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BRIEF REPORT

Evolution and Transmission of Cefiderocol-Resistant *Acinetobacter baumannii* During an Outbreak in the Burn Intensive Care Unit

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We report on 11 critically ill burn patients treated with cefiderocol for carbapenem-resistant *Acinetobacter baumannii* infections. Clinical success was achieved in 36% and complicated by treatment-emergent resistance and interpatient transmission of cefiderocol-resistant *A. baumannii*. Resistant isolates harbored disrupted *pirA and piuA* genes that were not disrupted among susceptible isolates.

Keywords. cefiderocol; carbapenem-resistant *Acinetobacter baumannii*; burn; antibiotic resistance; whole-genome sequencing.

Carbapenem-resistant *Acinetobacter baumannii* (CRAB) has been identified as an urgent threat accounting for an estimated 8500 cases, 700 deaths, and $281 million in attributable costs each year in the United States [1]. Numerous outbreaks have been reported during the coronavirus disease 2019 (COVID-19) pandemic [2], and mortality rates among those with invasive infections are as high as 52% [3]. Patients with burn injuries are at particularly high risk for CRAB infection due to impairment of host immunity and loss of skin barrier function. Common infection types include skin and soft tissue infections, bacteremia, and pneumonia. Mortality rates following infection in patients with severe burns range from 50% to 75% and increase to 86% when infections are due to multidrug-resistant (MDR) organisms [4].

Carbapenem-resistant *A. baumannii* harbor intrinsic and acquired mechanisms of antibiotic resistance that limit effective treatment [5]. Cefiderocol is a novel siderophore cephalosporin that has demonstrated promising in vitro activity against MDR gram-negative bacteria, including CRAB [6]. By binding to extracellular free iron, cefiderocol is actively transported across the outer cell membrane via iron transporters, circumventing common resistance mechanisms. Clinical data, however, have yielded mixed results. Mortality rates among patients receiving cefiderocol were higher than those who received best-available therapy for carbapenem-resistant, gram-negative infections in a randomized clinical trial; the greatest difference was among those with *Acinetobacter* infections [7]. Thus, the role of cefiderocol in the treatment of CRAB infections remains unclear, reinforcing the need for further real-world evidence. Herein, we report the outcomes of patients treated with cefiderocol for CRAB infections in a burn intensive care unit (BICU) and identify treatment-emergent resistance and interpatient transmission of cefiderocol-resistant CRAB.

METHODS

This study included patients treated with cefiderocol for more than 48 hours during an outbreak of CRAB infections in our BICU between May and December 2020. Types of infection were defined using previously reported criteria [7]. The primary outcome was clinical success, defined as resolution of signs and symptoms of infection without relapse or antibiotic escalation within 30 days. Secondary outcomes included microbiological failure at 90 days and adverse drug events. Microbiological failure was defined as isolation of CRAB 7 or more days after cefiderocol treatment initiation. Relapse was defined as a subsequent CRAB infection requiring treatment for more than 48 hours. The Naranjo algorithm was used to assess the likelihood that an adverse reaction was due to cefiderocol and these were graded using *Common Terminology Criteria for Adverse Events, Version 5* [8, 9].

Cefiderocol minimum inhibitory concentrations (MICs) were determined by broth microdilution in iron-depleted, cation-adjusted Mueller-Hinton broth [10], or by the local microbiology laboratory using disk diffusion methods. *Pseudomonas aeruginosa* American Type Culture Collection (ATCC) 27853 was used for quality control. Susceptibility testing was performed retrospectively on available isolates, and results were not available to clinicians at the onset of CRAB infections.

The first available isolate per patient and sequential isolates demonstrating a 4-fold or greater cefiderocol MIC shift were selected for whole-genome sequencing (WGS). Sequencing was performed on a NextSeq 550 instrument (Illumina, San Diego, CA), as described previously [11]. Raw sequences were assembled using SPAdes v3.14.1 [12]. The chronologically

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earliest isolate (E0278) was used as the reference genome for all subsequent isolates. Core genome single-nucleotide polymorphism (cgSNP) differences between genome pairs were identified using Snippy v4.4.5 (https://github.com/tseemann/snippy). Serial isolates collected from the same patient were compared using breseq [13]. β-Lactamase genes were identified through the Comprehensive Antibiotic Resistance Database (CARD) [14]. Raw sequence reads and draft genome assemblies have been deposited in the National Center for Biotechnology Information (NCBI) database under BioProject PRJNA823680.

RESULTS

Eleven patients were included (Table 1); 45% (5/11) were female and the median age was 39 (range: 18–65) years. The median total body surface area involvement was 61% (31.5–100%). At the onset of infection, median Abbreviated Burn Severity Index (ABSI) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were 11 (8–12) and 24 (13–36), respectively. The infection types were bloodstream infection (n = 5), ventilator-associated pneumonia (VAP; n = 5), and ventilator-associated tracheobronchitis (n = 1). Eighty percent (4/5) of VAP cases were complicated by secondary bacteremia. The median duration of initial cefiderocol treatment was 9 (3–21) days; 27% (3/11) received combination therapy with polymyxin B.

Overall, 30-day clinical success was achieved in 36% of patients (4/11). Initial clinical improvement was documented in 64% (7/11); however, 57% (4/7) had relapsing infections within 90 days (median time to relapse = 15 days [range: 11–56 days]). Among 8 patients who completed an initial treatment course, microbiological failures occurred in 88% (7). No adverse events with a probability greater than possible or a severity greater than grade 2 occurred. Adverse events of grade 1 or 2 severity determined to be possibly related to cefiderocol included hepatic enzyme elevation (n = 2), T-wave abnormality, hypokalemia, skin lesion, and ventricular tachycardia (n = 1 each).

Cefiderocol susceptibility testing was performed on 34 isolates from 10 patients. Baseline isolates collected prior to treatment were available from 6 patients; 33% (2/6) were infected by cefiderocol-susceptible and 67% (4/6) by cefiderocol-resistant CRAB. Among the remaining 4 patients where only post-treatment isolates were available for testing, 50% (2/4) were infected with susceptible isolates and 50% (2/4) with resistant isolates. Over time, cefiderocol-resistant CRAB predominated; 60% (6/10) of patients were infected by cefiderocol-resistant isolates either before or after treatment. Serial isolates from patient 1 demonstrated treatment-emergent resistance to cefiderocol.

Eleven CRAB isolates from 9 patients underwent WGS analysis. All isolates were identified as *A. baumannii* sequence type (ST) 2 as defined by Pasteur Institute scheme and ST208 by Oxford scheme [15], one of the major CRAB clones widely distributed in the United States [16]. cgSNPs ranged from 0 to 5 across isolates, suggesting that each patient was infected with the same clone (Supplementary Table 1). Median cgSNPs between cefiderocol-resistant isolates from different patients were lower (0; range: 0–1) than cgSNPs between cefiderocol-susceptible isolates (1.5; 1–4) and isolates with discordant susceptibilities (2.5; 0–5) (Supplementary Figure 1) (Dunn's test $P < .001$). No cgSNPs were unique to susceptible or resistant isolates (Supplementary Table 2). Each isolate harbored $bla_{\text{OXA-23}}$, $bla_{\text{OXA-66}}$, and $bla_{\text{ADC-73}}$. Isolate E0288 from patient 2 contained a novel substitution in ADC-73 (R148Q) that was associated with a cefiderocol MIC shift from 0.5 to 2 μg/mL following 2 treatment courses. Paired cefiderocol-susceptible and -resistant isolates were collected from patient 1 after an initial treatment course of 10 days; isolate E0278 demonstrated a cefiderocol MIC of 0.5 μg/mL. After 10 additional days of treatment (20 days total), a respiratory isolate E0296 demonstrated a cefiderocol MIC of greater than 32 μg/mL. Compared with E0278, isolate E0296 harbored disrupted *piuA*, a TonB-dependent siderophore receptor gene, and disrupted *pirA*, a ferric enterobactin gene. Further analysis showed that these genes were disrupted in all 6 cefiderocol-resistant isolates analyzed, including among isolates from 4 patients who were not previously treated with cefiderocol, but intact for all 5 cefiderocol-susceptible isolates (Supplementary Table 3). No other mutations were identified in antimicrobial resistance genes.

DISCUSSION

Real-world evidence with cefiderocol is limited, but the available data highlight complex cases with resistant pathogens, including CRAB, *P. aeruginosa*, Enterobacterales, and *Stenotrophomonas maltophilia*. Our case series is unique as it involves critically ill patients with underlying burn injury. Overall, we found a low rate of clinical success with cefiderocol treatment and high rates of recurrent infections. Most importantly, we identified the emergence and likely interpatient transmission of cefiderocol-resistant CRAB within our BICU. All cefiderocol-resistant isolates harbored disruptions in *piuA* and *pirA* that were not seen among cefiderocol-susceptible isolates. These data serve as a caution for the potential of treatment-emergent cefiderocol resistance and argue against using the agent in the absence of susceptibility testing.

Post hoc analysis of isolates from patients in this case series demonstrated high rates of cefiderocol resistance, including evidence of treatment-emergent resistance in the chronologically earliest patient treated. The spatial, temporal, and genomic relationship between these cases suggests that cefiderocol-resistant CRAB was selected for by increasing cefiderocol use on the unit and subsequently transmitted between patients.

Table 1. Description of Burn Intensive Care Unit Carbapenem-Resistant *Acinetobacter baumannii* Infection Cases Treated With Cefiderocol

Patient Number	Age/Sex	TBSA	ABSI	APACHE II Scores	Infection Type(s)	FDC MIC (Cumulative Days of Treatment)[a]	Prior Antibiotic Failure	FDC Regimen (Duration of Treatment, days)	Combination Therapy[b] (Duration of Treatment, days)	RRT (Effluent Flow Rate, L/Hour)	Clinical Success at 30 Days	Microbiologic Failure Within 90 Days (Days After Treatment Initiation)	Hospital Disposition (Days After Treatment Initiation)
1	48/F	50.5%	11	19	BSI	0.5 (10), >32 (20)	Yes	2 g q8h (10)	Polymyxin B (7)	No	Yes	Respiratory colonization (17) Relapse VAP (56)	Discharged (72), Readmit (82)
2	48/M	70%	12	19	BSI	0.5 (12), 2 (20), 2 (26)	No	2 g q6h (12)	No	No	No	Relapse VAP (19)	Discharged (76)
3	18/F	80.5%	12	24	VAP/BSI	-	No	1.5 g q12h (3)[c]	No	CVVHDF (2.5)	No	Indeterminate[d]	Expired (3)
4	19/F	61%	11	22	BSI	0.5 (0)	No	2 g q6h (8)	No	No	Yes	No	Discharged (37)
5	37/M	68.5%	10	27	VAP/BSI	>32 (0), >32 (17)	No	1.5 g q12h (21)[c]	No	CVVHDF (2.5)	No	Indeterminate[d]	Expired (21)
6	65/F	42%	12	13	BSI	1 (0), 0.25 (11)	No	750 mg q12h (11)	No	IHD	Yes	Respiratory colonization (70)	Discharged (182)
7	19/M	42.5%	8	27	VAP	>32 (0), >32 (13)	No	2 g q6h (13)	No	No	No	Respiratory colonization (21)	Discharged (75)
8	57/F	100%[e]	3[f]	36	BSI	>32 (0)	No	1.5 g q8h (9)[c]	Polymyxin B (8)	CVVHDF (4)	No	Indeterminate[d]	Expired (9)
9	62/M	41%	11	24	VAT	>32 (7)	No	2 g q8h (7)	Polymyxin B (7)	No	Yes	Respiratory colonization (16)	Discharged (56)
10	39/M	31.5%	8	17	VAP/BSI	>32 (0), >32 (8)	No	2 g q8h (8)	No	No	No	Relapse BSI (11)	Discharged (46)
11	37/M	71%	12	32	VAP/BSI	R[g] (17), R[g] (22)	No	1.5 g q8h (8)[c]	No	CVVHDF (3.2)	No	Relapse VAT (11)	Discharged (131)

Abbreviations: ABSI, Abbreviated Burn Severity Index; APACHE II, Acute Physiology and Chronic Health Evaluation II; BSI, bloodstream infection; CVVHDF, continuous venovenous hemodiafiltration; F, female; FDC, cefiderocol; IHD, intermittent hemodialysis; M, male; MIC, minimum inhibitory concentration; q6h, every 6 hours; q8h, every 8 hours; q12h, every 12 hours; R, resistant; RRT, renal replacement therapy; TBSA, total body surface area; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis.

[a]MICs from first sample, last sample, and those demonstrating categorical change in interpretation are listed. The total duration of prior cefiderocol exposure at the time of culture collection is in parentheses.

[b]Combination therapy was defined was >48 hours of therapy with confirmed or suspected in vitro activity against the infecting pathogen.

[c]Note that the manufacturer recommendations for dosing in continuous renal replacement therapy were revised during the study period. All patients received dosing consistent with manufacturer recommendations at time of management.

[d]Patient expired prior to completion of therapy.

[e]Steven Johnson syndrome.

[f]ScoreTen scale score (severity of illness score for toxic epidermal necrolysis).

[g]Resistant by Kirby-Bauer disk diffusion testing.

Indeed, isolates from 4 patients demonstrated resistance prior to receiving treatment with cefiderocol. In 1 patient, reduced susceptibility was mediated by a nonsynonymous substitution (R148Q) in ADC-73. This mutation has been identified in ADC-56, an ADC-30 descendant, that resulted in increased cefepime [17] and cefiderocol MICs (unpublished data, Iovleva and Doi, 2020). Among other patients, resistance was most likely due to disruptions in *piuA* and *pirA* genes. Both genes are involved in siderophore transport into the cell and have been reported as mechanisms of cefiderocol resistance in CRAB [5]. Further molecular surveillance and validation studies are needed to confirm the frequency and function of these disruptions, respectively.

Combination therapy was rarely used at our center, which mirrors rates reported in CREDIBLE-CR [7] and other observational studies [18]. This likely reflects an evolving understanding of the optimal use of cefiderocol against CRAB infections. It is not clear if response rates would have differed if combination therapy was used more broadly [19]. It is also unclear if combination therapy may have prevented the emergence of cefiderocol resistance, which evolved in patient 1 despite concomitant polymyxin B for 7 days.

Our data highlight high rates of clinical failure associated with CRAB infections; only 36% of patients experienced clinical success at 30 days. A key factor that likely contributed to poor treatment responses was that treating clinicians were unaware of cefiderocol susceptibility results. Timely antimicrobial susceptibility testing is often unavailable for new agents immediately after Food and Drug Administration approval and many laboratories still lack the ability to test cefiderocol susceptibility in-house. We also found that relapsing CRAB infections were common following treatment. This may be partially attributable to the burn patient population studied who are known to be susceptible to recurrent infections. Accordingly, it is our practice to conduct routine respiratory tract surveillance, which contributed to high rates of microbiologic failure. Adverse events were not clearly attributable to cefiderocol administration and align with those results previously published [7].

Other treatment options for CRAB include ampicillin-sulbactam, minocycline, tigecycline, and the polymyxins [19]. While combination therapy has been suggested by recent guidance, this has not been proven effective in the largest studies conducted to date [3, 20]. Sulbactam-durlobactam (SUL-DUR) is an investigational β-lactam/β-lactamase inhibitor combination uniquely designed to treat CRAB infections. Preliminary unpublished results from the phase 3 ATTACK trial found lower mortality in those treated with SUL-DUR compared with those receiving colistin; however, the full data have not yet been published [21].

In conclusion, our case series found low rates of clinical success with the use of cefiderocol for the treatment of invasive CRAB infections in the BICU. This was likely due to the evolution of cefiderocol resistance and subsequent transmission between patients. Cefiderocol resistance appears to be mediated by disruption of *piuA* and *pirA*. As with the use of all novel antibiotics, timely susceptibility testing and judicious use are essential in optimizing therapy and preserving the longevity of these agents in the clinic.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. S. M. S. has served on an advisory board for Shionogi and reports grants or contracts from Shionogi (sponsor-led chart review research contract, paid to their institution). S. R. was an employee of Cooperman Barnabas Medical Center at the time of this work and is now an employee of Amgen, Inc. R. K. S. has served as a consultant for Allergan, Cidara, Shionogi, Menarini, Melinta, Merck, Entasis, Utility, GlaxoSmithKline, and Venatorx; has received investigator-initiated funding from Merck, Melinta, Shionogi, Roche, and Venatorx; and reports honoraria for educational lectures from Menarini and Pfizer. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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