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Real-World Experience of Cefiderocol in Treating Bacterial Infections in US Hospitals (January 2020–June 2021)

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Purpose

- Cefiderocol is a siderophore cephalosporin that has broad activity against Gramnegative pathogens, including carbapenem-resistant isolates, through its unique mode of cell entry [1].
- It was approved in November 2019 by the US Food and Drug Administration to treat adult patients with complicated urinary tract infection, hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia caused by Gram-negative pathogens such as Acinetobacter baumannii complex, Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Escherichia coli, Enterobacter cloacae complex, and Klebsiella pneumoniae [2].
- This study describes the demographic and clinical characteristics of patients treated with cefiderocol in US hospitals since its approval.

Methods

Study design:

A retrospective study of an existing healthcare database

Data source:

• Since 2012, the Premier Healthcare Database (PHD) has collected anonymized patient-level data for the detailed daily service received during hospitalization from over 1000 geographically diverse non-profit, non-governmental, and community and teaching hospitals and health systems in rural and urban communities in the US [3].

Study population:

• Hospitalized patients who were treated with cefiderocol as part of routine clinical care for ≥3 consecutive days for the first time between January 2020 and June 2021 (overlapping the period of the coronavirus disease 2019 [COVID-19] pandemic) captured by the PHD were included

Study variables:

- Demographic and clinical characteristics, e.g., age, sex, comorbidity, discharge diagnoses, COVID-19 status, intensive care unit stay, and mechanical ventilation.
- Cefiderocol usage, e.g., when it started, treatment days, and number of antibiotics used before initiation.
- For subset of patients with microbiology results, the type of pathogen(s), susceptibility, and culture site associated with cefiderocol use are described.
- Index cultures were the culture(s) taken on the day closest to cefiderocol initiation: either before cefiderocol initiation, or on the day when the first culture was obtained after cefiderocol initiation if no microbiology evaluation was performed prior to cefiderocol use.
- Index pathogens were the Gram-negative pathogens identified from the index culture.
- Carbapenem resistance of the index pathogen was based on the susceptibility test of pathogens against doripenem, imipenem, meropenem, or ertapenem (excluded for A. baumannii and P. aeruginosa). The index pathogen was considered carbapenem resistant if the susceptibility test result was resistant or intermediate.
- Infection sites were based on the site from which positive cultures were taken.
- 14-day and 28-day in-hospital all-cause mortality, defined as any death that occurred during hospitalization within 14 days or 28 days after cefiderocol initiation.

Statistical analysis:

- Descriptive statistics are presented overall and by COVID status:
- Number (%) for categorical variables,
- Mean, standard deviation (SD), median (interquartile range [IQR; Q1–Q3]) for continuous variables.
- Univariate comparisons between non-COVID and COVID patients were conducted using a χ^2 test for categorical variables, a t-test (comparing means) and a Wilcoxon rank sum test (comparing medians) for continuous variables.



COVID-19, coronavirus disease 2019; ICD-10, 10th revision of the International Statistical Classification of Diseases and Related Health Problems; ICF, intermediate care facility; ICU, intensive care unit; Q, quartile; SD, standard deviation; SNF, skilled nursing facility.

aracteristics			
Overall (N=313)	COVID-19 (N=65)	Non-COVID-19 (N=248)	<i>P</i> value (COVID-19
N (%)	N (%)	N (%)	vs. non- COVID-19)
58.1 (15.3) 60 (49–69) 17, 89	59.8 (13.6) 61 (51–69) 21, 84	57.6 (15.7) 59 (47–69) 17, 89	0.31 0.40
122 (39.0%) 191 (61.0%)	24 (36.9%) 41 (63.1%)	98 (39.5%) 150 (60.5%)	0.70
196 (62.6%) 30 (9.6%) 87 (27.8%)	47 (72.3%) 5 (7.7%) 13 (20.0%)	149 (60.1%) 25 (10.1%) 74 (29.8%)	0.19
27 (8.6%) 286 (91.4%)	1 (1.5%) 64 (98.5%)	26 (10.5%) 222 (89.5%)	0.03
4.1 (3.1) 4 (2–6) 0, 15	4.3 (3.2) 4 (2–6) 0, 13	4.1 (3.0) 4 (2–6) 0, 15	0.57 0.63
107 (34.2%) 108 (34.5%) 120 (38.3%) 100 (32.0%) 127 (40.6%)	25 (38.5%) 19 (29.2%) 39 (60.0%) 27 (41.5%) 24 (36.9%)	82 (33.1%) 89 (35.9%) 81 (32.7%) 73 (29.4%) 103 (41.5%)	0.41 0.31 0.00 0.06 0.50
150 (47.9%) 118 (37.7%) 116 (37.1%) 114 (36.4%) 112 (35.6%)	50 (77.0%) 40 (62.0%) 33 (51.0%) 33 (51.0%) 27 (40.9%)	100 (40.0%) 78 (31.0%) 83 (34.0%) 81 (33.0%) 85 (34.1%)	<0.001 <0.001 0.01 0.01 0.31
112 (35.8%) 201 (64.2%)	8 (12.3%) 57 (87.7%)	104 (41.9%) 144 (58.1%)	<0.01
33.1 (38.5) 22 (11–43) 1, 295	31.8 (21.2) 23 (16–45) 3, 109	33.6 (43.6) 20 (9–38.5) 1, 295	0.69 0.06
21.5 (32.5) 11 (5–22) 1, 238	18.4 (13.3) 15 (8–28) 2, 61	22.9 (38.1) 10 (3–21) 1, 238	0.25 0.02
65 (20.8%) 248 (79.2%)	6 (9.2%) 59 (90.8%)	59 (23.8%) 189 (76.2%)	0.01
35.3 (44.0) 22 (9–44) 1, 309	38.2 (31.6) 29 (18–50) 1, 144	34.4 (47.3) 19 (7–41) 1, 309	0.48 0.01
Overall (N=187)	COVID-19 (N=45)	Non-COVID-19 (N=142)	P value (COVID-19 vs. non-
n (70)			COVID-19)
19 (10.2%) 97 (51.9%) 38 (20.3%) 23 (12.3%)	5 (11.1%) 15 (33.3%) 4 (8.9%) 6 (13.3%)	14 (9.9%) 82 (57.8%) 34 (23.9%) 17 (12.0%)	0.81 <0.01 0.03 0.81
137 (73.3%) 20 (10.7%) 30 (16.0%)	18 (40.0%) 12 (26.7%) 15 (22.2%)	119 (83.8%) 8 (5.6%)	<0.01

Table 2 Cefiderocol use

Characteristic	Overall (N=313)	COVID-19 (N=65)	Non-COVID-19 (N=248)	<i>P</i> value (COVID-19
	n (%)	n (%)	n (%)	vs. non- COVID-19)
Days on cefiderocol				
Mean (SD)	10.6 (8.2)	9.3 (6.3)	10.9 (8.6)	0.09
Median (Q1–Q3)	8 (5–14)	7 (5–12)	8 (5–14)	0.13
Minimum, maximum	3, 66	3, 31	3, 66	
3–7 days	131 (41.9%)	34 (52.3%)	97 (39.1%)	
8–14 days	114 (36.4%)	19 (29.2%)	95 (38.3%)	0.16
>14 days	68 (21.7%)	12 (18.5%)	56 (22.6%)	
Total days from cefiderocol initiation	on to discharge			
Mean (SD)	18.3 (17.9)	18.9 (20.7)	18.4 (17.2)	0.86
Median (Q1–Q3)	13 (7–24)	9 (6–25)	14 (8–23)	0.16
Minimum, maximum	3, 130	3, 100	3, 130	
3–7 days	83 (26.5%)	27 (41.5%)	56 (22.6%)	
8–14 days	85 (27.2%)	10 (15.4%)	75 (30.2%)	<0.01
>14 days	145 (46.3%)	28 (43.1%)	117 (47.2%)	
Days from admission to cefideroco	ol initiation			
Mean (SD)	22.1 (34.3)	29.5 (30.7)	20.1 (34.9)	0.05
Median (Q1–Q3)	12 (4–26)	23 (14–30)	8.5 (4–21)	<0.01
Minimum, maximum	1, 274	1, 199	1, 274	
1 day	30 (9.6%)	1 (1.5%)	29 (11.7%)	-0.04
2 days	22 (7.0%)	1 (1.5%)	21 (8.4%)	<0.01
3–7 days	67 (21.4%)	7 (10.8%)	60 (24.2%)	
8–14 days	63 (20.1%)	9 (13.9%)	54 (21.8%)	
>14 days	131 (41.9%)	47 (72.3%)	84 (33.9%)	
Number of Gram-negative antibioti	cs initiated before cefideroo	col initiation		
0	35 (11.2%)	1 (1.5%)	34 (13.7%)	-0.01
1	34 (10.9%)	3 (4.6%)	31 (12.5%)	<0.01
2	37 (11.8%)	3 (4.6%)	34 (13.7%)	
3	53 (16.9%)	11 (16.9%)	42 (16.9%)	
>3	154 (49.2%)	47 (72.3%)	107 (43.2%)	
Number of Gram-negative antibioti	cs initiated within 14 days c	of cefiderocol initiation	1	
0	62 (19.8%)	5 (7.7%)	57 (23.0%)	0.07
1	69 (22.0%)	19 (29.2%)	50 (20.2%)	
2	50 (16.0%)	11 (16.9%)	39 (15.7%)	
3	62 (19.8%)	15 (23.1%)	47 (19.0%)	
>3	70 (22.4%)	15 (23.1%)	55 (22.2%)	

P value from χ^2 , t-test or Wilcoxon rank sum test. COVID-19, coronavirus disease 2019; Q, quartile; SD, standard deviation

Table 3. Hospitalization Outcomes

Characteristic	Overall (N=313)	COVID-19 (N=65)		
	n (%)	n (%)		
Discharge Status				
Death	92 (29.4)	40 (61.5)		
Home	84 (26.8)	3 (4.6)		
Hospice	23 (7.4)	3 (4.6)		
Transfer to other health facilities	113 (36.1)	19 (29.2)		
Other	1 (0.3)	0 (0.0)		
Crude all-cause in-hospital mortality [95% Cl]				
Died within 14 days of	51 (16.3)	28 (43.1)		
initiating cefiderocol	[12.2–20.4%]	[31.0–55.1%]		
Died within 28 days of	74 (23.6)	37 (56.9)		
initiating cefiderocol	[18.9–28.4%]	[44.9–69.0%]		

Data are n (%) unless stated otherwise. CI, confidence interval; COVID-19, coronavirus disease 2019.

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Non-COVID-19

(N=248)

n (%)

52 (21.0)

81 (32.7)

20 (8.1)

94 (37.9)

23 (9.3)

[5.7–12.9%]

37 (14.9)

[10.5–19.4%]

1 (0.4)



Results

- 91% of patients were hospitalized via emergency department, trauma center, or urgent admission; the proportion was higher in COVID-19 patients vs. non-COVID-19 patients (98.5% vs. 89.5%, respectively).
- The most common conditions were severe sepsis with septic shock, palliative care, and multidrug-resistant infection. Also, 34% had a "do not resuscitate" order with 32% in COVID-19 patients vs. 68% in non-COVID-19 patients.
- About 64% of patients received mechanical ventilation and 79% had ICU stay.
- COVID-19 patients were more likely to be mechanically ventilated vs non-COVID-19 patients (88% vs. 58%, respectively), admitted to the ICU (91% vs. 76%, respectively), and stay longer in ICU (**Table 1**).
- Median length of hospital stay was 27 days (range: 3–310 days); this was longer in COVID-19 than non-COVID-19 patients.
- Median duration of cefiderocol treatment was 8 days (range: 3–66 days) (Table 2).
- Over 58% received ≥2 other Gram-negative antibiotics within 14 days of initiating cefiderocol (Table 2).
- The proportion was higher in COVID-19 than non-COVID-19 patients. Also, COVID-19 patients started cefiderocol much later than non-COVID-19 patients (Table 2).
- Median time from hospital admission to cefiderocol initiation was 23 days (IQR: 14–30 days) for COVID-19 patients and 8.5 days (IQR: 4–21 days) for non-COVID-19 patients (**Table 2**).
- Among 187 patients with microbiology results, 75% had index cultures with one pathogen [4], and 73% had confirmed carbapenem-resistant pathogens (**Table 1**). The most common pathogens were *P. aeruginosa*, *S. maltophilia*, *K. pneumoniae*, and *A. baumannii*. The most common index culture site was the respiratory tract[4].
- COVID-19 patients were less likely (than non-COVID-19 patients) to have carbapenem-resistant pathogens (40% vs. 84%, respectively) or non-fermenters (53% vs. 85%, respectively).
- COVID-19 patients were more likely to have a positive respiratory culture than non-COVID-19 patients (71% vs. 57%, respectively).
- The 14-day and 28-day crude in-hospital all-cause mortality after cefiderocol initiation was 16.3% (95% confidence interval [CI]: 12.2–20.4%) and 23.6% (95% CI: 18.9– 28.4%), respectively.
- 28-day in-hospital all-cause mortality was much higher in COVID-19 vs. non-COVID-19 patients: 56.9% vs. 14.9% respectively (Table 3).
- Among patients who died, 83% had severe sepsis with septic shock, 76% were in palliative care, 71% had a "do not resuscitate" order, and 44% had COVID-19.
- Of 40 deaths in COVID-19 patients, 24 were from one hospital during July-September 2020. After reviewing each of 40 cases, the cause of death was not attributed to antibiotic use, although, the role of infection could not be assessed.

Conclusion and Clinical Implications

- During the initial phase of the post-approval period, the most frequent use of cefiderocol was to treat critically ill patients (as shown by the high frequency of ICU stay, mechanical ventilation, and septic shock).
- In-hospital all-cause mortality was comparable with other studies [5,6], but it was impacted by COVID-19 status, especially a cluster of COVID-19 patients in one hospital. The crude in-hospital all-cause mortality rate in COVID-19 patients was almost four-fold higher than for non-COVID-19 patients.

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