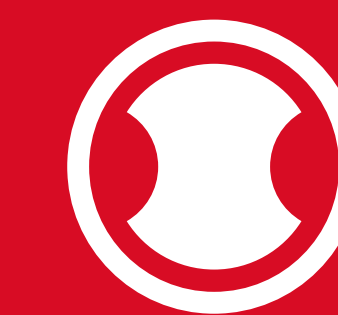# Cefiderocol in Treating Patients Confirmed with Gram-negative Infections in US Hospital During January 2020–Jun 2021

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Purpose

- Cefiderocol is a siderophore cephalosporin that has broad activity against Gram-negative 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 and outcomes of patients with microbiologically confirmed infections during the initial phase of the commercialization of cefiderocol.
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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].
- The present analysis is based on a subset of 442 hospitals that provided microbiology test results for Gram-negative pathogens, including specimen site, pathogen, and drug sensitivity for hospitalized patients from January 2018 to June 2021.

Study population:

- Hospitalized patients with laboratory-confirmed Gram-negative infections in US hospitals treated with cefiderocol consecutively for ≥3 days between March 2020 and June 2021, during the overlapping period of the coronavirus disease 2019 (COVID-19) pandemic, as part of routine clinical care captured by the PHD, were included.
- Index day is the day that is closest to cefiderocol treatment initiation with a positive culture for Gram-negative pathogen(s). The index day could be either before cefiderocol initiation or the day when the first culture was obtained after cefiderocol initiation if no microbiology evaluation was performed prior to cefiderocol use.
- Index cultures were all cultures taken on the index day.
- Index pathogens were the Gram-negative pathogens identified from the index culture(s).
- Carbapenem resistance of the index pathogen was based on the susceptibility test for pathogens against doripenem, imipenem, meropenem, or ertapenem (excluded for *A. baumannii* and *P. aeruginosa*). The pathogen was deemed carbapenem resistant if the susceptibility test result was resistant or intermediate.
- Infection sites were based on the sites from which positive cultures were taken.
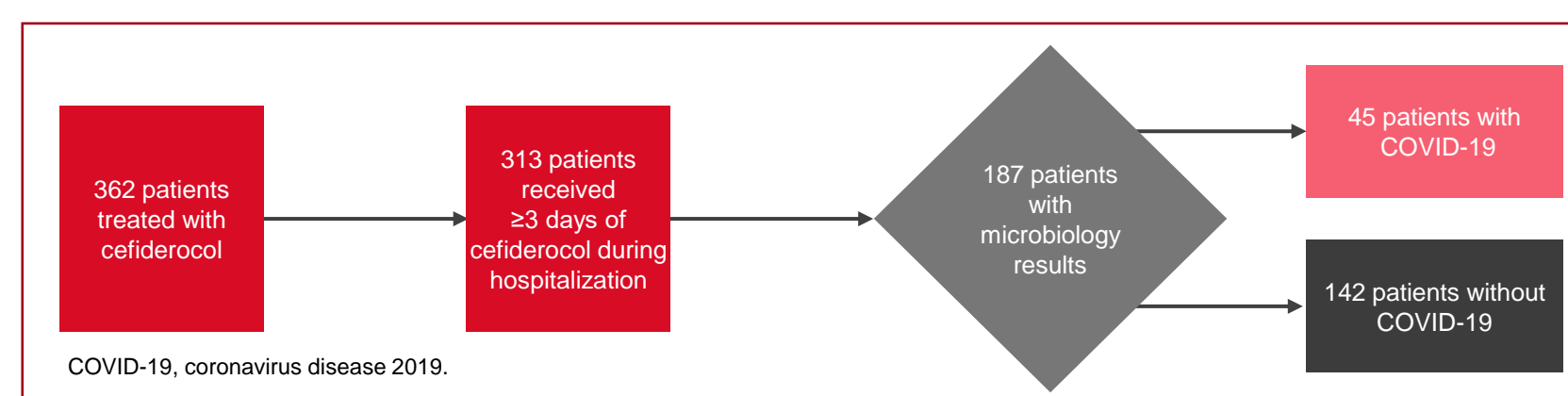
Study variables:

- Demographic and clinical characteristics, e.g., age, sex, comorbidity, 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.
- Microbiology profiles, e.g., type of pathogen(s), carbapenem resistance status, and culture site.
- 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.

Table 1. Patient demographics and clinical characteristics

Characteristic	Overall (N=187) n (%)	COVID-19 (N=45) n (%)	Non-COVID-19 (N=142) n (%)	P value (COVID-19 vs. non-COVID-19)
Race				
White	138 (73.8)	36 (80.0)	102 (71.8)	0.08
Black	22 (11.8)	2 (4.4)	20 (14.1)	
Other	8 (4.3)	4 (8.9)	4 (2.8)	
Unable to determine	19 (10.2)	3 (6.7)	16 (11.3)	
Age (years)				
Mean (SD)	58.6 (15.3)	60.9 (13.4)	57.9 (15.8)	0.25
Median (Q1–Q3)	60 (48–70)	62 (51–70)	58.5 (47–69)	0.30
Minimum, maximum	21, 89	21.0, 84	22.0, 89	
Sex				
Female	76 (40.6)	21 (46.7)	55 (38.7)	0.35
Male	111 (59.4)	24 (53.3)	87 (61.3)	
Admission source				
Nonhealthcare facility point of origin (Home)	110 (58.8)	32 (71.1)	78 (54.9)	0.16
Transfer from SNF or ICF	25 (13.4)	4 (8.9)	21 (14.8)	
Transfer from hospital or different facility	52 (27.8)	9 (20.0)	43 (30.3)	
Admission type				
Scheduled admission (elective)	14 (7.5)	1 (2.2)	13 (9.2)	0.03
Emergency, Trauma Center, or Urgent	173 (92.5)	44 (97.8)	129 (90.9)	
Charlson Comorbidity Score				
Mean (SD)	3.9 (3.1)	4.1 (3.0)	3.9 (3.1)	0.63
Median (Q1–Q3)	3 (1–6)	4 (2–6)	3 (1–6)	0.54
Minimum, maximum	0, 15	0, 12	0, 15	
Receipt of mechanical ventilation during hospitalization				
Yes	118 (63.1)	41 (91.1)	77 (54.2)	<0.01
No	69 (36.9)	4 (8.9)	65 (45.8)	
ICU stay during the hospitalization				
Yes	147 (78.6)	41 (91.1)	106 (74.7)	0.02
No	40 (21.4)	4 (8.9)	36 (25.4)	
Number of Gram-negative antibiotics initiated before cefiderocol initiation				
0	18 (9.6)	1 (2.2)	17 (12.0)	<0.01
1	26 (13.9)	2 (4.4)	24 (16.9)	
2	26 (13.9)	2 (4.4)	24 (16.9)	
3	31 (16.6)	9 (20.0)	22 (15.5)	
>3	86 (46.0)	31 (68.9)	55 (38.7)	
Days from admission to cefiderocol initiation				
Mean (SD)	19.3 (31.5)	22.9 (16.4)	18.1 (34.9)	0.21
Median (Q1–Q3)	11 (4–23)	22 (14–27)	8 (4–18)	0.00
Minimum, maximum	1, 274	1, 92	1, 274	
Days on cefiderocol				
Mean (SD)	11.0 (8.8)	8.8 (5.8)	11.7 (9.5)	0.02
Median (Q1–Q3)	8 (5–14)	6 (5–10)	9.5 (6–15)	0.04
Minimum, maximum	3, 66	3, 24	3, 66	

P value from χ², t-test, or Wilcoxon rank sum test. Data are n (%) unless stated otherwise.
COVID-19, coronavirus disease 2019; ICF, intermediate care facility; ICU, intensive care unit; Q, quartile; SD, standard deviation; SNF, skilled nursing facility.

Figure 1. Patient Attrition

362 patients treated with cefiderocol → 313 patients received ≥3 days of cefiderocol during hospitalization → 187 patients with microbiology results → 45 patients with COVID-19 / 142 patients without COVID-19

COVID-19, coronavirus disease 2019.

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.

Table 2. Profile of Gram-negative pathogens treated with cefiderocol

Gram-negative pathogen from index culture	Overall (N=187) n (%)	COVID-19 (N=45) n (%)	Non-COVID-19 (N=142) n (%)	P value (COVID-19 vs. non-COVID-19)
Patients with selected index pathogens (polymicrobial infection will be counted in each case)				
Any *Acinetobacter baumannii*	19 (10.2)	5 (11.1)	14 (9.9)	0.81
Any *Pseudomonas aeruginosa*	97 (51.9)	15 (33.3)	82 (57.8)	<0.01
Any *Stenotrophomonas maltophilia*	38 (20.3)	4 (8.9)	34 (23.9)	0.03
Any *Klebsiella pneumoniae*	23 (12.3)	6 (13.3)	17 (12.0)	0.81
Non-fermenters	145 (77.5)	24 (53.3)	121 (85.2)	<0.01
Carbapenem resistance status				
Any carbapenem resistance	137 (73.3%)	18 (40.0%)	119 (83.8%)	<0.01
Carbapenem susceptible only	20 (10.7%)	12 (26.7%)	8 (5.6%)	
Not available	30 (16.0%)	15 (33.3%)	15 (10.6%)	
Number of pathogens from the index culture(s)				
1 pathogen	140 (74.9)	35 (77.8)	105 (73.9)	0.65
2 pathogens	36 (19.3)	9 (20.0)	27 (19.0)	
3 pathogens	8 (4.3)	1 (2.2)	7 (4.9)	
4 pathogens	3 (1.6)	0 (0.0)	3 (2.1)	
Site of index culture				
Any blood	24 (12.8)	7 (15.6)	17 (12.0)	0.53
Blood only	18 (9.6)	5 (11.1)	13 (9.2)	0.70
Any respiratory	113 (60.4)	32 (71.1)	81 (57.0)	0.09
Respiratory only	101 (54.0)	29 (64.4)	72 (50.7)	0.11
Any urinary	24 (12.8)	4 (8.9)	20 (14.1)	0.36
Urinary only	17 (9.1)	3 (6.7)	14 (9.9)	0.52
Any wound	19 (10.2)	1 (2.2)	18 (12.7)	0.04
Wound only	10 (5.3)	1 (2.2)	9 (6.3)	0.30
Any other sites	27 (14.4)	4 (8.9)	23 (16.2)	0.22
Other sites only	24 (12.8)	4 (8.9)	20 (14.1)	0.36
Number of culture sites				
1 site	170 (90.9)	42 (93.3)	128 (90.1)	0.59
2 sites	14 (7.5)	3 (6.7)	11 (7.8)	
3 sites	3 (1.6)	0 (0.0)	3 (2.1)	
Number of pathogens and number of culture sites				
1 pathogen 1 site	136 (72.7)	35 (77.8)	101 (71.1)	0.93
1 pathogen 2 sites	3 (1.6)	0 (0.0)	3 (2.1)	
1 pathogen 3 sites	1 (0.5)	0 (0.0)	1 (0.7)	
2 pathogens 1 site	27 (14.4)	6 (13.3)	21 (14.8)	
2 pathogens 2 sites	8 (4.3)	3 (6.7)	5 (3.5)	
2 pathogens 3 sites	1 (0.5)	0 (0.0)	1 (0.7)	
3 pathogens 1 site	6 (3.2)	1 (2.2)	5 (3.5)	
3 pathogens 2 sites	2 (1.1)	0 (0.0)	2 (1.4)	
3 pathogens 3 sites	1 (0.5)	0 (0.0)	1 (0.7)	
4 pathogens 1 site	1 (0.5)	0 (0.0)	1 (0.7)	
4 pathogens 2 sites	1 (0.5)	0 (0.0)	1 (0.7)	

P value from χ². Data are n (%).
COVID-19, coronavirus disease 2019.

Results

- Among 187 patients with microbiology results (**Figure 1**), the median age was 60 years (**Table 1**).
- The most frequent pathogens from the index cultures were *P. aeruginosa*, *S. maltophilia*, *K. pneumoniae*, and *A. baumannii* (**Table 2**).
  - Nearly 75% of patients had one index pathogen.
  - 91% were collected from one culture site.
  - Almost 30% of patients had either one pathogen identified in multiple culture sites, or multiple pathogens from ≥1 culture site.
- Overall crude 28-day in-hospital all-cause mortality for patients was 23.5% with 95% confidence interval (CI) of 17.4–29.5%. In-hospital all-cause mortality was as follows (**Table 3**):
  - Any *A. baumannii*: 8.3% (95% CI: 0–19.4%).
  - Any *P. aeruginosa*: 17.3% (95% CI: 9.9–24.8%).
  - Any *S. maltophilia*: 18.4% (95% CI: 6.1–30.7%).
  - Any *K. pneumoniae*: 26.1% (95% CI: 8.1–44.0%).
- In-hospital all-cause mortality was markedly impacted by COVID-19 status.
  - Non-COVID-19 patients: 11.3% (95% CI: 6.1–16.5%).
  - COVID-19 patients: 62.2% (95% CI: 48.1–76.4%).
  - The difference remained the same for patients with bloodstream infection and respiratory tract infection.

Table 3. Hospitalization Outcomes

Characteristic	Overall Row total, N	Overall %	14-day all-cause in-hospital mortality n	14-day all-cause in-hospital mortality % row total (95% CI)	28-day all-cause in-hospital mortality n	28-day all-cause in-hospital mortality % row total (95% CI)
Overall	187	100	32	17.1 (11.7–22.5)	44	23.5 (17.4–29.6)
Time from admission to first Gram-negative culture						
≤2 weeks	158	84.5	18	11.4 (6.4–16.4)	29	18.4 (12.3–24.4)
>2 weeks	29	15.5	14	48.3 (30.1–66.5)	15	51.7 (33.5–69.9)
Time from admission to index culture						
≤2 weeks	127	67.9	11	8.7 (2.8–11.3)	18	14.2 (6.1–16.5)
>2 weeks	60	32.1	21	35.0	26	43.3
Time from first positive culture to first cefiderocol dose						
≤2 weeks	143	76.5	22	15.4 (9.9–24.8)	29	20.3 (11.6–55.1)
>2 weeks	44	23.5	10	22.7 (7.1–48.5)	15	34.1 (19.9–37.5)
Time from index culture to first cefiderocol dose						
≤2 weeks	184	98.4	32	17.4	44	23.9
>2 weeks	3	1.6	0	0.0	0	0.0
COVID-19 status						
No	142	75.9	10	7.0 (2.8–11.3)	16	11.3 (6.1–16.5)
Yes	45	24.1	22	48.9 (34.3–63.5)	28	62.2 (48.1–76.4)
Site of index culture						
Blood	18	9.6	5	27.8 (7.1–48.5)	6	33.3 (11.6–55.1)
Respiratory	101	54.0	23	22.8 (14.6–31.0)	29	28.7 (19.9–37.5)
Index pathogen						
Any *A. baumannii*	24	12.8	1	4.2 (0.0–12.2)	2	8.3 (0.0–19.4)
Any *P. aeruginosa*	98	52.4	10	10.2 (4.2–16.2)	17	17.3 (9.9–24.8)
Any *S. maltophilia*	38	20.3	6	15.8 (4.2–27.4)	7	18.4 (6.1–30.7)
Any *K. pneumoniae*	23	12.3	3	13.0 (0.0–26.8)	6	26.1 (8.1–44.0)
Site of index culture among patients without COVID-19						
Blood	13	9.2	2	15.4 (0.0–35.0)	2	15.4 (0.0–35.0)
Respiratory	72	50.7	7	9.7 (2.9–16.6)	9	12.5 (4.9–20.1)
Site of index culture among patients with COVID-19						
Blood	5	11.1	3	60% (17.1–100.0)	4	80% (44.9–100.0)
Respiratory	29	64.4	16	55.2% (37.1–73.3)	20	69.0% (52.1–85.8)

CI, confidence interval; COVID-19, coronavirus disease 2019.

Conclusion and Clinical Implications

- During the initial phase post approval, cefiderocol was most frequently used to treat critically ill patients (as shown by the high proportion of patients admitted to the ICU and/or receiving mechanical ventilation) with non-fermenters, and most frequently for respiratory tract infections.
- In-hospital all-cause mortality was comparable with other studies [4–6], and appears to be affected by infection characteristics, especially COVID-19 status.

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