the course of the study, we identified receipt of RRT as a risk factor for clinical failure and emergence of ceftazidime-avibactam resistance [1]. Given these data, our standard approach to ceftazidime-avibactam treatment for patients receiving CRRT was to administer 2.5g IV q 8h and enroll patients into this study. For each of these patients, we carefully monitored patients for any signs or symptoms of drug toxicity, including neurotoxicity and myelosuppression.

Sampling and storage
Whole blood samples were collected from November 2016 to March 2019 in sterile tubes containing EDTA as an anticoagulant. Samples were collected prior to a dose of ceftazidime-avibactam, and then at 2, 4, 6, and 8 hours after the infusion started. Collection tubes were centrifuged at 3,000 x rpm for 5 minutes immediately after collection. Plasma was stored in 0.5-1mL aliquots at -80°C until analysis.

Simultaneous measurement of avibactam and ceftazidime with a highly-sensitive, reproducible ultra high performance liquid chromatography mass spectrometry (UHPLC-MS) assay.

We developed an UHPLC-MS assay to quantify avibactam and ceftazidime on a Shimadzu Nexera XD UHPLC with a Shimadzu 8045 MS (Figure 1). Mobile phase A was 0.1% formic acid in water; mobile phase B was 0.1% formic acid in acetonitrile. Samples were prepared by adding 100µL of plasma to 200µL of water and 700µL of acetonitrile containing internal standards (ceftazidime-d5, Toronto Research Chemical, Toronto Canada; avibactam-H2; Alsachim, Illkirch, France). Samples were vortexed, allowed to rest on ice, then centrifuged at 13,000 x rpm for 5 minutes, and allowed to rest on ice again. In an LCMS vial, 100µL of supernatant was added to 400µL mobile phase A and samples were loaded into a 4°C autosampler. A Waters Atlantis T3 column (3µm, 50x2.1mm; with guard) was used. An elution gradient at 0.5mL/min started at 5% B increasing to 90% B, where it was held for 30 seconds before returning to 5% B. The total run time was 5.5 minutes and the injection volume was 3µL. Transitions were monitored in positive mode for ceftazidime (*m/z* 274.1 < 80.05) and negative mode for avibactam (264.00 < 95.90). The assay was reproducible and linear over a range of 0.1 - 20µg/mL for avibactam and 1 - 200µg/mL for ceftazidime.

Figure 1. Chromatograms of Ceftazidime and Avibactam.



Pharmacokinetic and Pharmacodynamic analysis.

Pharmacokinetic analysis of serum concentrations was performed with WinNonlin version 8.2 (Certara, Princeton, NJ) for IV infusion noncompartmental model analysis. Predicted PK values were calculated for each patient. Descriptive statistics are provided, including mean and standard deviation for continuous variables. Dichotomous or continuous variables were compared by chi-squared test or Mann-Whitney U, respectively.

Results.

A total of 20 patients (Table 1) were enrolled in the study. Fifteen patients received a standard dosing regimen of 2.5g ceftazidime-avibactam every 8 hours intravenously. Five patients received dose-adjustments due to renal insufficiency. Two received 1.25g of ceftazidime-avibactam every 8 hours intravenously, 2 received 0.94g every 48 hours, and 1 received 0.94g every 24 hours. For patients receiving CRRT, dialysis settings and flow rates are provided in Table 2.

Table 1. Patient Demographics (n=20).

Patient #	Age	Sex	Race[1]	Height (cm)	Weight[2] (kg)	Dose	SCr on day of sampling	Cockroft-Gault IBW (kg)	Renal Replacement Therapy
7	74	F	D	160	50.9	0.94g q 24h	2.3	CRRT	CRRT
2	64	M	W	178	66	0.94g q 48h	2	HD	HD
5	69	F	W	173	54.5	0.94g q 48h	2.1	HD	HD
1	60	M	W	185	120.8	1.25g q 8h	2.1	42.0	None
16	51	F	W	168	65.7	1.25g q 8h	1.5	42.0	None
Mean (non-standard dosing):	**63.6**			**172.8**	**71.6**		**1.93**		
3	59	F	W	163	70.1	2.5g q 8h	1	52.6	None
4	59	F	W	163	78.2	2.5g q 8h	0.6	87.7	None
6	59	F	W	185	85.8	2.5g q 8h	0.7	133.5	None
8	66	M	W	175	132	2.5g q 8h	0.4	CRRT	CRRT
9	68	M	W	175	75.6	2.5g q 8h	1.2	CRRT	CRRT
10	48	F	W	173	67	2.5g q 8h	1.5	CRRT	CRRT
11	35	M	W	163	66	2.5g q 8h	1	CRRT	CRRT
12	59	M	U	170	120	2.5g q 8h	1.5	CRRT	CRRT
13	58	M	W	178	96	2.5g q 8h	1.5	CRRT	CRRT
14	45	F	W	163	46.2	2.5g q 8h	0.4	154.2	None
15	44	F	W	168	132	2.5g q 8h	0.4	168.6	None
17	31	M	W	193	75.5	2.5g q 8h	0.7	187.1	None
18	61	M	W	168	104.6	2.5g q 8h	1	70.2	None
19	41	M	W	171	73.2	2.5g q 8h	2.5	36.8	None
20	63	M	W	177	114	2.5g q 8h	0.8	96.3	None
Mean (standard dosing):	**53.1**			**172.3**	**89.0**		**1.01**		
Mean (overall):	**55.7**			**172.4**	**84.7**		**1.21**		

[1]White (W), declined race (D), race unknown (U)
[2]Adjusted body weight was used for obese patients when >120% IBW

Table 2. Renal Replacement Therapy Settings.

Patient	CRRT Machine	Type of CRRT	Filter Model	Blood Flow Rate (mL/hr)	Replacement Fluid Infusion Rate (mL/hr)	Dialysate Flow Rate (mL/hr)
7	Prismaflex	CVVHDF	M100	250	250	1750
8	Prismaflex	CVVHDF	M100	250	250	3000
9	Prismaflex	CVVHDF	M100	200	500	2000
10	Prismaflex	CVVHDF	M100	250	250	1500
11	Prismaflex	CVVHDF	M100	250	250	1700
12	Prismaflex	CVVHDF	M150	300	250	3500
13	Prismaflex	CVVHDF	M100	250	250	2500

Ceftazidime Pharmacokinetics

A total of 96 plasma samples were collected from 20 patients. Figure 2 shows total ceftazidime concentrations plotted for each patient. Table 3 lists PK parameters for all patients stratified by dosing strategy. There was no statistical difference (Mann-Whitney) between patients receiving a standard 2.5g dose q8h with normal renal function and patients on CRRT for C_{max}, AUC, CL, and V_d. Median values were statistically different for C_{min} (normal function 29.01 vs CRRT 46.59, $p = 0.0496$), $t_{1/2}$ (normal function 4.478h vs CRRT 10.12h, $p = 0.0496$), and the rate elimination constant (K_e) (normal function 0.15 vs CRRT 0.07, $p = 0.0496$). Figure 3 compares the concentrations over time per patient for those with and without CRRT.

Figure 2. Ceftazidime Plasma Concentrations in Patients Receiving 2.5g IV q 8h.

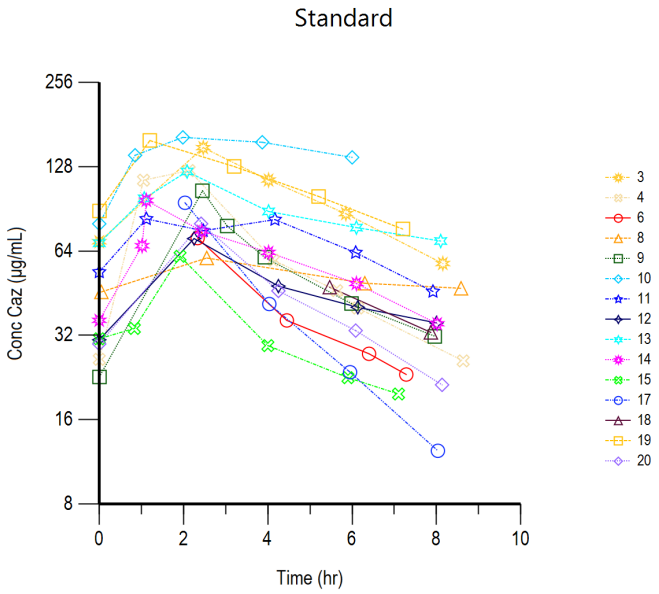


Table 3. Calculated Ceftazidime PK parameters by Patient Group.

Median (IQR)	All patients (n=20)	Standard Dose				Other (n=5)
		All 2.5g q8h (n=15)	CrCl > 50ml/min (n=9); 2.5g IV q8h	CRRT (n=6); 2.5g IV q8h	*P* value	
C_{max} (µg/ml)	80.6 (61.2, 104.1)	87.0 (69.2, 108.2)	81.3 (76.5, 88.1)	96.3 (69.6, 112.4)	0.4559	69.9 (59.3, 73.2)[1]
C_{min} (µg/ml)	40.4 (28.3, 55.0)	35.4 (27.7, 53.5)	29.0 (20.9, 35.5)	46.6 (37.9, 64.4)	0.0496	46.1 (46.0, 53.7)[1]
AUC_{0-8h} (hr*µg/mL)[2]	456.3 (400.3 588.1)	456.6 (388.7, 651.8)	437.4 (328.2, 550.3)	522.2 (455.1, 683.7)	0.3277	444.8 (432.7, 456.9)
K_e (1/hr)	0.13 (0.06, 0.16)	0.15 (0.10, 0.16)	0.15 (0.14, 0.19)	0.07 (0.05, 0.14)	0.0496	0.04 (0.04, 0.07)
$t_{1/2}$ (hr)	5.2 (4.3, 12.6)	4.5 (4.2, 7.0)	4.5 (3.7, 5.1)	10.1 (5.5, 15.1)	0.0496	15.7 (8.9, 16.5)
V_d (L)	34.6 (22.5, 49.3)	28.7 (20.6, 46.0)	26.0 (16.3, 36.1)	43.2 (31.3, 56.9)	0.1135	40.7 (33.1, 55.1)
CL (L)	3.6 (2.3, 5.2)	4.4 (3.2, 5.5)	5.3 (3.6, 6.2)	4.0 (3.0, 4.7)	0.2238	2.3 (1.8, 2.3)

[1] See Table 6 for details.
[2] For AUC, patients with 24 or 48 hour dosing were excluded; All patients n = 17, Other n = 2

Figure 3. Ceftazidime Concentration-time Profile: Patients Receiving 2.5g IV q 8h, Stratified by those with or without CRRT.

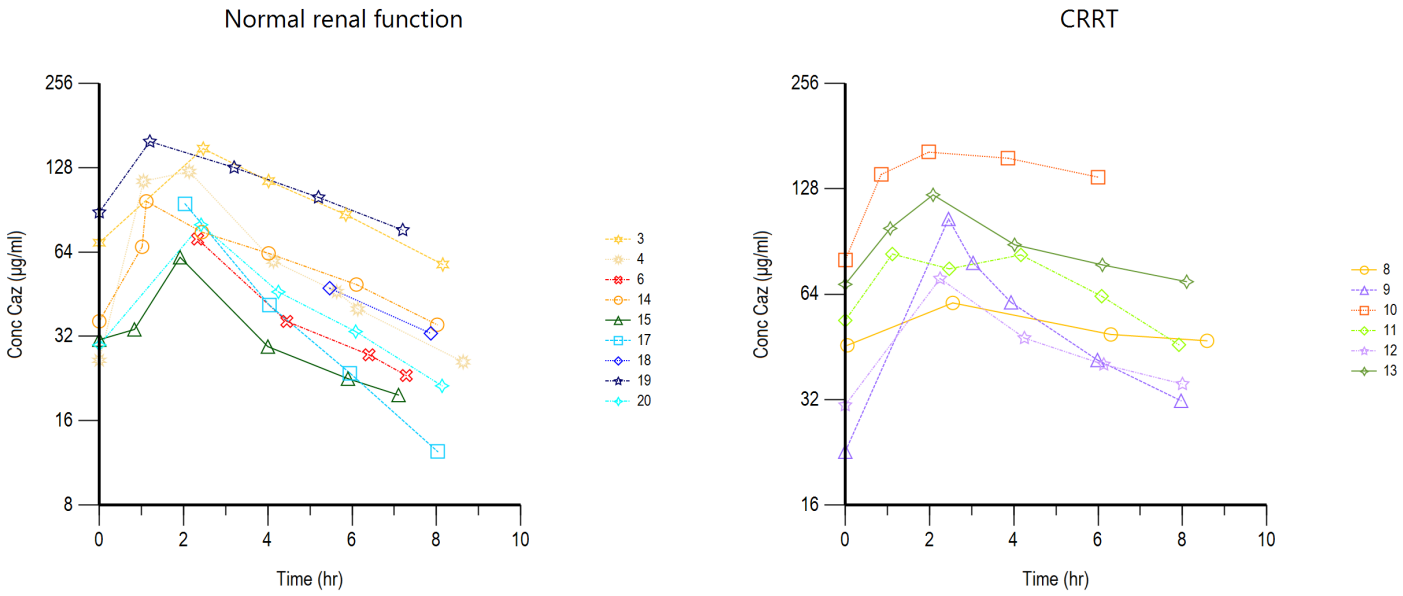


Table 4. Ceftazidime PK Parameters for Patients Receiving Continuous Renal Replacement Therapy.

Patient	Regimen	C_{min} (µg/ml)	C_{max} (µg/ml)	AUC_{0-8h} (hr*µg/mL)	$t_{1/2}$ (hr)	CL (L/hr)	V_d (L)	Blood Flow Rate (mL/hr)	Replacement Fluid Infusion Rate (mL/hr)	Dialysate Flow Rate (mL/hr)
8	2.5g IV q 8h	45.73	60.43	456.3	16.24	5.92	143.92	250	250	3000
9	2.5g IV q 8h	22.72	104.95	454.7	4.32	5.54	34.43	200	500	2000
10	2.5g IV q 8h	80.03	162.85	1156.4	16.77	2.18	53.24	250	250	1500
11	2.5g IV q 8h	45.88	83.33	588.1	4.40	4.45	30.40	250	250	1700
12	2.5g IV q 8h	30.85	70.91	377.1	8.60	6.46	76.61	300	250	3500
13	2.5g IV q 8h	68.26	122.98	715.6	11.64	3.48	54.80	250	250	2500

Avibactam Pharmacokinetics

The same 96 samples were simultaneously analyzed for avibactam total drug concentrations; Figure 4 shows the results for each patient. Table 5 lists PK parameters for all patient groups. There was no statistical difference (Mann-Whitney) between patients receiving a standard 2.5g dose q8h with normal renal function and patients on CRRT for C_{max} or V_d. Median values for C_{min}, AUC, $t_{1/2}$, K_e, and CL were statistically different (normal function vs CRRT, respectively: 4.45 vs 11.1, $p = 0.0028$, 73.4 vs 126.4, $p = 0.0496$, 3.3 vs 10.3, $p = 0.0048$, 0.21 vs 0.07, $p = 0.0048$, 6.6 vs 4.2, $p = 0.0256$). Figure 5 shows the time course results for the 15 standard dose patients.

Figure 4. Avibactam Plasma Concentrations in Patients Receiving 2.5g IV q 8h.

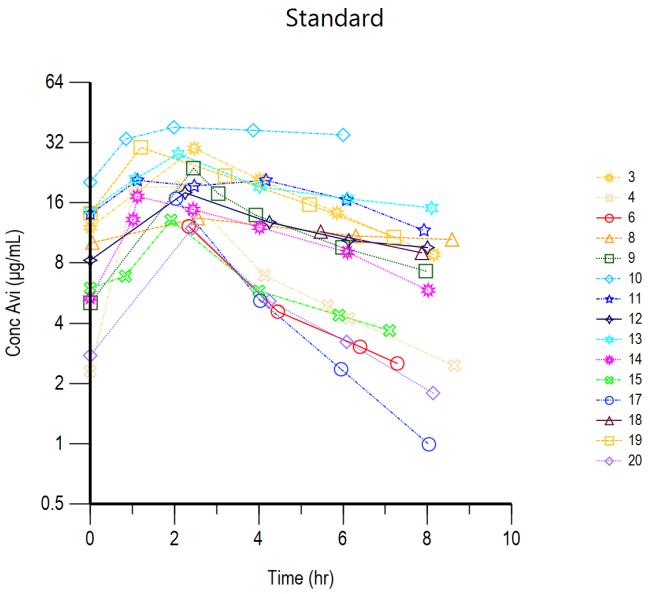


Table 5. Calculated Avibactam PK Parameters by Patient Group.

Median (IQR)	All patients (n=20)	Standard Dose				Other (n=5)
		All 2.5g q8h (n=15)	CrCl > 50ml/min (n=9); 2.5g IV q8h	CRRT (n=6); 2.5g IV q8h	*P* value	
C_{max} (µg/ml)	15.6 (11.8, 23.0)	15.9 (12.7, 24.3)	13.3 (11.3, 16.3)	21.3 (16.7, 27.1)	0.1135	14.1 (8.9, 21.5)[1]
C_{min} (µg/ml)	8.5 (4.2, 9.8)	8.9 (3.9, 10.1)	4.5 (2.8, 8.9)	11.1 (9.8, 14.2)	0.0028	6.11 (5.8, 9.0)[1]
AUC_{0-8h} (hr*µg/mL)[2]	98.8 (58.3, 149.4)	99.1 (62.0, 150.2)	73.4 (48.3, 99.1)	126.4 (101.9, 154.5)	0.0496	74.7 (66.5, 82.9)
K_e (1/hr)	0.15 (0.07, 0.21)	0.16 (0.09, 0.21)	0.21 (0.16, 0.23)	0.07 (0.05, 0.13)	0.1135	0.07 (0.05, 0.07)
$t_{1/2}$ (hr)	4.6 (3.3, 10.2)	4.4 (3.3, 7.9)	3.3 (3.0, 4.2)	10.3 (5.6, 15.2)	0.0048	9.8 (9.3, 12.6)
V_d (L)	43.2 (23.4, 58.9)	38.1 (22.6, 56.8)	32.1 (20.6, 43.8)	56.1 (35.4, 78.9)	0.1135	43.8 (42.6, 57.7)
CL (L)	4.5 (3.3, 6.2)	5.3 (3.4, 8.0)	6.6 (5.6, 9.6)	4.2 (3.3, 4.9)	0.0256	3.0 (1.6, 3.6)

[1] See Table 6 for details.
[2] For AUC, patients with 24 or 48 hour dosing were excluded; All patients n = 17, Other n = 2

Figure 5. Avibactam Concentration-time Profile: Patients Receiving 2.5g IV q 8h, Stratified by those with or without CRRT.

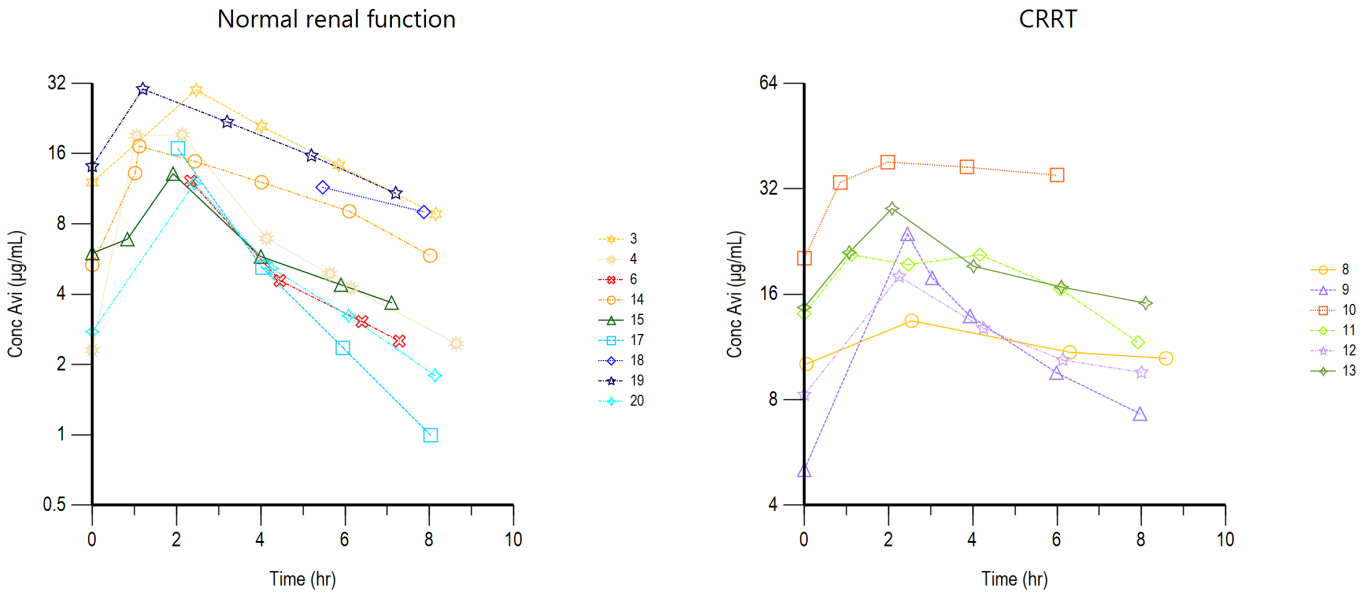


Table 6. Avibactam PK Parameters for Patients Receiving Continuous Renal Replacement Therapy.

Patient	Regimen	C_{min} (µg/ml)	C_{max} (µg/ml)	AUC_{0-8h} (hr*µg/mL)	$t_{1/2}$ (hr)	CL (L/hr)	V_d (L)	Blood Flow Rate (mL/hr)	Replacement Fluid Infusion Rate (mL/hr)	Dialysate Flow Rate (mL/hr)
8	2.5g IV q 8h	10.11	13.43	101.4	16.36	5.33	130.64	250	250	3000
9	2.5g IV q 8h	5.04	23.79	103.4	4.35	4.87	30.64	200	500	2000
10	2.5g IV q 8h	20.28	38.15	279.5	31.83	1.79	84.40	250	250	1500
11	2.5g IV q 8h	11.66	20.74	149.4	4.52	3.49	24.26	250	250	1700
12	2.5g IV q 8h	8.26	17.97	98.8	8.94	4.97	62.56	300	250	3500
13	2.5g IV q 8h	14.66	28.12	156.2	11.66	3.17	49.66	250	250	2500

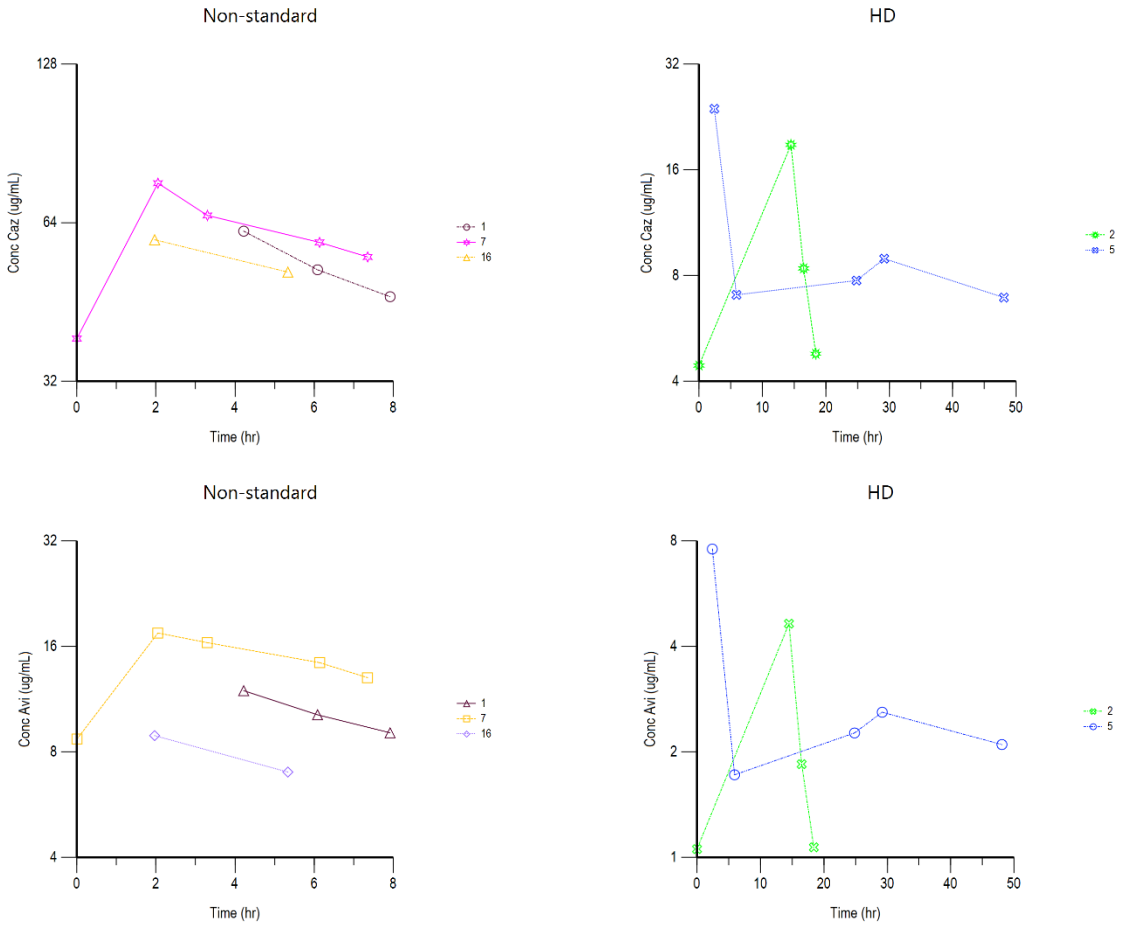
Pharmacokinetic Parameters: Patients Receiving Renally-Adjusted Doses of CAZ-AVI.
Five patients received non-standard dosing. Table 7 details the dose received, as well as the observed concentrations of both ceftazidime and avibactam at specific times following start of drug infusion. Figure 6 show the concentration-time profiles of these patients for both ceftazidime (top panels) and avibactam (bottom panels).

Table 7. Measured Total Drug Values of Ceftazidime and Avibactam in Critically Ill Patients.

Patient	Dosing	Creatinine clearance or RRT	Actual Draw Time (hours)[1]	Ceftazidime (µg/mL)	Avibactam (µg/mL)
7	0.94g IV q 24h	CRRT	Pre-dose	38.563	8.692
			2.1	76.049	17.473
			3.3	66.048	16.391
			6.1	58.712	14.380
			7.4	55.094	13.026
2	0.94g IV q 48h	HD[2]	Pre-dose	4.436	1.056
			14.5 (Pre-HD)	18.848	4.643
			16.5 (Mid-HD)	8.385	1.845
			18.4 (Post-HD)	4.790	1.069
5	0.94g IV q 48h	HD[3]	2.4 (Pre-HD)	23.864	7.583
			5.9 (Post-HD)	7.049	1.721
			24.8	7.742	2.265
			48.1	6.925	2.099
1	1.25g IV q 8h	42mL/min	4.2	61.665	11.960
			6.1	52.092	10.208
			7.9	46.306	9.071
16	1.25g IV q 8h	42mL/min	2.0	59.388	8.903
			5.3	51.557	7.009

[1]Time relative to start of drug infusion.
[2] Patient received a full 4-hour HD session with 1L ultrafiltration. Samples were collected immediately before, during, and after HD.
[3] Patient received a 3-hour HD session with 1.5L ultrafiltration. Samples were collected immediately before and after HD, as well as 24 and 48 hours after the dose. The latter time point represents the trough values for this patient.

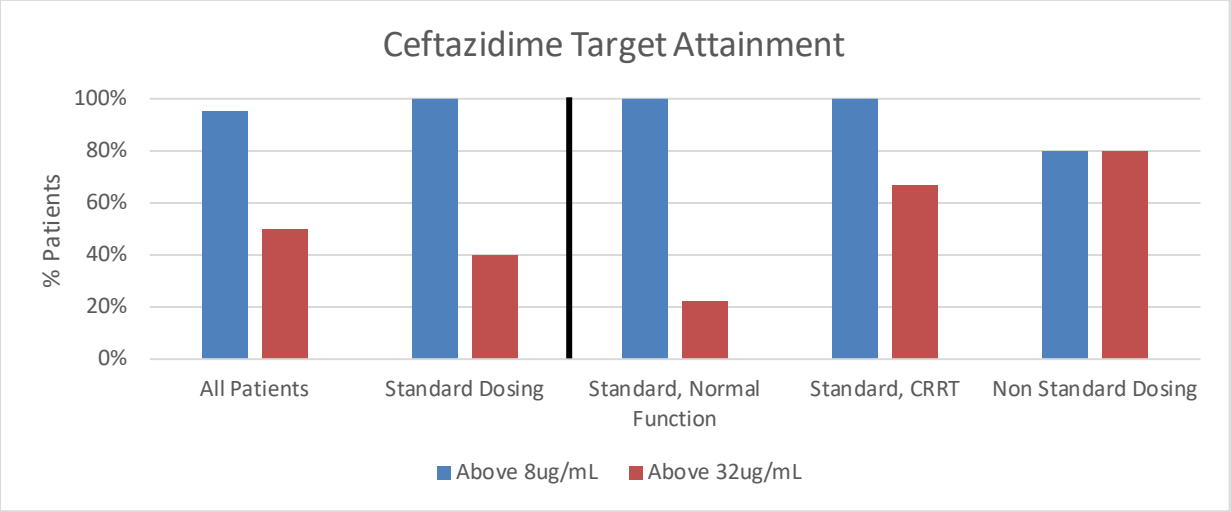
Figure 6: Concentration-time profiles of Patients Receiving Non-standard Dosing.



Pharmacodynamics and Target Attainment

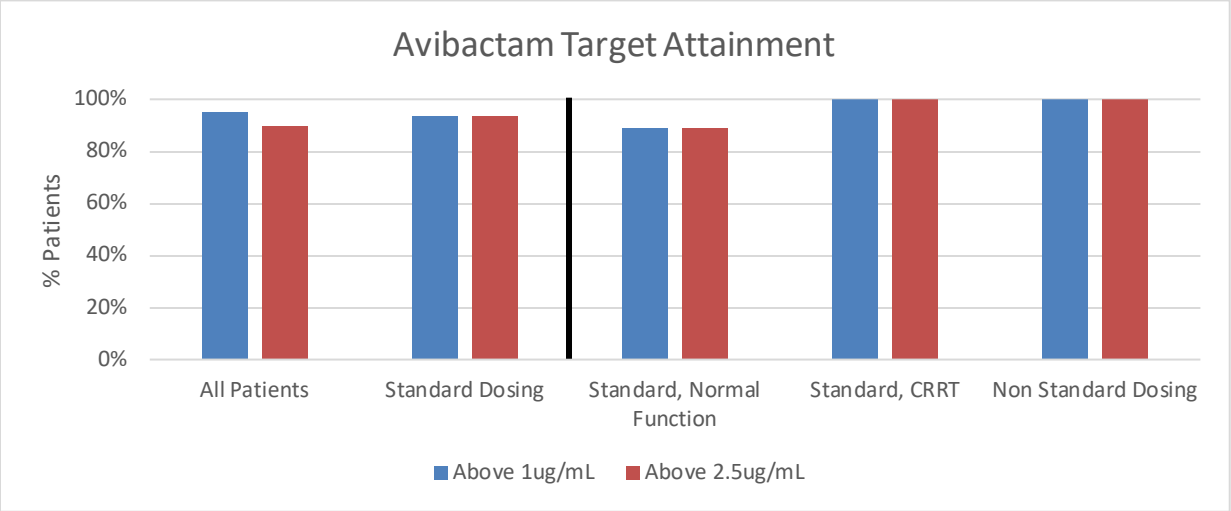
Ceftazidime free drug concentration was calculated by adjusting for 10% protein binding. To determine if patients in the study met pre-determined PD targets, we assessed the time free drug concentrations (*f*T) remained above the MIC and 4x MIC, using the CLSI susceptibility breakpoint for ceftazidime (8 µg/mL) as the representative MIC value. All patients dosed every 8 hours had ceftazidime exposures of 100% *f*T>MIC (Figure 7). Both patients receiving intermittent dialysis achieved targets before, but not after HD. Excluding patients on HD, 56% of patients achieved exposures of 100% *f*T>4xMIC, an exposure reported to suppress the emergence of resistance [2].

Figure 7. Target Attainment for Ceftazidime.



For analysis purposes, we estimated the avibactam free drug concentration using 10% protein binding as well [3]. Although PD targets are not as well elucidated for β-lactamase inhibitors, we used surrogate targets of 1 and 2.5 µg/mL and evaluated free trough concentrations of avibactam. As shown in Figure 8, 95% and 90% of patients met targets of 100% *f*T>1 µg/mL and >2.5 µg/mL, respectively [2-4]. Only one patient (patient #17) with normal function on a standard 2.5g q8h dose did not meet targets.

Figure 8. Target Attainment for Avibactam.



Safety

The safety of ceftazidime-avibactam has been well-defined for patients with normal renal clearance, but not for patients receiving standard doses during CRRT. We assessed 6 such patients as part of this study to ensure exposures, which clearly met PD targets, were not associated with undue toxicity. Among the 6 patients receiving 2.5g IV q 8h on CRRT (Table 2), 50% died within 72 hours of sample collection due to underlying multi-system organ failure. One additional patient was transitioned to HD the day after study enrollment. The last two patients received treatment courses of 12 and 14 days with no apparent toxicity, including myelosuppression, neurotoxicity, or further renal toxicity.

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Appendix.

Observed Drug Concentrations.

Patient	# hours post start of infusion	Total Measured CAZ (µg/mL)	Total Measured AVI (µg/mL)
1	4.22	61.665	11.960
	6.08	52.092	10.208
	7.92	46.306	9.071
2	-2.28	4.436	1.056
	14.50	18.848	4.643
	16.50	8.385	1.845
	18.42	4.790	1.069
3	-0.70	69.076	12.027
	2.47	149.718	29.957
	4.02	114.670	20.922
	5.85	87.003	14.256
	8.15	57.749	8.816
4	1.05	114.512	19.102
	2.13	124.009	19.293
	4.13	59.349	6.936
	5.63	46.217	4.894
	6.13	40.060	4.245
	8.63	25.943	2.461
	-0.25	26.280	2.302
5	2.42	23.864	7.583
	5.92	7.049	1.721
	24.83	7.742	2.265
	29.20	8.935	2.596
	48.07	6.925	2.099
6	2.33	71.190	12.212
	4.45	36.178	4.575
	6.40	27.501	3.054
	7.28	23.193	2.521
7	-0.12	38.563	8.692
	2.05	76.049	17.473
	3.30	66.048	16.391
	6.13	58.712	14.380
	7.35	55.094	13.026
8	0.05	45.727	10.111
	2.55	60.427	13.428
	6.30	49.106	10.919
	8.58	47.102	10.487
9	-0.17	22.724	5.042
	2.45	104.953	23.793
	3.03	78.604	17.805

	3.93	60.631	13.852
	5.98	41.508	9.548
	7.97	31.745	7.291
10	-0.18	80.026	20.284
	0.85	140.574	33.392
	1.98	162.853	38.147
	3.87	156.434	36.869
	6.00	138.158	34.962
11	0.00	53.859	14.073
	1.12	83.329	20.740
	2.47	75.611	19.423
	4.17	82.851	20.739
	6.08	63.154	16.557
	7.92	45.877	11.657
12	-0.03	30.852	8.260
	2.25	70.914	17.969
	4.25	47.960	12.786
	6.13	40.304	10.379
	8.00	35.450	9.563
13	-0.10	68.263	14.656
	1.07	98.623	21.050
	2.08	122.983	28.116
	4.02	88.581	19.227
	6.10	77.589	16.771
	8.10	69.466	15.085
14	1.02	66.823	13.196
	2.43	75.367	14.827
	4.02	63.294	12.060
	6.10	48.993	9.059
	8.02	35.207	5.852
	-0.62	36.211	5.340
	1.12	97.037	17.224
15	-1.75	31.124	5.997
	0.83	33.864	6.882
	1.92	61.286	13.123
	4.00	29.411	5.797
	5.90	22.595	4.390
	7.10	19.758	3.679
16	1.97	59.388	8.903
	5.33	51.557	7.009
17	2.03	95.156	16.796
	4.03	41.400	5.188
	5.95	23.634	2.358
	8.03	12.392	0.994
18	5.47	47.534	11.478

	7.87	32.785	8.997
19	-0.97	88.724	14.151
	1.20	158.668	30.242
	3.20	128.146	21.859
	5.20	100.281	15.687
	7.20	76.658	10.822
20	-0.08	29.811	2.762
	2.42	80.068	11.926
	4.25	46.112	5.162
	6.08	33.278	3.229
	8.13	21.301	1.792