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Outcomes Using Cefiderocol for the Treatment of *Acinetobacter baumannii* Infections from the PROVE (Real-World Evidence) Study

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Introduction

- Carbapenem-resistant *Acinetobacter baumannii* (CRAB) infections are difficult to treat and have limited treatment options.[1,2]
- Cefiderocol (CFDC) is a novel siderophore cephalosporin with potent *in vitro* activity against CRAB.[3]
- PROVE is an ongoing, international, multicenter, retrospective chart review study assessing CFDC use for the treatment of Gram-negative (GN) infections. This analysis describes the outcomes and treatment patterns of CFDC treatment in the subset of patients with AB, most of which are CRAB.

Methods

- The main objectives of PROVE are to describe the clinical and microbiological characteristics of infections treated with CFDC and patient outcomes including safety.
- Eligibility criteria include documented GNBI (before or after starting CFDC), at least 72 hours of first-time use of CFDC in routine clinical practice, and documentation of the following data: CFDC dosing, description of the GNBI for which CFDC was prescribed, and clinical outcomes. Exclusion criteria include receipt of CFDC prior to local commercial availability.
- Key descriptive characteristics include patient characteristics, type of infection and pathogen, and CFDC treatment patterns. Outcomes include clinical resolution of GNBI at the end of CFDC treatment (evidence of resolution/improvement of clinical signs and/or symptoms without relapse), 30-day all-cause mortality (ACM) calculated from the day of initiation of CFDC treatment), length of hospitalization, post-treatment LOS, and safety (i.e., adverse events).
- Index culture samples were collected before CFDC initiation that supported its use or, less commonly, those cultures reported after CFDC was started if used empirically.
- Susceptibility to carbapenem was assessed by local antibiotic susceptibility testing (AST). A patient was classified as having a carbapenem-resistant (CR) pathogen if any AB isolate(s) were CR.
- AST results were zone size or minimum inhibitory concentration (MIC) as reported by each site's laboratory. Clinical and Laboratory Standards Institute (CLSI) M100 31st and 32nd editions[4,5] and the US Food and Drug Administration (FDA) recommended breakpoints[6] were used to determine susceptibility. Descriptive statistics are used to present the data.

Results

Baseline characteristics of patients

- On August 9, 2022, a total of 220 total patients from 21 sites had completed and validated chart abstractions. The current results include data from 76 patients with a documented AB infection: 63 from the USA and 13 from the Europe (**Table 1**).
- The median age was 57.5 years, 56.6% were male, and 38.2% were admitted from a healthcare facility (**Table 1**). Comorbidities and risk factors for CR GNI are shown in **Table 1**. Only 5.3% had no listed comorbidities. The most common risk factor was prior mechanical ventilation.

Infection characteristics

- Monomicrobial and polymicrobial infections with AB accounted for 63% and 37% of infections, respectively. Respiratory infections were the most common site for both mono- and polymicrobial infections (**Figure 1A, 1B**). One infection (1%) was a co-infection unrelated to the primary.
- Other pathogens associated with AB in polymicrobial infections are shown in **Figure 2**, most of which were *Pseudomonas aeruginosa.*

Table 1. Demographics and clinical characteristics of patients with *Acinetobacter baumannii* infection

Characteristic	N	%
Total number of patients	76	
Age at admission (years)		
Mean (SD)	56.3	18.6
Median (Q1–Q3)	57.5	43.0-68.5
Min, Max	19	97
<50	26	34.2%
50–65	27	35.5%
>65	23	30.3%
Sex		
Female	33	43.4%
Male	43	56.6%
Country where patients were enrolled		
United States	63	82.9%
Germany	1	1.3%
Italy	11	14.5%
United Kingdom	1	1.3%
Race (for US patients only)		
White	23	30.3%
Black	32	42.1%
Hispanic	2	2.6%
Asian	1	1.3%
Other	5	6.6%
N/A (non-US)	13	17.1%
Place of residence before admission		
Private Residence (home)	44	57.9%
Healthcare facility[a]	29	38.2%
Assisted living, residential care/group home	-	-
Other	3	3.9%
Comorbid conditions prior to hospitalization (>10%)		
No comorbid conditions	4	5.3%
Hypertension	25	32.9%
Diabetes with end-organ damage	14	18.4%
Hemiplegia, paraplegia, or quadriplegia	14	18.4%
Cerebrovascular disease	12	15.8%
Chronic pulmonary disease	12	15.8%
Diabetes mellitus uncomplicated	11	14.5%
Moderate or severe renal disease	11	14.5%
Dementia	10	13.2%
COVID-19	10	13.2%
Severe burns	9	11.8%
Brain injury	8	10.5%
Patients with risk factors for CR-GNBI >5%		
No risk factors	6	7.9%
Mechanical ventilation prior to index culture sample	39	51.3%
Admitted to hospital in the past 6 months	36	47.4%
Exposed or non-response to carbapenem = 30 days	20	26.3%
Trauma surgery	22	28.9%
History of CR GNBI	15	19.7%
Other bacterial infections	6	7.9%
Received high-dose corticosteroids	4	5.3%

Data are n (%) unless otherwise stated. [a]Healthcare facility includes transfer from nursing/skilled nursing facilities, rehabilitation facilities, and long-term acute care hospitals. COVID-19, coronavirus disease 2019; CR, carbapenem resistant; GNBI, Gram-negative bacterial infection; max, maximum; min, minimum; N/A, not applicable; Q, quartile; SD, standard deviation.

Pathogen susceptibility to CFDC and other GN antibiotics

- **Table 2** shows AB susceptibility within four categories (n=39, 51%). Infections not tested for CFDC accounted for 37 (49%).
- 77% of AB tested were susceptible by FDA criteria (i.e., MIC ≤1, zone size ≥19). Three additional AB isolates were susceptible under the higher CLSI threshold (i.e., MIC 2–4, zone size 15–18) giving an overall susceptibility rate of 85%.
- 95.8% (n=69) of those tested were found to be carbapenem resistant (CR).

Figure 1. *Acinetobacter baumannii* monomicrobial sites of infection (A) (N=48) and polymicrobial sites of infection (B) (N=27)

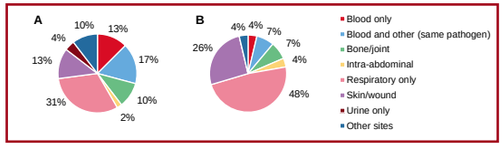

Figure 2. Other pathogens accompanying *Acinetobacter baumannii* in polymicrobial infections

Table 2. Antibiotic susceptibility compared with cefiderocol

All isolates (N=76)				*Acinetobacter baumannii* susceptibility to cefiderocol											
				Susceptible by FDA & CLSI			Susceptible by CLSI, not FDA			Intermediate by CLSI (ed. 31)			Resistant by CLSI		
Cefiderocol cut-points	Not Tested			≤1 µg/mL or Zone ≥19 mm[a]			2–4 µg/mL or Zone 15–18 mm[b]			8 µg/mL or Zone 11–14 mm[c]			≥16 µg/mL or Zone ≤10 mm[d]		
All isolates (N=76); n, row %	37	49%		30	39%		3	4%		1	1%		5	7%	
Susceptible to CFDC of those tested (N=39); n/N (%)				30/39 (77%)			3/39 (8%)			1/39 (3%)			5/39 (13%)		
Antibiotic	**N**	**NT**	**%S[e]**	**N**	**NT**	**%S[e]**	**N**	**NT**	**%S[e]**	**N**	**NT**	**%S[e]**	**N**	**NT**	**%S[e]**
Meropenem	32	5	13%	27	3	4%	3	0	0%	1	0	0%	5	0	0%
Imipenem	10	27	0%	4	26	25%	0	3	-	0	1		0	5	-
Ampicillin/sulbactam	23	14	13%	26	4	8%	3	0	0%	1	0	0%	5	0	0%
Piperacillin/tazobactam	22	15	9%	21	9	5%	2	1	0%	1	0	0%	4	1	0%
Colistin or polymyxin B	10	27	90%	6	24	17%	0	3	-	1	0	0%	0	5	-
Cefepime	22	15	9%	29	1	3%	2	1	50%	1	0	0%	5	0	0%
Meropenem/vaborbactam	0	37	-	0	30	-	0	3	-	0	1	-	0	5	-
Ceftazidime/avibactam	1	36	100%	2	28	0%	0	3	-	1	0	0%	0	5	-
Ceftolozane/tazobactam	1	36	0%	1	29	0%	0	3	-	0	1	-	0	5	-
Imipenem/relebactam	0	37	-	0	30	-	0	3	-	0	1	-	0	5	-
Aztreonam/avibactam	0	37	-	0	30	-	0	3	-	0	1	-	0	5	-
Tigecycline	0	37	-	0	30	-	0	3	-	0	1	-	0	5	-
Minocycline	10	27	20%	11	19	9%	1	2	100%	0	1	-	5	0	0%
Eravacycline	0	37	-	0	30	-	0	3	-	0	1	-	0	5	-

[a]Based on FDA (2022) breakpoints for *Acinetobacter baumannii* susceptibility to cefiderocol. [b]Based on CLSI (32nd edition, 2022) breakpoints for *Acinetobacter baumannii* susceptibility to cefiderocol. [c]Based on CLSI (32nd edition, 2022) breakpoints for *Acinetobacter baumannii* susceptibility to cefiderocol. [d]Based on CLSI (31st edition, 2021) breakpoints for *Acinetobacter baumannii* resistance to cefiderocol. [e]Percentage of those tested that are susceptible from local laboratory determination to other antibiotics. CFDC, cefiderocol; CLSI, Clinical and Laboratory Standards Institute; FDA, Food and Drug Administration; N, number tested; NT, number not tested; S, susceptible.

Table 3. Outcomes by key characteristics of patients with *A. baumannii* infection

Characteristic	Overall		Clinical cure[a]			30-day mortality		
	N	%	N	%	Row %	N	%	Row %
Number of patients	76		48		63%	16		21%
Index infection type								
Monomicrobial - primary infection site (n=48)								
Blood only	6	8%	3	6%	50%	2	13%	33%
Blood and other (same pathogen)[b]	8	11%	2	4%	25%	4	25%	50%
Bone/joint	5	7%	4	8%	80%	0	0%	0%
Intra-abdominal	1	1%	0	0%	0%	1	6%	100%
Respiratory only	15	20%	9	19%	60%	2	13%	13%
Skin and skin structure	6	8%	5	10%	83%	0	0%	0%
Urine only	2	3%	2	4%	100%	0	0%	0%
Other sites	5	7%	3	6%	60%	2	13%	40%
Polymicrobial - primary infection site (n=27)								
Blood only	1	1%	1	2%	100%	0	0%	0%
Blood & other (same pathogen)[b]	2	3%	1	2%	50%	1	6%	50%
Bone/joint	2	3%	2	4%	100%	1	6%	50%
Intra-abdominal	1	1%	0	0%	0%	0	0%	0%
Respiratory only	13	17%	10	21%	77%	1	6%	8%
Skin and skin structure	7	9%	4	8%	57%	2	13%	29%
Urine only	0	0%	0	0%	-	0	0%	-
Other sites	1	1%	1	2%	100%	0	0%	0%
***Acinetobacter baumannii* as co-infection, not primary (n=1)**								
Skin and skin structure	1	1%	1	2%	100%	0	0%	0%
Severity upon starting cefiderocol								
Baseline comorbid conditions								
Age >65 years	23	30%	16	33%	70%	5	31%	22%
0–1 major comorbid conditions	29	38%	16	33%	55%	4	25%	14%
2–3 major comorbid conditions	33	43%	23	48%	70%	7	44%	21%
≥4 major comorbid conditions	14	18%	9	19%	64%	5	31%	36%
COVID-19 during index hospitalization	10	13%	8	17%	80%	3	19%	30%
Patient in ICU while receiving CFDC								
Yes	41	54%	18	38%	44%	13	81%	32%
No	35	46%	30	63%	86%	3	19%	9%
Received mechanical ventilation								
Yes	31	41%	14	29%	45%	8	50%	26%
No	45	59%	34	71%	76%	8	50%	18%
Vasopressor support								
Yes	21	28%	9	19%	43%	7	44%	33%
No	55	72%	39	81%	71%	9	56%	16%
CFDC utilization								
Positive culture to first CFDC dose								
1 week or less	58	76%	37	77%	64%	12	75%	21%
More than 1 week	18	24%	11	23%	61%	4	25%	22%
Reason for starting CFDC								
Documented infection	61	80%	36	75%	59%	15	94%	25%
Salvage treatment (failure of prior GNA)	8	11%	6	13%	75%	1	6%	13%
Empirical for suspected CR GNBI	6	8%	5	10%	83%	0	0%	0%
Other	1	1%	1	2%	100%	0	0%	0%
CFDC as monotherapy[c]								
Yes	42	55%	29	60%	69%	6	38%	14%
No	34	45%	19	40%	56%	10	63%	29%
Local S,I,R classification								
Sensitive	33	43%	21	44%	64%	9	56%	27%
Intermediate	0	-	0	-	-	0	-	-
Resistant	5	7%	0	0%	0%	2	13%	40%
Not tested or not available	38	50%	27	56%	71%	5	31%	13%

[a]Clinical cure based on answer to the clinical assessment question: resolved, improved = cured; resolved then relapse, failure, or unknown = not cured. [b]Same *Acinetobacter baumannii* pathogen at both sites. [c]Monotherapy defined as receiving only CFDC without overlap of other GNAs. CFDC, cefiderocol; COVID-19, coronavirus disease 2019; CR, carbapenem resistant; GNA, Gram-negative antibiotic; GNBI, Gram-negative bacterial infection; I, intermediate; ICU, intensive care unit; R, resistant; S, susceptible.

Severity of illness and treatment patterns

- More than half of patients were in an ICU when receiving CFDC, 41% of which were on mechanical ventilation and 28% on vasopressors (**Table 3**).
- Time from culture to first treatment with CFDC was 1 week or less in 58 patients (76%). A documented infection, either first-time (80%) or after a prior treatment failure (salvage) (11%) was the main reason given for starting CFDC. Empirical use was noted in 6 patients (8%) (**Table 3**).
- The median (interquartile range) hospital length of stay (LOS) was 42.5 (19.0–75.5) days. The median post-CFDC LOS was 22.5 (10.5-48.0) days.

Outcomes

- In total most (63%) had achieved clinical cure. 30-day ACM was 21% (**Table 3**).
- Clinical cure and mortality varied by infection site. Patients with monomicrobial co-infections of blood and other sites (n=8) had achieved cure in 25% with and ACM rate of 50%.
- Conversely, the most common monomicrobial site, respiratory infections without bacteremia, (n=15) had a 60% cure rate and a 30-day ACM of 13% (**Table 3**). Polymicrobial respiratory infections (n=13) had a 77% cure rate and a 30-day ACM of 8%.
- Severity of infection as measured by ICU stay or organ support was associated with both lower clinical cure and higher 30-day ACM **(Table 3).**
- First-time treated documented infections (n=61) achieved clinical cure in 59% and had an ACM of rate of 25%. Documented infections classified as salvage (n=8) had a 75% cure rate and 13% 30-day ACM. Empirically treated patients (n=6) had an 83% cure rate and no mortality.

Safety

- Of the total cohort of 220 patients, 5 had adverse drug reactions (ADRs), of which two had rashes, one had an increase in liver function tests, and two had diarrhea. One had a serious ADR (interstitial nephritis). CFDC was withdrawn in two of these patients.

Conclusions

- Patients with an AB infection in the PROVE study are mostly complex patients with moderate to severe disease. There was a large variety of primary infection sites, including polymicrobial infections.
- Nearly all AB isolates were CRAB; susceptibility to CFDC was 77% using FDA breakpoints and 85% using CLSI.
- Documented infections accounted for 69 (91%) of those treated.
- Overall clinical cure was achieved in 63% and a 30-day ACM of 21% with the lowest in respiratory infections.
- A limitation is the small number of observations within each stratum and the limited ability to use multivariable techniques to estimate independent contributions of factors to outcomes. Additional patients including those from the EU will facilitate more detailed and generalizable evaluations of the outcomes.

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