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Effectiveness and Safety of Cefiderocol in Clinical Practice for Treatment of Patients with Gram-Negative Bacterial Infections: US Interim Results of the PROVE Study

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Purpose: The international PROVE retrospective chart-review study aims to assess the real-world effectiveness and safety of cefiderocol for treatment of patients with carbapenem-resistant Gram-negative infections.

Patients and Methods: US centers selected hospitalized patients receiving their first cefiderocol treatment for ≥72 hours for a Gram-negative bacterial infection (November 2020–March 2023). Patient demographics, clinical characteristics, hospitalization, course of infection, antibiotic use, clinical cure (excluding patients with a relapse/reinfection), clinical response at the end of treatment, microbiology, in-hospital all-cause mortality (IH-ACM) at Day 30, and safety were analyzed using descriptive statistics.

Results: This interim analysis included 244 patients. The most frequent infection sites were respiratory tract (55.7%), skin and skin structure (16.8%), and blood (9.8%). The median duration of cefiderocol use was 12 days (interquartile range 8–18.5). Clinical cure was reported for 64.8% (158/244) of patients, clinical response for 74.2% (181/244), and 9.4% (23/244) had relapse/reinfection; 30-day IH-ACM was 18.4% (45/244). Of 82 patients with monomicrobial *Pseudomonas aeruginosa* infections, 64.6% (n = 53) and 74.4% (n = 61) had clinical cure and clinical response, respectively, and 30-day IH-ACM was 25.6%. Among 43 patients with monomicrobial *Acinetobacter baumannii* infections, 60.5% (n = 26) and 74.4% (n = 32) had clinical cure and clinical response, respectively, and 30-day IH-ACM was 18.6%. Five patients experienced six adverse drug reactions (one serious event: interstitial nephritis/acute kidney injury), and cefiderocol was discontinued in two cases.

Conclusion: Cefiderocol had similar clinical cure and response rates to previous retrospective studies and lower mortality. Cefiderocol was well tolerated in real-world settings in critically ill US patients with problematic Gram-negative pathogens.

Keywords: bloodstream infection, carbapenem resistance, cefiderocol, nonfermenters, real-world evidence, respiratory tract infection

Introduction

According to the World Health Organization, the Centers for Disease Control and Prevention and the Antimicrobial Resistance Collaborators, antimicrobial resistance has reached an alarming level globally. Carbapenem-resistant (CR) *Acinetobacter baumannii* (AB), CR *Pseudomonas aeruginosa*, and CR *Klebsiella pneumoniae* are among the ten most critical pathogens for deaths associated with resistance, including in the USA.[1–5]

The first-in-class siderophore cephalosporin, cefiderocol, was developed to address the unmet need posed by problematic Gram-negative pathogens, particularly CR strains of nonfermenters and Enterobacterales.[6] It has potent in vitro activity

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against a broad range of Gram-negative bacteria, including CRAB and CR strains of *K. pneumoniae, P. aeruginosa*, and *Stenotrophomonas maltophilia*.[4,5,7]

Cefiderocol is approved in the USA for the treatment of patients with complicated urinary tract infections (cUTIs), including pyelonephritis, hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia caused by Gram-negative pathogens, including CR and multidrug-resistant (MDR) strains.[8] Real-world data on drugs can better reflect the actual clinical settings in which therapeutic interventions are applied and can help overcome the limitations of clinical trials. Since regulatory approval of cefiderocol,[8,9] its effectiveness in the treatment of Gram-negative bacterial infections in real-world settings has been described in several case reports, case series, and observational studies.[10–17] These data revealed that cefiderocol treatment, either as monotherapy or combination therapy, for a range of infections was associated with clinical cure rates of 46–100% and 28- or 30-day all-cause mortality rates of 23.1%–51%.[10–17]

The international PROVE (Retrospective Cefiderocol Chart Review Study) study was designed to describe the real-world effectiveness and safety of cefiderocol in a large cohort of hospitalized patients following its regulatory approval. We report here data from a pre-planned interim analysis of the US cohort and discuss the clinical and demographic characteristics, utilization of cefiderocol and other antibiotics, microbiology, and outcomes in patients treated with cefiderocol for a documented Gram-negative bacterial infection.

Materials and Methods

Study Design

PROVE is an international, multicenter, retrospective chart-review study of existing medical records for hospitalized patients treated with cefiderocol in real-world settings (EU PAS number: EUPAS40551). Investigators at each center sequentially selected patients who received their first cefiderocol treatment at their centers, according to routine clinical practice for a Gram-negative bacterial infection. A single online electronic study questionnaire was completed for each patient. It has been planned that the USA will include 500 patients and five European countries each will select approximately 100 patients. Analysis of the global and country-specific datasets will be published after this pre-planned US-based interim analysis. The PROVE study was ongoing at the time of the analysis of the current data set.

Ethics

The study is being conducted in accordance with local legal and regulatory requirements, and the Declaration of Helsinki. Ethics and/or institutional review board approval (Supplementary Table 1) is sought from each hospital prior to chart review initiation. Only fully anonymized data are entered into the pooled database for analysis.

Patient Consent Statement

Informed consent for US patients has been waived.

Inclusion/Exclusion Criteria

The inclusion criteria are all of the following: 1) hospitalized adult patients have a documented Gram-negative bacterial infection with information on the infection site(s) and species; 2) continuous cefiderocol treatment for the first time for at least 72 hours (with known start and stop dates, starting dose, and duration) during the current hospitalization; 3) known outcome at the end of cefiderocol treatment; and 4) discharge status at end of the current hospitalization.

Patients are excluded if they have incomplete information on cefiderocol use, Gram-negative bacterial infection, outcome assessment or vital status, or if they are enrolled in other cefiderocol clinical trials. Exclusion also covers cefiderocol use in compassionate use and early access programs, prior to regulatory approval, or as treatment before the current hospitalization within the same hospital system.

Outcomes and Safety Assessments

Information on data collection is provided in the Supplementary Methods. Patients' demographics and clinical characteristics (including mechanical ventilation, organ support [extracorporeal membrane oxygenation, continuous renal

replacement therapy, dialysis, vasopressors], intensive care unit [ICU] stay at the time of initiation of cefiderocol treatment), type of infection (site, monomicrobial or polymicrobial Gram-negative bacterial infection [all polymicrobial infections refer to only Gram-negative bacterial infections], source of infection), the Gram-negative pathogen that prompted cefiderocol use (species, antibiotic susceptibility status), use of cefiderocol (time elapsed between culture sample collection and first dose, the starting cefiderocol dose, total duration [days], monotherapy or combination therapy) were collected at baseline. Among outcomes (Supplementary Table 2), clinical cure (defined as resolution or improvement of signs/symptoms at end of treatment (EOT) without a later relapse as judged by the physician; patients who died during therapy or had a relapse or reinfection due to the same pathogen after EOT during current hospitalization were considered as clinical failure), clinical response at EOT (defined as resolution or improvement of signs/symptoms at EOT as judged by the physician, excluding patients who died during therapy), in-hospital all-cause mortality (IH-ACM; 14-day, 30-day, overall), length of hospital stay (LOS; total), length of ICU stay (while on cefiderocol treatment), and infection-associated LOS (defined as time between date of index culture and date of discharge) were analyzed. Patients discharged alive within 30 days from initiation of treatment were considered alive at Day 30. The primary infection site was the site that prompted the use of cefiderocol. Clinical response at EOT, clinical cure, and IH-ACM were also analyzed by carbapenem susceptibility status, pathogen, infection site, age, risk factors for CR Gram-negative bacterial infections, and patterns of antibiotic treatment.

Safety assessments included adverse drug reactions (ADRs) or serious ADRs considered to be associated with cefiderocol by the treating physician.

Statistics

The study aims to collect information on approximately 1000 patients by the planned completion date of June 2024. Given the noncomparative, descriptive nature of the study, sample size calculation is not applicable because the study was not designed to test a prior hypothesis.

Numbers and percentages are calculated to describe categorical variables. Median and interquartile range (IQR; Q1–Q3) are calculated to describe continuous variables. The normality of data for each variable is determined through inspection of histograms. Missing data are not imputed. 95% confidence intervals (CI) were calculated for precision of the estimates via normal distribution approximation, for overall and selected subgroups. Statistical analysis was performed with SAS v9.4 (Cary, NC, USA).

Results

This interim analysis examines data from 244 patients at 15 US centers, collected between November 2020 and March 2023.

Patients' Baseline Demographics and Clinical Characteristics

The median (IQR) age of patients was 56 years (43.5–65.0), 27.0% were aged 65 years or older, and 61.5% were men (Table 1). The median (IQR) Charlson Comorbidity Index (CCI) was 2 (1.0–4.0) (Table 1). Almost all patients (95.9%) had at least one comorbid condition, most frequently moderate/severe renal disease (21.7%), chronic pulmonary disease (19.7%), uncomplicated diabetes mellitus (19.3%), or diabetes with end-organ damage (18.4%) (Supplementary Table 3). Thirty (12.3%) patients had a history of COVID-19 infection prior to hospitalization (Supplementary Table 3).

Most infections were monomicrobial (69.3% [169/244]). Over half of patients had primary respiratory tract infections (RTIs) and accounted for a similar proportion of patients within monomicrobial and polymicrobial Gram-negative bacterial infections (Figure 1). Bloodstream infections (BSIs) were primary infections in 9.8% (24/244) of patients (Figure 1) and secondary infections in 9.0% (22/244) of patients.

In monomicrobial infections, the most frequent pathogens were *P. aeruginosa* (48.5% [82/169]), followed by *A. baumannii* (17.6%), Enterobacterales (10.7%), and *S. maltophilia* (4.1%) (Table 1 and Supplementary Table 4). *P. aeruginosa* (46.7% [35/75]) was the most frequent coinfecting pathogen in polymicrobial Gram-negative bacterial infections (Table 1 and Supplementary Table 4).

Table 1 Patient Demographics, Clinical Characteristics, Risk Factors, Pathogens, and Sites of Infection

	Overall N=244
Age at admission, years	
Median (Q1–Q3)	56 (43.5–65.0)
≥65 years, n (%)	66 (27.0)
Sex, n (%)	
Male	150 (61.5)
Female	93 (38.1)
Other/unknown	1 (0.4)
Race/Ethnicity, n (%)[a]	
White	129 (52.9)
Black	79 (32.4)
Hispanic	14 (5.7)
Asian	4 (1.6)
Other	18 (7.4)
Type of admission, n (%)	
Emergency or urgent admission	162 (66.4)
Direct transfer from another medical care facility	60 (24.6)
Scheduled admission	22 (9.0)
Other	0 (0)
Charlson Comorbidity Index	
Median (Q1–Q3)	2 (1.0–4.0)
Risk factors for CR Gram-negative bacterial infection, n (%)[b]	
No risk factors	11 (4.5)
History of CR Gram-negative bacterial infection or colonization within last 6 months	79 (32.4)
Admitted to hospitals in last 6 months	163 (66.8)
Transplant in last 90 days	16 (6.6)
Trauma, major surgery in last 30 days before initiation of cefiderocol treatment	17 (7.0)
Cytotoxic chemotherapy in last 90 days	9 (3.7)
High-dose corticosteroids for ≥14 days in last 90 days	26 (10.7)
Recent travel history to a foreign country	1 (0.4)
Carbapenem or nonresponse to carbapenem in last 30 days	81 (33.2)
Mechanical ventilation at any point before index culture sample	141 (57.8)
Other risk factors	18 (7.4)

(*Continued*)

Table 1 (Continued).

	Overall N=244
Infection site, n (%)	
Respiratory	136 (55.7)
Bloodstream	24 (9.8)
Urinary	15 (6.1)
Intra-abdominal	12 (4.9)
Bone and joint	14 (5.7)
Skin and skin structure	41 (16.8)
Other site[c]	2 (0.8)
Gram-negative bacteria	
Monomicrobial infections, n (%)	169 (69.3)
Acinetobacter baumannii	43 (17.6)
Pseudomonas aeruginosa	82 (33.6)
Enterobacterales	26 (10.7)
Stenotrophomonas maltophilia	10 (4.1)
Other	8 (3.3)
Polymicrobial infections, n (%)[d]	75 (30.7)
A. baumannii + *P. aeruginosa*	7 (2.9)
A. baumannii + Enterobacterales	10 (4.1)
A. baumannii + *S. maltophilia*	2 (0.8)
P. aeruginosa + Enterobacterales	20 (8.2)
P. aeruginosa + *S. maltophilia*	8 (3.3)
Any other combination of 2 pathogens	11 (4.5)
Any other combination of 3 or more pathogens	17 (7.0)
Cefiderocol susceptibility status (by patient), n (%)	
Susceptible	124 (50.8)
Nonsusceptible (intermediate, resistant)	18 (7.4)
Unknown	102 (41.8)
Carbapenem susceptibility status (by patient), n (%)	
Susceptible	20 (8.2)
Resistant	209 (85.7)
Unknown	15 (6.1)

Notes: [a]Flanagin A, Frey T, Christiansen SL; AMA Manual of Style Committee. Updated Guidance on the Reporting of Race and Ethnicity in Medical and Science Journals. *JAMA*. 2021;326(7):621–627. Doi: 10.1001/jama.2021.13304. [b]Patients could have >1 risk factor. [c]Other: single site not in any of the above categories. [d]Polymicrobials are defined as two or more different Gram-negative pathogens identified from the index culture from the same site.
Abbreviations: CR, carbapenem resistant; Q, quartile.

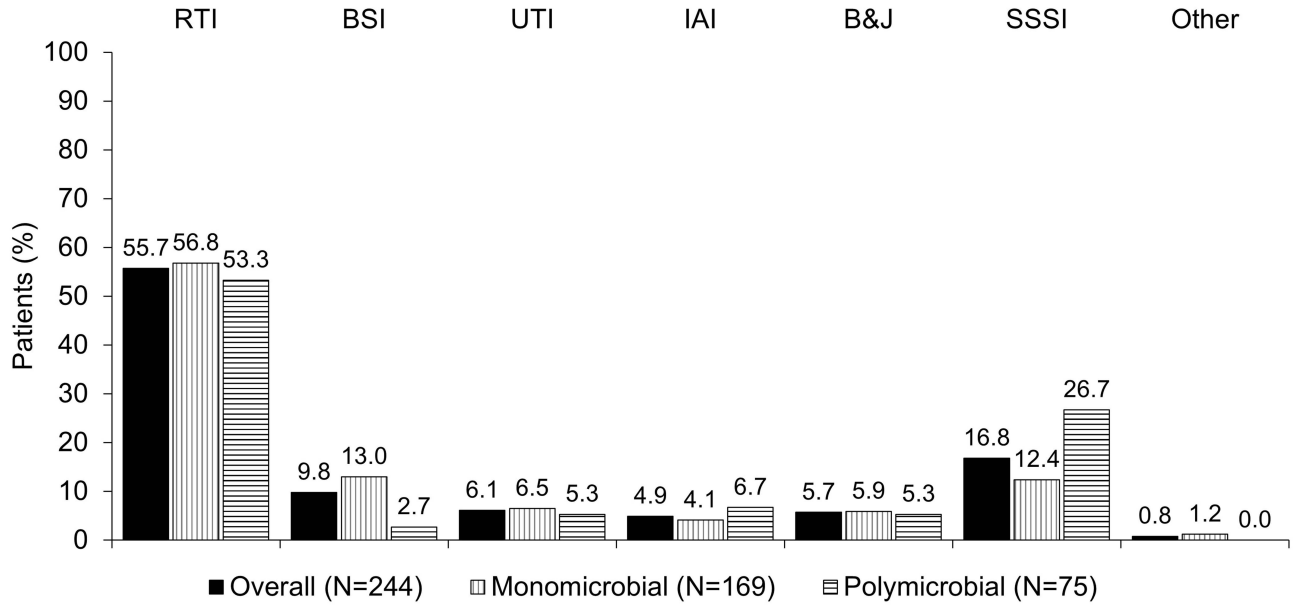

Figure 1 Distribution of primary infection site overall, and in monomicrobial and polymicrobial infections.
Abbreviations: BSI, bloodstream infection; B&J, bone and joint infection; IAI, intra-abdominal infection; RTI, respiratory tract infection; SSSI, skin and skin structure infection; UTI, urinary tract infection.

Nearly all patients (95.5%) had at least one risk factor for being infected or colonized with a CR Gram-negative pathogen at admission, most commonly previous hospitalization in the past 6 months (66.8%), mechanical ventilation (57.8%), carbapenem use (33.2%), and history of CR Gram-negative bacterial infection or colonization (32.4%) (Table 1). Altogether, 91.3% (209/229) of patients with a reported carbapenem susceptibility test result had CR pathogens, and 87.3% (124/142) of patients with cefiderocol susceptibility test results had cefiderocol-susceptible pathogens (Table 1).

Hospitalization Characteristics and Resource Utilization

The median (IQR) total hospital LOS was 43 days (22.0–83.0), and median (IQR) infection-associated LOS was 29 days (17.0–53.0). Among 152 (62.3%) patients with an infection-related ICU stay associated with cefiderocol treatment, the median (IQR) LOS duration was 39 days (16.0–78.0). Overall, 126 (51.6%) patients received organ support when cefiderocol treatment was initiated in the ICU (Table 2 and Supplementary Table 5). As discharge status, in-hospital death was reported for 69 patients (28.3%), and 52 patients (21.3%) were discharged home (Table 2). A total of 19.7% (48/244) were receiving oral or intravenous antibiotics with activity against Gram-negative bacteria at the time of discharge or transfer.

Table 2 Hospitalization Characteristics, Severity of Illness, and Resource Utilization

	Overall N=244
Total hospital LOS, days[a]	
Median (Q1–Q3)	43 (22.0–83.0)
Infection-associated LOS, days[b]	
Median (Q1–Q3)	29 (17.0–53.0)
ICU stay when cefiderocol was initiated or within 2 days after initiation of cefiderocol, n (%)[c]	
Yes	152 (62.3)
No	92 (37.7)

(*Continued*)

Table 2 (Continued).

	Overall N=244
ICU LOS, days[c]	
Median (Q1–Q3)	39 (16.0–78.0)
Received organ support when cefiderocol was initiated or within 2 days after initiation of cefiderocol, n (%)	
Yes	126 (51.6)
No	118 (48.4)
Organ support type, n (%)[d]	
Mechanical ventilation	111 (45.5)
CRRT	33 (13.5)
ECMO	10 (4.1)
Vasopressor use	64 (26.2)
Dialysis[e]	7 (2.9)
Patients' location when the index culture was obtained, n (%)	
Outpatient clinic	9 (3.7)
Emergency room	23 (9.4)
General ward	53 (21.7)
ICU	131 (53.7)
Operating room or theatre (intra-operative sample)	25 (10.2)
Other	3 (1.2)
Discharge status, n (%)	
Home	52 (21.3)
Healthcare facility	102 (41.8)
Assisted living	2 (0.8)
Hospice	10 (4.1)
Other institution	0 (0)
Other (not classified)	9 (3.7)
In-hospital death	69 (28.3)

Notes: [a]Total length of hospital stay was calculated as the time between admission date and discharge date or date of death. [b]Infection-associated LOS was calculated as the time between index culture date and discharge date or date of death. [c]ICU stay and ICU LOS only includes patients with ICU stay during which cefiderocol was initiated or for which stay admission occurred within 2 days of initiating cefiderocol. [d]Types of organ support are not mutually exclusive. [e]Cefiderocol was initiated for one patient while receiving dialysis and was admitted to the ICU 7 days later (while receiving both cefiderocol and dialysis).
Abbreviations: CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LOS, length of stay; Q, quartile.

Cefiderocol Usage Patterns

Cefiderocol was prescribed for a documented infection in 74.2% of patients, while 11.1% received it empirically (see definitions in Supplementary Methods). Cefiderocol was prescribed as salvage therapy for 12.7% (Table 3). The main reason for stopping cefiderocol treatment was resolution of clinical signs and symptoms (54.9%),

Table 3 Cefiderocol Usage Patterns

	Overall N=244
Reason for starting cefiderocol, n (%)	
Documented infection	181 (74.2)
Empiric for suspected CR Gram-negative bacterial infection	27 (11.1)
Salvage treatment	31 (12.7)
Other including unknown	5 (2.0)
Reason for stopping cefiderocol, n (%)	
Clinical sign/symptoms resolved	134 (54.9)
Clinical failure/infection not resolved	6 (2.5)
Suspected ADR	3 (1.2)
Susceptibility test result showed cefiderocol nonsusceptible	4 (1.6)
Patient died	33 (13.5)
Palliative care commenced	11 (4.5)
Switched to alternative susceptible drug(s) including oral drug	25 (10.2)
Other[a]	28 (11.5)
Time from admission to sampling of a positive culture resulting in cefiderocol use, days[b]	
Median (Q1–Q3)	9 (2.0–33.0)
Time from sampling of a positive culture to first cefiderocol dose, days	
Median (Q1–Q3)	5.0 (3.0–7.0)
Time from sampling of a positive culture to first cefiderocol dose, n (%)	
≤2 days	33 (13.5)
3–4 days	64 (26.2)
5–7 days	78 (32.0)
>7 days	59 (24.2)
Cefiderocol given prior to index culture sample	10 (4.1)
Cefiderocol starting dose	
2 grams every 6 hours	38 (15.6)
2 grams every 8 hours	98 (40.2)
1.5 grams every 8 hours	35 (14.3)
1 gram every 8 hours	10 (4.1)
0.75 gram every 12 hours	43 (17.6)
2 grams every 12 hours	6 (2.5)
1.5 grams every 12 hours	9 (3.7)
1 gram every 12 hours	2 (0.8)

(*Continued*)

Table 3 (Continued).

	Overall N=244
2.5 grams every 8 hours	1 (0.4)
1.5 grams every 6 hours	1 (0.4)
2 grams every 3 hours	1 (0.4)
Duration of cefiderocol treatment, days	
Median (Q1–Q3)	12 (8.0–18.5)
Duration of cefiderocol treatment, n (%)	
3 days	1 (0.4)
4–6 days	32 (13.1)
7–13 days	101 (41.4)
14–20 days	57 (23.4)
≥21 days	53 (21.7)

Notes: [a]Completed scheduled treatment: 10; discharged but cefiderocol continued: 10; lack of improvement, including for lack of source control: 2; improved, not resolved: 2; logistical or nonmedical reasons, or noncompliance: 2; unknown: 1; new intervening co-infection: 1. [b]Index culture sample closest to initiation of cefiderocol treatment may have been collected and tested in outpatient settings prior to hospitalization.
Abbreviations: ADR, adverse drug reaction; Q, quartile.

followed by death (13.5%), switch to alternative susceptible therapy (10.2%), and cefiderocol nonsusceptibility (1.6%) (Table 3).

The median time from admission to a culture sampling (resulting in the identification of a Gram-negative pathogen for which cefiderocol was used) was 9 days, and the median time from a culture sampling to the first dose of cefiderocol was 5 days (Table 3). Cefiderocol treatment was administered for a median (IQR) of 12 days (8.0–18.5) (Table 3). Duration of treatment varied by infection site; the longest treatment duration was found in patients with bone and joint infections and other infection sites (median 21 days [14.0–36.0] and 27 days [23.0–31.0], respectively) (Supplementary Table 5).

Treatment with antimicrobial agents up to 14 days prior to initiation of cefiderocol was common (47.1%). In addition, 70.1% of patients received any concomitant antimicrobial agents, which frequently included tetracyclines, aminoglycosides, and polymyxins. Alternative antibiotics after cefiderocol treatment up to 3 days from the last day of cefiderocol were given to 13.9% of patients (Supplementary Table 6).

Outcomes Overall and According to Key Characteristics of Patients, Hospitalization, Primary Infection Site, and Pathogen

Clinical Cure and Clinical Response

Clinical cure was achieved in 64.8% of patients (158/244; 95% CI: 58.8–70.8); 74.2% of patients (181/244; 95% CI: 68.7–79.7) responded to cefiderocol treatment at EOT (Table 4 and Supplementary Table 7). Overall, 9.4% (23 patients) had a relapse or re-infection (Supplementary Table 8).

Clinical cure rates were similar among male and female patients, and 69.7% and 75.8% of patients aged ≥65 years had cure and response, respectively (Table 4). Clinical cure rate was higher in patients without organ support or ICU admission than in those with organ support or ICU admission (Table 4). Clinical cure (64.6%) and clinical response (73.5%) rates were similar to the overall population among patients receiving cefiderocol for a documented Gram-negative infection, while these rates (77.8% and 88.9%, respectively) were numerically higher in a small proportion of patients who received cefiderocol as empiric therapy (Table 4). Clinical cure (51.6%) and response (64.5%) rates were the lowest for patients receiving salvage cefiderocol treatment (Table 4). Clinical cure and response rates were similar in patients with monomicrobial (63.3% and 74.0%) and polymicrobial (68.0% and 74.7%) infections, respectively

Table 4 Outcomes According to Key Characteristics of Patients, Hospitalization, and Primary Infection

	Overall N	Clinical Cure, n (%)[a]	Clinical Response at EOT, n (%)[b]	14-Day IH-ACM, n (%)	30-Day IH-ACM, n (%)
Overall	244	158 (64.8) (95% CI: 58.8; 70.8)	181 (74.2) (95% CI: 68.7; 79.7)	23 (9.4) (95% CI: 5.8; 13.1)	45 (18.4) (95% CI: 13.6; 23.3)
Infection site, n (%)					
Respiratory	136	81 (59.6)	97 (71.3)	15 (11.0)	31 (22.8)
Bloodstream	24	14 (58.3)	17 (70.8)	3 (12.5)	5 (20.8)
Urinary	15	14 (93.3)	14 (93.3)	1 (6.7)	1 (6.7)
Intra-abdominal	12	5 (41.7)	6 (50.0)	2 (16.7)	3 (25.0)
Bone and joint	14	10 (71.4)	12 (85.7)	0 (0)	2 (14.3)
Skin and skin structure	41	32 (78.0)	33 (80.5)	2 (4.9)	3 (7.3)
Other site[c]	2	2 (100)	2 (100.0)	0 (0)	0 (0)
Baseline characteristics, n (%)					
Age ≥65 years	66	46 (69.7)	50 (75.8)	6 (9.1)	9 (13.6)
Sex					
Male	150	98 (65.3)	112 (74.7)	12 (8.0)	21 (14.0)
Female	93	59 (63.4)	68 (73.1)	11 (11.8)	24 (25.8)
Other/unknown	1	1 (100)	1 (100.0)	0 (0)	0 (0)
ICU stay when cefiderocol was initiated or within 2 days after initiation of cefiderocol, n (%)					
Yes	152	83 (54.6)	102 (67.1)	19 (12.5)	36 (23.7)
No	92	75 (81.5)	79 (85.9)	4 (4.3)	9 (9.8)
Received organ support when cefiderocol was initiated or within 2 days after initiation of cefiderocol, n (%)					
Yes	126	62 (49.2)	79 (62.7)	18 (14.3)	34 (27.0)
No	118	96 (81.4)	102 (86.4)	5 (4.2)	11 (9.3)

Reason for starting cefiderocol, n (%)					
Documented infection	181	117 (64.6)	133 (73.5)	17 (9.4)	37 (20.4)
Empiric for suspected CR Gram-negative bacterial infection	27	21 (77.8)	24 (88.9)	0 (0.0)	1 (3.7)
Salvage treatment	31	16 (51.6)	20 (64.5)	6 (19.4)	7 (22.6)
Other including unknown	5	4 (80.0)	4 (80.0)	0 (0.0)	0 (0.0)
Infection characteristics, n (%)					
Time from sampling of a positive culture to first cefiderocol dose					
≤2 days	33	24 (72.7)	28 (84.8)	2 (6.1)	2 (6.1)
3–4 days	64	43 (67.2)	50 (78.1)	4 (6.3)	12 (18.8)
5–7 days	78	46 (59.0)	51 (65.4)	10 (12.8)	17 (21.8)
>7 days	59	42 (71.2)	46 (78.0)	7 (11.9)	10 (16.9)
Cefiderocol given prior to index culture sample	10	3 (30.0)	6 (60.0)	0 (0)	4 (40.0)
Monomicrobial infections by pathogen, n (%)	169	107 (63.3) (95% CI: 56.1; 70.6)	125 (74.0) (95% CI: 67.3; 80.6)	20 (11.8) (95% CI: 7.0; 16.7)	35 (20.7) (95% CI: 14.6; 26.8)
Pseudomonas aeruginosa	82	53 (64.6)	61 (74.4)	11 (13.4)	21 (25.6)
Acinetobacter baumannii	43	26 (60.5)	32 (74.4)	4 (9.3)	8 (18.6)
Enterobacterales	26	19 (73.1)	20 (76.9)	4 (15.4)	4 (15.4)
Stenotrophomonas maltophilia	10	7 (70.0)	8 (80.0)	1 (10.0)	2 (20.0)
Other	8	2 (25.0)	4 (50.0)	0 (0)	0 (0)
Polymicrobial infections by pathogen, n (%)	75	51 (68.0) (95% CI: 57.4; 78.6)	56 (74.7) (95% CI: 64.8; 84.5)	3 (4.0) (95% CI: 0; 8.4)	10 (13.3) (95% CI: 5.6; 21.0)
A. baumannii + other Gram-negative species	19	13 (68.4)	14 (73.7)	3 (15.8)	5 (26.3)
A. baumannii + *P. aeruginosa*	7	3 (42.9)	4 (57.1)	2 (28.6)	2 (28.6)
A. baumannii + Enterobacterales	10	8 (80.0)	8 (80.0)	1 (10.0)	3 (30.0)
A. baumannii + *S. maltophilia*	2	2 (100.0)	2 (100.0)	0 (0)	0 (0)

(*Continued*)

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Table 4 (Continued).

	Overall N	Clinical Cure, n (%)[a]	Clinical Response at EOT, n (%)[b]	14-Day IH-ACM, n (%)	30-Day IH-ACM, n (%)
P. aeruginosa + Other Gram-negative species	28	19 (67.9)	22 (78.6)	0 (0)	2 (7.1)
P. aeruginosa + Enterobacterales	20	13 (65.0)	15 (75.0)	0 (0)	2 (10.0)
P. aeruginosa + *S. maltophilia*	8	6 (75.0)	7 (87.5)	0 (0)	0 (0)
Any other combination of 2 pathogens	11	9 (81.8)	10 (90.9)	0 (0)	1 (9.1)
Any other combination of 3 or more pathogens	17	10 (58.8)	10 (58.8)	0 (0)	2 (11.8)
CR status, n (%)					
Resistant (or nonsusceptible)	209	135 (64.6)	155 (74.2)	21 (10.0)	41 (19.6)
Susceptible	20	13 (65.0)	15 (75.0)	1 (5.0)	2 (10.0)
Unknown or not tested	15	10 (66.7)	11 (73.3)	1 (6.7)	2 (13.3)

Notes: [a]Clinical cure is defined as resolution or improvement of signs and symptoms without a later relapse, excluding patients who had a relapse or reinfection after EOT. [b]Clinical response is defined as resolution or improvement of signs and symptoms at EOT. [c]Other: single site not in any of the above categories.

Abbreviations: CI, confidence interval; CR, carbapenem resistant; EOT, end of treatment; ICU, intensive care unit; IH-ACM, in-hospital all-cause mortality.

(Table 4). Clinical cure and clinical response rates were 56.3% and 69.8% in monomicrobial RTIs and 67.5% and 75.0% in polymicrobial RTIs, respectively (Supplementary Table 9).

In RTIs caused by *P. aeruginosa*, clinical cure and clinical response rates were 60.7% and 73.2% in monomicrobial infections and 75.0% and 87.5% in polymicrobial infections, respectively. Among patients with RTIs caused by *A. baumannii*, 50.0% and 63.6% clinical cure and clinical response rates were reported in monomicrobial infections, while 66.7% and 77.8%, respectively, in polymicrobial infections (Supplementary Table 9). Patients with *S. maltophilia* infections had 70.0% clinical cure and 80.0% clinical response rates in monomicrobial infections across all infection sites (Supplementary Table 9). Patients infected by CR Gram-negative pathogens had a clinical cure rate of 64.6% and a clinical response rate of 74.2% (Table 4).

Mortality

Overall, 9.4% (23/244; 95% CI: 5.8–13.1) and 18.4% (45/244; 95% CI: 13.6–23.3) of patients died in hospital by Day 14 and Day 30, respectively (Table 4). For patients with RTI, BSI, and UTI, IH-ACM overall was 11.0%, 12.5%, and 6.7% at Day 14 and 22.8%, 20.8%, and 6.7% at Day 30, respectively. IH-ACM rates were numerically lower for patients with polymicrobial infections than with monomicrobial infections (Table 4 and Supplementary Table 10). IH-ACM at Day 30 was 25.6% among patients with *P. aeruginosa* infections, 18.6% among patients with *A. baumannii* infections, and 20.0% among patients with *S. maltophilia* (Table 4). In polymicrobial infections with *P. aeruginosa* or *A. baumannii*, IH-ACM rate was 7.1% and 26.3% at Day 30, respectively, and no patients died with polymicrobial *S. maltophilia* infections (Table 4).

Safety

Cefiderocol was well tolerated. Five patients (2%) experienced six ADRs (rash [n = 1], increased liver function test [n = 1], diarrhea [n = 2], urticarial rash [n = 1]); the latter patient also experienced a serious ADR (interstitial nephritis/acute kidney injury [n = 1]). Cefiderocol was discontinued for two events in two patients, and there were no changes in treatment for four events (Supplementary Table 11).

Discussion

This interim analysis of the PROVE study highlights some important information about the pattern of use and effectiveness of cefiderocol in US hospitalized patients. Approximately two-thirds had respiratory tract or bloodstream as primary sites that prompted the use of cefiderocol, >50% of patients were in the ICU when their index pathogen was isolated, and >50% required organ support in the form of mechanical ventilation, vasopressors, and/or renal replacement therapy, indicating a severely ill population. The most frequent pathogens were *P. aeruginosa*, followed by *Acinetobacter* spp, Enterobacterales, and *S. maltophilia*.

Clinical response (defined as resolution or improvement of signs and symptoms based on physicians' judgement at EOT) overall was 74.2%; however, 9.4% patients had a relapse or reinfection subsequently during their hospitalization, resulting in a 64.8% overall clinical cure rate. The 23 patients with relapses (including recurrence and reinfection) at any time during the remainder of hospitalization had some distinctive characteristics: 15 were exposed to carbapenems prior to cefiderocol, nearly all had mechanical ventilation at any point prior to index culture, and four had infections with cefiderocol-nonsusceptible Gram-negative pathogens. They had markedly prolonged hospitalizations and ICU stays, suggesting the presence of exacerbating conditions. Nevertheless, treating physicians reported favorable clinical responses for nearly 70% of these patients at EOT.

In the randomized, Phase 3 APEKS-NP study, cefiderocol treatment for a median of 10 days was noninferior to meropenem for a similar duration in the primary endpoint of ACM at Day 14 in patients with nosocomial pneumonia (NP), caused by a range of carbapenem-susceptible Gram-negative bacteria, (ie, cefiderocol 12.4% versus meropenem 11.6%).[18] In the phase 3 CREDIBLE-CR study, similar clinical cure rates at test of cure were found in the cefiderocol arm and the best available therapy (BAT) arm in patients with NP (cefiderocol 50%, BAT 53%) or BSI/sepsis (cefiderocol 43%, BAT 43%) caused by CR Gram-negative bacteria.[19] However, in patients with CRAB infections, there was a numerically higher ACM rate in the cefiderocol arm, which perhaps stemmed from imbalances in baseline clinical characteristics (eg, age, renal function, and shock).[19] These results led to a warning to monitor patients in the prescribing information and summary of product characteristics.[8,9]

In the current analysis, clinical cure and response rates were higher in patients with cUTI, skin and skin structure infections, and bone and joint infections than in patients with RTI, BSI, and intra-abdominal infection, as expected in these subgroups, which also had the highest proportion of ICU admission (58.3–79.2%), vasopressor use (33.3–41.7%), and Day 30 mortality rates (20.8–25.0%). Despite these severe illness indicators, the substantial proportion (28.6%) of patients with cUTI, skin and skin structure infections and bone and joint infections, and subsequent high clinical cure rates would have influenced the overall clinical cure rate with cefiderocol in this analysis. In this analysis, the overall 14-day and 30-day IH-ACM rates from initiation of cefiderocol were 9.4% and 18.4%, respectively. The Day 30 IH-ACM rates by pathogen ranged between 0% and 25.6% in monomicrobial infections, including 18.6% for *A. baumannii*. Day 30 ACM was 26.2% in polymicrobial infections with *A. baumannii*, which is lower than that observed in the CREDIBLE-CR study in patients with CRAB (38%).[19] Following regulatory approval, the effectiveness of cefiderocol was investigated in patients with NP or BSI caused by CRAB and with or without COVID-19 infection.[11,16,20–23] Patients in these studies were in the ICU, had high rates of septic shock, and nearly all received mechanical ventilation when they were treated with cefiderocol. In comparative investigations, the Day 30 crude mortality rate for cefiderocol-treated patients ranged between 31.5% and 55%, and between 37% and 98% in the comparator groups with colistin-based therapy.[11,16,20–23] In cohort studies in cefiderocol-treated patients with CRAB infections and similar clinical characteristics, mortality rates were similar (23.1–51.0%).[24–27] It may be possible that the relatively younger age, lower percentage of individual comorbidities, lower CCI score, low percentage of COVID-19 infection, and/or fewer patients relying on organ support contributed to the lower mortality rates in this interim analysis compared with studies during the initial phase of the COVID-19 pandemic.[11,16,20–27]

The clinical cure and clinical response rates following cefiderocol treatment from this interim analysis are similar to data obtained in other real-world settings with various Gram-negative pathogens.[10,12,13,15,17,28–32] In a French retrospective study of 16 patients in the ICU infected by difficult-to-treat resistant *P. aeruginosa, A. baumannii*, and *S. maltophilia*, and with a 50% rate of COVID-19 pneumonia, high rates of clinical cure and 1-year survival were reported with cefiderocol treatment despite the presence of persistent colonization and relapses.[29] In a recent study, cefiderocol as salvage therapy in monotherapy or combination therapy showed 85% clinical and microbiological cure and 23% 28-day mortality rates in infections caused by CR Gram-negative pathogens, excluding *Acinetobacter* spp.[17] In a US retrospective study of 48 patients treated with cefiderocol, a microbiological failure rate of 29% and clinical failure rate of 36% were reported in an elderly cohort with multiple comorbidities and CCI of 6.[15] A recent investigation of cefiderocol-treated patients in the compassionate use program showed a 72% clinical response rate among patients infected by MDR/CR *P. aeruginosa*, and the Day 28 all-cause mortality rate was 24%.[33] Cefiderocol was administered as a salvage antibiotic for patients with no alternative treatment options.[33] In the current analysis, clinical response rates in patients infected by *P. aeruginosa* were similar in monomicrobial and polymicrobial infections (74.4% and 78.6%), with mortality rates of 25.6% and 7.1%, respectively. Additional retrospective studies, in which *P. aeruginosa* was the predominant pathogen, showed clinical cure or clinical success rates in the range of 68.8% to 90%, with respective mortality rates of 10% to 16.1%.[30–32]

The proportion of elderly patients was less than 30% in the current US cohort; however, nearly all patients had at least one comorbid condition, most frequently renal disease and diabetes. Furthermore, nearly all patients had at least one risk factor for being infected or colonized by CR pathogens. Among isolates with information on carbapenem susceptibility, >90% were carbapenem resistant. The presence of risk factors for CR Gram-negative species, including prior hospitalization in the last six months, history of CR Gram-negative bacterial infection or colonization, carbapenem use or no response to carbapenem treatment in the last 30 days, coupled with a high rate of carbapenem resistance may explain the frequent use of cefiderocol for a documented Gram-negative bacterial infection, in which both the pathogen and its resistance phenotype (data not shown) were known to guide therapy. Gram-negative antibiotics were administered prior to the initiation of cefiderocol treatment in approximately 45% of the patient cohort, mainly beta-lactam antibiotics. An estimated 27% of patients had concomitant antibiotics against Gram-negative species, and the most frequently administered adjunctive antibiotics included tetracyclines, aminoglycosides, and polymyxins, while the newer beta-lactam–beta-lactamase inhibitors were administered to a small percentage of patients (<8%). Thus, cefiderocol was administered to patients with underlying risk factors for CR pathogens, who were at risk of prolonged hospitalization or death and for whom cefiderocol represented a more optimal antibiotic treatment option with its known safety profile.[34,35]

Studies have shown that shortening the time to initiation of appropriate antibiotics in patients at risk of CR Gram-negative infections could be beneficial in minimizing the risk of treatment failure, specifically mortality.[36] Although guideline-recommended carbapenems and beta-lactam–beta-lactamase inhibitors had been utilized among patients with prior antimicrobial treatment,[37] escalation or switch to cefiderocol treatment was required in this patient population. The small subgroup of patients (12.7%) who received salvage cefiderocol treatment after failure of a prior antibiotic treatment or due to intolerance to other antibiotics had the lowest clinical response and clinical cure rates. Although 30-day mortality among these patients was similar to those patients who received cefiderocol for a documented infection (documented infection: 20.4% and salvage treatment: 22.6%, respectively). Of note, patients receiving empiric treatment, before culture results were known, had numerically the highest clinical response and clinical cure rates, with only one death. These data are similar to the findings of the retrospective PERSEUS study, in which the greatest benefit of cefiderocol treatment was observed among patients treated with cefiderocol empirically.[38] Data show that cefiderocol retains activity against a large proportion of Enterobacterales (89.2–95.1%) and MDR *P. aeruginosa* (88.3–100%) that are resistant to the newer beta-lactam–beta-lactamase inhibitor agents.[4,5,7,33,39] Cefiderocol susceptibility information was available for 58.2% of all isolates and 124 (87.3%) of these isolates were reported as susceptible to cefiderocol, which is similar to rates found in large surveillance studies.[4,5]

An important limitation of the study is that it was designed as a noncomparative descriptive study. Currently, no single comparator agent is available with in vitro coverage against different Gram-negative bacterial species such as cefiderocol; this limits the design of a controlled clinical study, particularly in the case of polymicrobial infections. In most comparative retrospective studies, colistin-based therapy was the comparator against CRAB; however, acute kidney injury was also reported for colistin-treated patients.[11] The information collected in the PROVE study on antibiotic use may help to design controlled or parallel-group studies of cefiderocol against CR Gram-negative pathogens.

Other limitations include that susceptibility results were based on local testing reports; thus, susceptibility rates cannot be extrapolated to a wider population. Microbiological assessments were not consistently repeated on patients with clinical cure and presumed eradication; therefore, true microbiological success or failure rates accurately could not be obtained. Although reporting on relapses was requested if they occurred due to the same pathogen species, information was very limited and without a pre-specified time period; thus, relapses could have occurred due to the same or a different sequence type of the same species. The severity of illness in the enrolled patients could not be confirmed by a severity score, such as the Acute Physiology and Chronic Health Evaluation II score, as the medical charts inconsistently provided such parameters for ICU patients. The study was also limited by its relatively short follow-up period, particularly for assessment of patients with osteomyelitis. This study is a descriptive study, and subgroups may have small patient numbers; thus, efficacy findings should be interpreted with caution. As other antibiotics were administered concomitantly with cefiderocol, clinical response and cure cannot be attributed solely to cefiderocol treatment. Lastly, routine clinical practice may differ across the centers when physicians prescribe cefiderocol.

Conclusion

In conclusion, cefiderocol treatment in real-world clinical practice in this large US population with predominantly CR Gram-negative bacterial infections, including *P. aeruginosa, A. baumannii*, CR Enterobacterales, and *S. maltophilia*, demonstrated good effectiveness in a variety of infection types, including RTI, UTI, and BSI, similarly to previous retrospective studies. Polymicrobial infections with nonfermenting pathogens were common, and interestingly, nonfermenters at other infection sites, such as bone and joint and skin and skin structure, were also commonly found. Most Gram-negative isolates with a reported susceptibility testing result suggested a high rate of cefiderocol susceptibility in US hospitals. In this patient population with a high rate of ICU admission, organ support, and ICU-acquired pathogens but a low percentage of COVID-19, cefiderocol treatment was well tolerated with infrequent adverse drug reactions. Thus, patients who are at risk of more severe acute infections or those with risk factors of being colonized or infected by CR nonfermenters may benefit from cefiderocol-containing therapy.

Data Sharing Statement

Data are not publicly available; however, Shionogi is committed to sharing clinical trial data at reasonable request from researchers or healthcare personnel. Further information is available at: https://www.shionogi.com/shionogi/global/en/company/policies/shionogi-group-clinical-trial-data-transparency-policy.html.

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