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Real-World Experience of Cefiderocol with *Pseudomonas aeruginosa* in the PROVE (Retrospective Cefiderocol Chart Review) Study

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Introduction

- Multidrug-resistant (MDR) *Pseudomonas aeruginosa* (PA) infections are often difficult-to-treat with limited treatment options.[1,2]
- Cefiderocol (CFDC) is a novel siderophore cephalosporin with activity against MDR PA.[3]
- PROVE is an ongoing, international, retrospective study assessing CFDC treatment of Gram-negative (GN) infections. This analysis describes the results of a subset of 120 patients *P. aeruginosa* infections.

Methods

- The main objectives of PROVE are to describe the clinical and microbiological characteristics of infections treated with CFDC, patient characteristics, treatment patterns, and patient outcomes including safety.
- PROVE uses chart reviews to abstract existing medical records of patients receiving a first-time prescription of CFDC for the treatment of an indicated Gram-negative bacterial infection (GNBI) (defined as the documented GNBI prompting CFDC use).
- Eligibility criteria include documented GNBI (before or after starting CFDC) attributed to the use of CFDC, at least 72 hours of first-time use of CFDC used in routine clinical practice, and availability of data regarding 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, site(s) of infection, pathogen characteristics, and CFDC treatment patterns. Outcomes include clinical resolution of GNBI at the end of CFDC treatment (evidence documenting resolution/improvement of clinical signs and/or symptoms without relapse), and 30-day all-cause mortality (ACM), calculated from the day of initiation of CFDC treatment. Length of stay (LOS), post-CFDC LOS, and safety (i.e., adverse events) are also described.
- Index culture samples were those attributed to CFDC use, collected either before treatment or less commonly after, if used empirically.
- Antibiotic susceptibility testing (AST) was done at the local site level. Carbapenem resistance (CR) was defined as pathogen resistance to any carbapenem.
- AST results used disk zone size or minimum inhibitory concentrations. Breakpoints from the Clinical and Laboratory Standards Institute (CLSI) M100 31st and 32nd editions were used plus those defined by the US Food and Drug Administration (FDA) with lower breakpoints.
- Descriptive statistics are used to present the data.

Results

Baseline characteristics of patients

- On August 9, 2022, a total of 220 patients at 21 sites were enrolled. Results include data from 120 patients with a documented PA infection.
- Most patients (n=105/120; 87.5%) were from the USA (**Table 1**).
- The median age was 55.5 years, 66.7% were male, and 29.2% were admitted from a healthcare facility (**Table 1**).
- Only 6.7% had no comorbidities. The most common comorbidities were moderate or severe renal disease (n=34, 28.3%), hypertension (n=30, 25.0%), and diabetes with end-organ damage (n=27, 22.5%) (**Table 1**).
- All but two patients (1.7%) had one or more risk factors for CR GN infections. The most common risk factor was prior hospitalization in the past 6 months (67.5%) (**Table 1**).

Infection characteristics

- PA monomicrobial infections accounted for 77 infections (64%). The most frequent diagnosis prompting CFDC use for monomicrobial infections was respiratory tract infection (n=47, 61%) followed by infections of blood and other sites (n=14, 18%) (**Figure 1A**).
- Polymicrobial infections with PA accounted for 32.5% of infections (n=39), of which the most common site was respiratory tract (n=21, 54%) (**Figure 1B**). The next most common site was skin and skin structure infections (n=8, 21%). *Acinetobacter baumannii* was the most common accompanying pathogen in polymicrobial infections at the primary site (**Figure 2**).
- PA was also documented as a co-infection, i.e., not the primary infection, in four patients.

Figure 1. *Pseudomonas aeruginosa* monomicrobial infection sites (A) and polymicrobial infection sites (B)

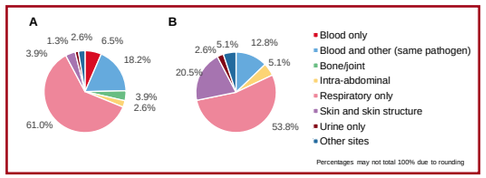
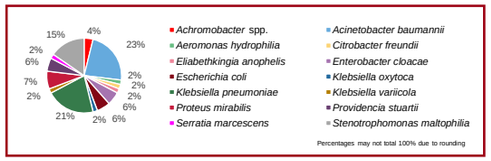


Figure 2. Other pathogens accompanying *Pseudomonas aeruginosa* in polymicrobial infections



Pathogen susceptibility to CFDC and other GN antibiotics

- **Table 2** shows the susceptibility of PA isolates within four categories of 76 that were tested (63%). 44 (37%) isolates were not tested for CFDC.
- 96% (n=73) of 76 tested isolates were susceptible to CFDC as measured by either the FDA or CLSI criterion for susceptibility. Three isolates were classified as either intermediate or resistant to CFDC using CLSI criteria.
- 97% of PA isolates (111 of 114) tested were CR.

Severity of illness and treatment patterns

- 76% (n=91) were in an intensive care unit (ICU) setting overlapping with the course of CFDC, 55% (n=66) were on mechanical ventilation support, and 44% (n=53) were on vasopressors during this ICU stay (**Table 3**).
- There were 17 (14%) patients listed as having COVID-19 during the index hospitalization and 83 (69%) had two or more comorbidities (**Table 3**).
- Time from culture to treatment with CFDC was 1 week or less in 85 patients (71%). The most common reason for starting CFDC was a documented infection without prior treatment in 91 patients (76%) followed by a documented prior treatment failure (salvage) in 14 (12%) (**Table 3**).
- The median (interquartile range) hospital LOS was 52 (29–91) days and post-CFDC LOS was 21 (13–41) days.

Table 1. Demographics and clinical characteristics of patients with *Pseudomonas aeruginosa* infection

Characteristic	N	%
Total number of patients	120	
Age at admission (years)		
Mean (SD)	53.0	15.2
Median (Q1–Q3)	55.5	41.0–64.5
Min, Max	19	81
<50	49	40.8%
50–65	46	38.3%
>65	25	20.8%
Sex		
Female	39	32.5%
Male	80	66.7%
Country where patients were enrolled		
United States	105	87.5%
Germany	4	3.3%
Italy	-	-
United Kingdom	11	9.2%
Race (for US patients only)		
White	53	44.2%
Black	35	29.2%
Hispanic	8	6.7%
Asian	1	0.8%
Other	8	6.7%
N/A (non-US)	15	12.5%
Place of residence before admission		
Private Residence (home)	79	65.8%
Healthcare facility[a]	35	29.2%
Assisted living, residential care/group home	-	-
Other	6	5.0%
Comorbid conditions prior to hospitalization (>10%)		
No comorbidities	8	6.7%
Moderate or severe renal disease	34	28.3%
Hypertension	30	25.0%
Diabetes with end-organ damage	27	22.5%
Diabetes mellitus uncomplicated	24	20.0%
Chronic pulmonary disease	23	19.2%
Congestive heart failure	19	15.8%
Stroke	18	15.0%
Coronavirus disease 2019 (COVID-19)	17	14.2%
Hemiplegia, paraplegia, or quadriplegia	12	10.0%
Patients with risk factors for CR-GNBI (> 10%)		
No risk factors	2	1.7%
Mechanical ventilation prior to index culture sample	78	65.0%
Admitted to hospital in the past 6 months	81	67.5%
Exposed or non-response to carbapenem = 30 days	50	41.7%
History of CR GNBI	47	39.2%
Trauma surgery	32	26.7%
Received high-dose corticosteroids	16	13.3%

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.

Outcomes

- 76 /120 patients (63%) achieved clinical cure. 30-day ACM was 21% (**Table 3**).
- Clinical cure and mortality varied by infection site. Monomicrobial infections of blood and other sites (n=14) had a lower clinical cure rate (57%) and greater 30-day ACM rate (29%) than most other sites (**Table 3**). Respiratory polymicrobial infections had one of the highest cure rates (71%) and the lowest 30-day ACM (5%).
- An ICU stay and the presence of mechanical ventilation or vasopressor use were associated with lower cure rates and greater 30-day ACM (**Table 3**).
- Empirical treatment of 13 patients was associated with a 77% cure rate and no mortality. Documented infections, either first-time treated (n=91), or salvage (n=14) were associated with a clinical cure rate of 61% and 24% ACM at day 30. First time treated patients had a greater cure rate (65% vs. 36%) compared to salvage treatment (**Table 3**).

Table 2. Antibiotic susceptibility compared with cefiderocol

All isolates (N=120)				*Pseudomonas aeruginosa* susceptibility to cefiderocol											
				Sensitive by FDA & CLSI			Sensitive by CLSI, not FDA			Intermediate by CLSI (ed. 31)			Resistent by CLSI		
Cefiderocol cut-points	Not Tested			≤1 µg/mL or Zone ≥22 mm[a]			2–4 µg/mL or Zone 18–21 mm[b]			8 µg/mL or Zone 13–17 mm[c]			≥16 µg/mL or Zone ≤12 mm[d]		
All isolates (N=120); n, row %	44	37%		59	49%		14	12%		1	1%		2	2%	
Susceptible to CFDC of those tested (N=76)				59/76 (77.6%)			14/76 (18.4%)								
Antibiotic	N	NT	% S[e]	N	NT	% S[e]	N	NT	% S[e]	N	NT	% S[e]	N	NT	% S[e]
Meropenem	38	6	29%	59	0	2%	14	0	7%	1	0	0%	0	2	-
Imipenem	19	25	16%	30	29	10%	10	4	20%	1	0	0%	2	0	0%
Ampicillin/sulbactam	0	44	-	0	59	-	0	14	-	0	1	-	1	1	0%
Piperacillin/tazobactam	27	17	44%	45	14	11%	12	2	8%	1	0	0%	1	1	0%
Colistin or polymyxin B	5	39	80%	5	54	60%	2	12	0%	0	1	-	0	2	-
Cefepime	28	16	43%	50	9	16%	13	1	8%	1	0	0%	1	1	0%
Meropenem/vaborbactam	1	43	0%	1	58	0%	0	14	-	0	1	-	0	2	-
Ceftazidime/avibactam	14	30	43%	48	11	50%	13	1	31%	0	1	-	1	1	0%
Ceftolozane/tazobactam	12	32	50%	38	21	76%	9	5	33%	0	1	-	1	1	0%
Imipenem/relebactam	3	41	0%	20	39	40%	4	10	25%	0	1	-	1	1	0%
Aztreonam/avibactam	0	44	-	0	59	-	0	14	-	0	1	-	0	2	-
Tigecycline	0	44	-	0	59	-	0	14	-	0	1	-	0	2	-
Minocycline	0	44	-	0	59	-	0	14	-	0	1	-	0	2	-
Eravacycline	0	44	-	0	59	-	0	14	-	0	1	-	0	2	-

[a]Based on FDA (2022) breakpoints for *P. aeruginosa* susceptibility to cefiderocol. [b]Based on CLSI (32nd edition, 2022) breakpoints for *P. aeruginosa* susceptibility to cefiderocol. [c]Based on CLSI (31st edition, 2021) breakpoints for *P. aeruginosa* intermediate susceptibility to cefiderocol. [d]Based on CLSI (31st edition, 2021) breakpoints for *P. aeruginosa* 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.

Safety

- In the total cohort of 220 patients treated for any pathogen with CFDC, five had at least one adverse drug reaction (ADR), two each having diarrhea or a rash. One had an increase in liver function tests.
- There was one serious ADR of interstitial nephritis that resolved with withdrawal of CFDC.

Conclusions

- In this study of 120 patients with PA infection, the use of CFDC was employed mostly in complex patients, over half with mechanical ventilatory support.
- Nearly all of the pathogens were resistant to carbapenems. The most frequent infection site was respiratory tract, of which a third was polymicrobial.
- Treatment was mostly based on documented cultures, appropriate for such infections in complex patients, but empirical use was associated with high cures and low ACM.
- A limitation is the small number of patients within each stratum and the limited ability to use multivariable techniques to estimate independent contributions of factors to outcomes.

References

1. Horcajada JP, Montero M, Oliver A, Sorlí L, Luque S, et. al. Epidemiology and treatment of multidrug-resistant and extensively drug-resistant *Pseudomonas aeruginosa* Infections. *Clin Microbiol Rev*. 2019 Aug 28;32(4):e00031-19.
2. O'Donnell JN, Bidell MR, Lodise TP. Approach to the treatment of patients with serious multidrug-resistant *Pseudomonas aeruginosa* Infections. *Pharmacotherapy*. 2020 Sep;40(9):952-969.
3. Sato T, Yamawaki K. *Clin Infect Dis*. 2019;69(Suppl. 7):S538–S543.

Table 3. Outcomes by key characteristics of patients with *Pseudomonas aeruginosa* infection

Characteristic	Overall		Clinical cure[a]			30-day mortality		
	N	%	N	%	Row %	N	%	Row %
Number of patients	120		76		63%	25		21%
Index infection type								
Monomicrobial - primary infection site (n=77)								
Blood only	5	4%	3	4%	60%	1	4%	20%
Blood and other (same pathogen)[b]	14	12%	8	11%	57%	4	16%	29%
Bone/joint	3	3%	3	4%	100%	0	0%	0%
Intra-abdominal	2	2%	1	1%	50%	1	4%	50%
Respiratory only	47	39%	30	39%	64%	13	52%	28%
Skin and skin structure	3	3%	2	3%	67%	0	0%	0%
Urine only	1	1%	1	1%	100%	0	0%	0%
Other sites	2	2%	2	3%	100%	0	0%	0%
Polymicrobial - primary infection site (n=39)								
Blood & other (same pathogen)[b]	5	4%	3	4%	60%	1	4%	20%
Intra-abdominal	2	2%	1	1%	50%	0	0%	0%
Respiratory only	21	18%	15	20%	71%	1	4%	5%
Skin and skin structure	8	7%	4	5%	50%	3	12%	38%
Urine only	1	1%	1	1%	100%	0	0%	0%
Other sites	2	2%	0	0%	0%	0	0%	0%
***Pseudomonas aeruginosa* as co-infection, not primary (n=4)**								
Blood only	2	2%	1	1%	50%	1	4%	50%
Intra-abdominal	1	1%	0	0%	0%	0	0%	0%
Skin and skin structure	1	1%	1	1%	100%	0	0%	0%
Severity upon starting cefiderocol								
Baseline comorbid conditions								
Age >65 years	25	21%	15	20%	60%	3	12%	12%
0–1 major comorbid conditions	37	31%	23	30%	62%	7	28%	19%
2–3 major comorbid conditions	55	46%	37	49%	67%	9	36%	16%
≥4 major comorbid conditions	28	23%	16	21%	57%	9	36%	32%
COVID-19 during index hospitalization	17	14%	9	12%	53%	4	16%	24%
Patient in ICU while receiving CFDC								
Yes	91	76%	53	70%	58%	25	100%	27%
No	29	24%	23	30%	79%	0	0	0%
Received mechanical ventilation								
Yes	66	55%	37	49%	56%	19	76%	29%
No	54	45%	39	51%	72%	6	24%	11%
Vasopressor support								
Yes	53	44%	24	32%	45%	19	76%	36%
No	67	56%	52	68%	78%	6	24%	9%
CFDC utilization								
Positive culture to first CFDC dose								
1 week or less	85	71%	55	72%	65%	18	72%	21%
More than 1 week	35	29%	21	28%	60%	7	28%	20%
Reason for starting CFDC								
Documented infection	91	76%	59	78%	65%	22	88%	24%
Salvage treatment (failure of prior GNA)	14	12%	5	7%	36%	3	12%	21%
Empirical for suspected CR GNBI	13	11%	10	13%	77%	0	0	0%
Other	2	2%	2	3%	100%	0	0	0%
CFDC as monotherapy[c]								
Yes	81	68%	56	74%	69%	13	52%	16%
No	39	33%	20	26%	51%	12	48%	31%
Local S,I,R classification								
Sensitive	78	65%	52	68%	67%	18	72%	23%
Intermediate	6	5%	3	4%	50%	0	0	0%
Resistant	3	3%	2	3%	67%	1	4%	33%
Not tested or not available	33	28%	19	25%	58%	6	24%	18%

[a]Clinical cure based on answer to the clinical assessment question: resolved, improved = cured; resolved then relapse, failure, or unknown = not cured. [b]Same *Pseudomonas aeruginosa* 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.

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