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BRIEF REPORT

Case series of cefiderocol for salvage therapy in carbapenem-resistant Gram-negative infections

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Abstract

Purpose This case series describes real-world utilization of cefiderocol and associated clinical outcomes in the setting of carbapenem-resistant Gram-negative bacterial infections.

Methods Adult hospitalized patients administered at least 5 days of cefiderocol as definitive treatment from October 1, 2020 to September 16, 2021 were included in this retrospective cohort analysis. The primary outcome was clinical success defined as a composite of 30 day survival, resolution of infection, and absence of 30 day recurrence of the same organism.

Results Among 24 patients, pneumonia (19, 79%) was the most common source of infection with *Acinetobacter baumannii* (14, 58%) and *P. aeruginosa* (10, 42%) as the predominant organisms isolated. Cefiderocol monotherapy was used as definitive treatment in 16 (67%) patients. Eleven patients (46%) met clinical success. Thirty-day mortality occurred in ten (42%) patients while seven (29%) patients had recurrence of infection. Thirteen out of 21 total isolates (62%) tested for susceptibility were deemed susceptible. Of the 16 patients with available susceptibility, 9 (56%) had an infection where all isolated organisms were susceptible to cefiderocol.

Conclusions Our results provide additional insight into the in vivo activity of cefiderocol. Cefiderocol remains a salvage option for carbapenem-resistant Gram-negative organisms.

Keywords Cefiderocol · Multidrug resistant · Carbapenem-resistant · *Acinetobacter baumannii*

Introduction

Cefiderocol is a first-in-class siderophore cephalosporin approved for the treatment of complicated urinary tract infections (cUTI) and hospital acquired/ventilator-associated pneumonia (HABP/VABP) [1]. Cefiderocol has demonstrated potent in vitro activity against several carbapenem-resistant Gram-negative bacteria including *Pseudomonas aeruginosa, Acinetobacter baumannii,* and carbapenem-resistant Enterobacterales (CRE) [2, 3]. However, clinical trial outcomes suggest increased mortality when used to treat infections caused by carbapenem-resistant non-fermenting Gram-negative bacteria [4]. While cefiderocol use in resistant infections seems promising in select patients and infections, limited data are available with real-world utilization and off-label prescribing. Outside of clinical trials, cefiderocol is often reserved as salvage therapy in the setting of complex patients with challenging infections and limited treatment options [4–6]. We aim to report an evaluation of cefiderocol use in the setting of carbapenem-resistant infections with associated patient outcomes.

Materials and methods

This study is a retrospective cohort analysis of hospitalized patients within Advocate Aurora Health (AAH). We included all patients ≥ 18 years old who were administered a course of at least 5 days of cefiderocol as definitive treatment from October 1, 2020 to September 16, 2021. The cefiderocol duration of at least 5 days of therapy was chosen to limit our cohort to those patients who received cefiderocol for the majority of their treatment course. All relevant demographic and clinical data were extracted from the electronic medical record (EMR).

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Isolate identification and susceptibility were performed at ACL Laboratories, a central processing laboratory that follows Clinical and Laboratory Standards Institute (CLSI) standards and guidelines. MALDI-TOF MS was used for organism identification with automated susceptibility testing performed through VITEK 2 (biomerieux, Durham, NC). Ceftazidime–avibactam and ceftolozane–tazobactam susceptibilities were only automatically reported for multidrug resistant organisms as part of cascade reporting. However, ceftolozane–tazobactam was on shortage during the majority of the study period so was, therefore, not reported as providers had to use alternatives. Cefiderocol susceptibility testing was not automatically done unless requested by an infectious diseases (ID) provider since broth microdilution was outsourced to ARUP Laboratories with a 1 week turnaround time. US Food & Drug Administration (FDA) approved susceptibility breakpoints were utilized for Enterobacterales (≤ 4 mg/L), *P. aeruginosa* (≤ 1 mg/L), and *A. baumannii* (≤ 1 mg/L) [7]. Phenotypic testing with the Carba NP test was utilized to detect carbapenemase production for Enterobacterales isolates.

Cefiderocol utilization was at the discretion of the provider but restricted to ID consultation. Patients were evaluated for demographic information, infection source, microbiologic data, empiric and definitive therapy, adverse effects, length of stay, development of resistance, and clinical success. Empiric therapy was defined as antimicrobial agents administered for at least 24 hours prior to initial ACL susceptibility results (not including the cefiderocol send out test) and definitive therapy was defined as the antimicrobials received following susceptibility results. Time to effective therapy (TTET) was defined by the number of days from initial culture collection to the administration of active antimicrobial therapy. Clinical success was a composite of 30 day survival with resolution of signs and symptoms of infection as documented by the treating physician and the absence of 30 day infection recurrence of the same organism following the onset of infection. All variables related to clinical success were assessed from the first cefiderocol administration. The study received a non-human subjects research determination from the AAH Institutional Review Board.

Results

Cefiderocol was initiated in 39 patients with 24 subjects meeting the inclusion criteria. Of the 15 patients excluded, 13 received cefiderocol for less than 5 days. The remaining two patients were initiated on cefiderocol and switched to an alternative regimen for definitive therapy. The majority of the cohort were male (17, 71%) with a median age of 66.5 years. Most patients were from a skilled nursing facility (16, 67%) while six patients were transferred from an outside hospital and two were admitted from the community. Five (21%) patients were diagnosed with SARS-COV-2 infection and received standard of care treatment in addition to cefiderocol secondary to a superimposed bacterial infection. Eight patients were receiving hemodialysis, with one patient who transitioned to continuous veno-venous hemofiltration. The average hospital length of stay was 18.5 days with most patients being admitted to an ICU (19, 79%) with an average ICU stay of 9 days. A history of carbapenem-resistant organisms in the previous 90 days was demonstrated in 14 (58%) patients.

Pneumonia (19, 79%) was the primary indication followed by wound infection (4, 17%), cUTI (1, 4%), and driveline infection (1, 4%). Concomitant bacteremia occurred in five patients (21%). The predominant pathogens isolated were *A. baumannii* (14, 58%) and *P. aeruginosa* (10, 42%) followed by *K. pneumoniae* (4, 17%) and *S. maltophilia* (2, 8%). Seven (29%) patients had polymicrobial infections with two or more of the above isolated pathogens. Two (8%) patients did not have an organism isolated. Of patients with isolated organisms and confirmed susceptibilities ($n = 20$), 17 (85%) were not on effective therapy. There were 16 patients with available cefiderocol susceptibility results. Of those, two patients were initiated on effective empiric therapy at the time of culture obtainment while a total of six patients were never on effective therapy. Of the remaining eight patients, the TTET was 3.4 days.

Cefiderocol monotherapy was used as definitive therapy in 16 (67%) patients. The remaining eight patients were on combination with tigecycline, gentamicin, colistin, tobramycin, or minocycline. In most instances, cefiderocol was utilized due to resistance to carbapenems, ceftazidime–avibactam, and ceftolozane–tazobactam as applicable. Among 24 patients, there were 30 pathogens included with cefiderocol susceptibility testing performed on 21 isolates (70%), of which 13 (62%) were susceptible, 5 (24%) were intermediate, and 2 (10%) were resistant. Interpretation of susceptibility was not able to be determined for one isolate as the FDA does not offer established breakpoints for *S. maltophilia.* Of the ten *A. baumannii* isolated, the median MIC was 1.5 mg/L and five were susceptible, four intermediate, and one resistant. Of the eight *P. aeruginosa* isolates tested, the median MIC was 0.5 mg/L and seven were susceptible, one intermediate, and no isolates were resistant. One patient had a documented *Klebsiella pneumoniae* carbapenemase and two

patients had New Delhi metallo-β-lactamases as indicated by Carba NP. Three patients had been previously exposed to cefiderocol prior to this study. The average treatment duration with cefiderocol was 10.7 days.

Eleven (46%) patients met criteria for clinical success. A summary of the total cohort, including the 13 patients considered to have failed therapy with cefiderocol, is provided in Appendix Table 1. Among these patients, ten (42%) expired within 30 days of initiation of cefiderocol. Of the patients who expired, one (10%) patient had confirmed resistance to cefiderocol, six (60%) had a documented *A. baumannii* infection, and three (30%) had a documented *P. aeruginosa* infection. Monotherapy was used in 16 patients and 5 (31%) patients met the mortality endpoint compared to 5 of 8 (63%) patients who received combination therapy. Eight patients were on renal replacement therapy and 5 (65%) patients expired compared to 5 (31%) of the 16 patients who were not on renal replacement therapy. In those with monomicrobial *A. baumannii* and *P. aeruginosa* infections, five of nine (56%) patients and three of six (50%) patients, respectively, expired within 30 days. In comparison, two of seven (29%) patients with polymicrobial infections met mortality. In patients on effective therapy upon finalized susceptibility, six of ten (60%) expired within 30 days compared to one of six (17%) patients that were never on effective therapy. Recurrence of infection with the same organism occurred in seven (29%) patients, two of which developed increased MICs to cefiderocol upon repeat susceptibility testing with MICs of 2 mg/L and 32 mg/L, with one patient meeting the mortality endpoint. Of the five patients with concomitant bacteremia, three (60%) patients experienced clinical failure. No adverse events were observed throughout the treatment courses.

Discussion

Limited data are available on utilization of cefiderocol as salvage therapy for carbapenem-resistant infections outside of clinical trials and FDA-approved indications. Most patients in our cohort were initiated on cefiderocol due to a documented infection with a carbapenem-resistant non-fermenting Gram-negative organism. Our findings provide significant insights into real-world utilization of cefiderocol in infections with limited therapies available, adding additional clinical context to the available data of in vitro activity.

Several clinical trials have been conducted to examine the efficacy and safety of cefiderocol in Gram-negative infections. In a phase 2 trial, cefiderocol was found to be superior to imipenem–cilastatin in both clinical and microbiologic response for cUTI [5]. The efficacy of cefiderocol has been further demonstrated in two phase 3 trials, APEKS-NP and CREDIBLE-CR [4, 6]. The results of these trials found no difference in outcomes between cefiderocol and meropenem in the setting of HABP/VABP and no difference when compared to best available therapy for treatment of severe infections caused by carbapenem-resistant Gram-negative infections, respectively [4, 6]. However, the results of CREDIBLE-CR demonstrated higher all-cause mortality in the subgroup of patients with carbapenem-resistant *A. baumannii* infections driven by higher rates of septic shock and more frequent hospitalization in the ICU, suggesting an increased baseline risk of mortality for this subset of patients [1, 4]. The results of our study show a similar pattern of increased mortality associated with *A. baumannii* with 60% of patients meeting the all-cause mortality endpoint in association with this organism. Notably, 81% of our patients were not on effective empiric therapy upon initial in-house susceptibility results, prompting the use of salvage therapy with cefiderocol and subsequent susceptibility send out testing to ARUP. The TTET was 3.4 days in those patients with available cefiderocol susceptibility. This delay in therapy could also contribute to the increased mortality and clinical failures observed. An additional contributing factor for high mortality rates observed could be that our cohort included patients who presented with hypoxic respiratory failure secondary to the SARS-COV-2 virus. Similarly, a recent retrospective study found that in severe COVID-19 diagnosed with carbapenem-resistant *A. baumannii*, the 28 days mortality was 55% in patients receiving cefiderocol [8].

A recent review of patients at a tertiary care center administering cefiderocol in combination with colistin suggests that cefiderocol is a promising treatment option for difficult-to-treat resistant infections [9]. Of the eight cases analyzed in this review, most patients were treated for uncomplicated healthcare associated infections with either *A. baumannii*, *P. aeruginosa*, or carbapenem-resistant *K. pneumoniae* and only one patient met the mortality endpoint [9]. Similarly, an additional study reported that 3 of 13 patients treated with cefiderocol for *A. baumannii, K. pneumoniae,* or *P. aeruginosa* bacteremia or intraabdominal infections in the setting of previously failed regimens experienced mortality [10]. These studies may have observed lower mortality rates as opposed to our study (42%) due to less severe infections, different patient populations, delay in effective therapy in our cohort, and an overall smaller sample size. There have been several additional studies that have analyzed clinical

outcomes with cefiderocol use. In one study, cefiderocol was shown to have a lower mortality rate when compared to colistin-based regimens for carbapenem-resistant *A. baumannii* infections (56 vs 34%) which is lower than our observed mortality rate for this organism (60%) [11]. Another study observed a higher rate of 30 day clinical success of 70% in ten ICU patients with *A. baumannii, S. maltophilia,* and *K. pneumoniae* infections as opposed to our cohort where only 46% of patients experienced clinical success [12]. In addition, our case series also provides new insight into outcomes in patients with renal dysfunction in contrast to previous reports. Our study found that of the eight patients on renal replacement therapy, five patients expired. Further studies are warranted for these special populations to assess if renal failure is a predictor of mortality.

Of the 21 isolates in our cohort with available cefiderocol susceptibility reports, only 62% were susceptible based on FDA breakpoints, which is lower than available global in vitro data from carbapenem-resistant *A. baumannii, P. aeruginosa*, and Enterobacterales isolates where 95% were susceptible to cefiderocol [13]. In comparison, these studies utilized CLSI breakpoints, which are less stringent than FDA breakpoints and also analyzed organisms isolated from the urinary tract. When compared to our cohort, only one patient had a documented urinary tract infection. This may account for the observed increase in susceptible isolates compared to the present cohort. Interestingly, of the patients who were previously exposed to cefiderocol, two experienced an increase in the MIC upon repeat susceptibility testing. Similarly, a recent prospective study in patients with difficult-to-treat resistant *P. aeruginosa* found that when re-testing cefiderocol in one isolate, the MIC increased from 0.25 to 1 mg/L further solidifying selective pressures that may predispose cefiderocol to resistance [14]. Due to the collective amount of data available regarding increased morality and concerns of treatment failure with cefiderocol as monotherapy, new treatment guidelines suggest that cefiderocol be utilized as combination therapy, especially for infections caused by *A. baumannii* [15]. This demonstrates the importance of increased stewardship and surveillance upon the initiation of cefiderocol and the necessity of confirming susceptibilities in all isolates.

Limitations of this study include a small sample size, the retrospective nature of a case series, and reliance on documentation within the EMR for clinical outcomes. Due to limitations in EMR reporting, patients discharged from the hospital without documented follow up were assumed to have met clinical success. Additionally, the decision to use cefiderocol as well as requesting susceptibility testing was at the discretion of the treating ID provider rather than an automatic cascade reporting. Not all isolates were sent for cefiderocol susceptibility testing, which may affect clinical outcomes as we were unable to confirm susceptibility of these isolates. Finally, a severity of illness score as well as patients with concomitant infections due to Gram-positive pathogens or fungi were not analyzed in the present study. These may be additional considerations for future studies to aid in the assessment of clinical outcomes and real-world application of cefiderocol in patients with carbapenem-resistant infections.

Our study was conducted to demonstrate cefiderocol utilization in a cohort with associated clinical outcomes for carbapenem-resistant cases outside of the early access compassionate use program. Our results provide insight into patient exposures on cefiderocol and correlated mortality as well as rate of infection recurrence. Key factors that likely contributed to the high rates of clinical failure seen in the present study may have been the delay in therapy as demonstrated by our calculated TTET as well as cefiderocol usage without knowledge of susceptibility results. Timely antimicrobial susceptibility testing for agents such as cefiderocol is difficult when in-house susceptibility reporting is unavailable. It is important to stress the utilization of performing susceptibility testing even for new agents such as cefiderocol purported to have excellent in vitro potency for the management of carbapenem-resistant infections as 6 of 14 patients in this study who were initiated on cefiderocol prior to susceptibility results had a non-susceptible isolate. Cefiderocol continues to remain a salvage option for carbapenem-resistant Gram-negative organisms. However, special consideration should be taken regarding utilization as empiric monotherapy, susceptibility reporting, and clinical response to this novel antibiotic.

Appendix

Table 1 Summary of cases

Patient age, years/sex	Organism isolated	Infection type	History of carbapenem resistant organism?[a]	Empiric treatment	Ineffective empiric therapy?[b]	Definitive treatment	Cefiderocol dosing[c]	Reason for cefiderocol use	Cefiderocol MIC[d]	Treatment duration of cefiderocol, d	Total antimicrobial duration, d	Outcome
72, M	*A. baumannii*	PNA	Yes	Levofloxacin, colistin, tigecycline	No	Cefiderocol	ESRD on HD; 0.75 g Q12H	Failure of empiric therapy	NR	4.9	11.8	Expired
61, M	*A. baumannii*	PNA BSI	No	Cefepime	Yes	Cefiderocol, minocycline	1.5 g Q8H	Documented resistance to empiric therapy	0.5 (S)	6.1	7.6	Expired
75, F	*A. baumannii*	Wound BSI	No	Meropenem, Polymyxin B	Yes	Cefiderocol, tigecycline	1.5 g Q8H	Documented resistance to empiric therapy	0.25 (S)	12.1	14.5	Expired
70, M	*A. baumannii*	PNA BSI	No	Meropenem	Yes	Cefiderocol, colistin	2 g Q8H	Documented resistance to empiric therapy	1 (S)	12.6	15.8	Expired
47, M	*A. baumannii*	PNA	Yes	CZA, aztreonam	Yes	Cefiderocol	2 g Q8H	Documented resistance to empiric therapy	NR	9.2	14.5	Infection recurrence
73, M	*A. baumannii*	PNA	Yes	CZA, tigecycline	Yes	Cefiderocol, tigecycline	1.5 g Q8H	Documented resistance to empiric therapy	2 (I)	17.6	18.6	Infection recurrence
73, M	*A. baumannii*	UTI	No	TZP	Yes	Cefiderocol	2 g Q8H	Documented resistance to empiric therapy	2 (I)	6.9	8.9	Clinical success
75, M	*A. baumannii*	PNA	Yes	Cefiderocol	No	Cefiderocol, tigecycline	2 g Q8H	History of carbapenem resistant pathogen	1 (S)	6.2	6.2	Clinical success
55, M	*A. baumannii*	PNA	Yes	Cefiderocol	N/a	Cefiderocol	ESRD on HD; 0.75 g Q12H	History of carbapenem resistant pathogen	NR	6.1	6.1	Expired

Table 1 (continued)

Patient age, years/sex	Organism isolated	Infection type	History of carbapenem resistant organism?[a]	Empiric treatment	Ineffective empiric therapy?[b]	Definitive treatment	Cefiderocol dosing[c]	Reason for cefiderocol use	Cefiderocol MIC[d]	Treatment duration of cefiderocol, d	Total antimicrobial duration, d	Outcome
53, M	*A. baumannii, K. pneumoniae*	PNA	No	Cefepime	Yes	Cefiderocol	ESRD on HD; 0.75 g Q12H	Documented resistance to empiric therapy	1 (S), ≥ 64 (R)	14.2	22.0	Clinical success
60, M	*A. baumannii, P. aeruginosa*	PNA	No	Meropenem	Yes	Cefiderocol, tigecycline	1 g Q8H	Documented resistance to empiric therapy	16 (R), 1 (S)	7.7	19.9	Clinical success
63, M	*A. baumannii, P. aeruginosa*	PNA	No	CZA	Yes	Cefiderocol	ESRD on HD; 0.75 g Q12H	Documented resistance to empiric therapy	2 (I), 0.5 (S)	5.1	20.2	Clinical success
50, F	*A. baumannii, P. aeruginosa*	PNA	No	Colistin, tigecycline	Yes	Cefiderocol	1.5 g Q8H	Documented resistance to empiric therapy	NR	17.0	21.0	Infection recurrence
74, M	*A. baumannii, K. pneumoniae, S. maltophila*	PNA	Yes	Meropenem	Yes	Cefiderocol	ESRD on HD; 0.75 g Q12H	Documented resistance to empiric therapy	2 (I), 1 (S), 0.25 (N/a)	11.1	16.9	Expired
74, M	*K. pneumoniae, S. maltophilia*	PNA	Yes	Cefiderocol	N/a	Cefiderocol	ESRD on HD; 0.75 g Q12H	History of carbapenem resistant pathogen	NR	10.3	10.3	Infection recurrence, Expired
62, M	*P. aeruginosa*	LVAD BSI	Yes	IMI/REL	Yes	Cefiderocol	2 g Q8H	Documented resistance to empiric therapy	0.5 (S)	46.2	51.5	Clinical success
63, M	*P. aeruginosa*	PNA	Yes	Cefiderocol	No	Cefiderocol	2 g Q8H	History of carbapenem resistant pathogen	0.5 (S)	6.6	6.6	Clinical success
78, F	*P. aeruginosa*	Wound BSI	Yes	TZP	Yes	Cefiderocol	ESRD on HD; 0.75 g Q12H	Documented resistance to empiric therapy	2 (I)	11.1	17.9	Clinical success

Table 1 (continued)

Patient age, years/sex	Organism isolated	Infection type	History of carbapenem resistant organism?[a]	Empiric treatment	Ineffective empiric therapy?[b]	Definitive treatment	Cefiderocol dosing[c]	Reason for cefiderocol use	Cefiderocol MIC[d]	Treatment duration of cefiderocol, d	Total antimicrobial duration, d	Outcome
72, F	*P. aeruginosa*	PNA	Yes	CZA	Yes	Cefiderocol	ESRD CVVH; 1.5 g Q12H	Documented resistance to empiric therapy	1 (S)	5.7	8.1	Infection recurrence, Expired
61, M	*P. aeruginosa*	Wound PNA	Yes	Meropenem	Yes	Cefiderocol, tobramycin	2 g Q8H	Documented resistance to empiric therapy	0.25 (S)	14.4	18.9	Infection recurrence, Expired
92, F	*P. aeruginosa*	PNA	Yes	Meropenem	Yes	Cefiderocol, gentamicin	1 g Q8H	Documented resistance to empiric therapy	0.5 (S)	6.7	14.3	Infection recurrence, Expired
79, F	*P. aeruginosa, K. pneumoniae*	Wound	No	Meropenem	Yes	Cefiderocol	1.5 g Q8H	Documented resistance to empiric therapy	NR	5.3	8.3	Clinical success
32, M	No organism isolated	PNA	No	Levofloxacin	N/a	Cefiderocol	2 g Q8H	Failure of empiric therapy	NR	6.7	13.6	Clinical success
60, F	No organism isolated	PNA	Yes	Cefiderocol	N/a	Cefiderocol	1.5 g Q8H	History of carbapenem resistant pathogen	NR	6.0	6.0	Clinical success

BSI bloodstream infection, *CZA* ceftazidime−avibactam, *DTR* difficult−to−treat resistance, *ESRD* end−stage renal disease, *HD* hemodialysis, *I* intermediate, *IMI/REL* imipenem−cilastatin−relebactam, *LVAD* left ventricular assist device, *MIC* minimum inhibitory concentration, *N/a* not applicable, *NR* not reported, *PNA* pneumonia, *R* resistant, *S* susceptible, *TZP* piperacillin−tazobactam, *UTI* urinary tract infection

[a]History of carbapenem resistant organism in the previous 90 days

[b]Empiric treatment reported as resistant or intermediate upon final susceptibility results

[c]All patients on initiated cefiderocol were dosed appropriately based on renal function

[d]US Food & Drug Administration (FDA) approved susceptibility breakpoints were utilized for Enterobacterales (≤4 mg/L), *P. aeruginosa* (≤1 mg/L), and *A. baumannii* (≤1 mg/L); breakpoints are listed in order according to organism isolated

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Declarations

Conflict of interest All authors declare no conflict of interest.

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Consent to publish All the authors gave consent for the submission and publication of the manuscript.

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