J Antimicrob Chemother 2023; **78**: 2752–2761
https://doi.org/10.1093/jac/dkad298 Advance Access publication 9 October 2023

Journal of Antimicrobial Chemotherapy

Cefiderocol use for the treatment of infections by carbapenem-resistant Gram-negative bacteria: an Italian multicentre real-life experience

Matteo Piccica[1]*, Michele Spinicci[1,2], Annarita Botta[3], Vincenzo Bianco[3], Filippo Lagi[2], Lucia Graziani[1], Alessandro Faragona[4], Roberto Parrella[3], Tommaso Giani[1,5], Andrea Bartolini[1], Gianluca Morroni[6], Mariano Bernardo[7], Gian Maria Rossolini[1,5], Marcello Tavio[8], Andrea Giacometti[4,6] and Alessandro Bartoloni[1,2]

[1]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; [2]Infectious and Tropical Diseases Unit, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; [3]Department of Infectious Disease and Infectious Emergencies, AORN dei Colli, Cotugno Hospital, Naples, Italy; [4]Department of Biomedical Sciences and Public Health, Università Politecnica delle Marche, Ancona, Italy; [5]Clinical Microbiology and Virology Unit, Florence Careggi University Hospital, Florence, Italy; [6]Clinic of Infectious Diseases, Azienda Ospedaliero-Universitaria delle Marche, Ancona, Italy; [7]Microbiology Unit, AORN Ospedali dei Colli-Monaldi Hospital, Naples, Italy; [8]Unit of Emerging and Immunosuppressed Infectious Diseases, Department of Gastroenterology and Transplantation, Azienda Ospedaliero-Universitaria 'Ospedali Riuniti', Ancona, Italy

*Corresponding author. E-mail: piccicamatteo@gmail.com

Received 2 July 2023; accepted 14 September 2023

Background: Cefiderocol is a novel siderophore cephalosporin with promising activity against most carbapenem-resistant Gram-negative bacteria (CRGNB). However, extensive postmarketing experiences are lacking. This study aimed to analyse the early experience on cefiderocol postmarketing use at three tertiary care hospitals in Italy.

Methods: We retrospectively included patients with infections caused by CRGNB treated with cefiderocol at three Italian tertiary care hospitals from 1 March 2021 to 30 June 2022. A multivariate Cox model was used to identify predictors of 30 day mortality. A propensity score (PS) analysis with inverse probability weighting (IPW) was also performed to compare the treatment effect of cefiderocol monotherapy (CM) versus combination regimens (CCRs).

Results: The cohort included 142 patients (72% male, median age 67 years, with 89 cases of *Acinetobacter baumannii* infection, 22 cases of *Klebsiella pneumoniae*, 27 cases of *Pseudomonas aeruginosa* and 4 of other pathogens). The 30 day all-cause mortality was 37% (52/142). We found no association between bacterial species and mortality. In multivariate analysis, a Charlson Comorbidity Index >3 was an independent predictor of mortality (HR 5.02, 95% CI 2.37–10.66, $P<0.001$). In contrast, polymicrobial infection (HR 0.41, 95% CI 0.21–0.82, $P<0.05$) was associated with lower mortality. There was no significant difference in mortality between patients receiving CM ($n=70$) and those receiving a CCR ($n=72$) (33% versus 40%, respectively), even when adjusted for IPW-PS (HR 1.11, 95% CI 0.63–1.96, $P=0.71$).

Conclusions: Real-life data confirm that cefiderocol is a promising option against carbapenem-resistant Gram-negative infections, even as monotherapy.

Introduction

The last decades have been characterized by an increasing prevalence of MDR Gram-negative pathogens and related infections. The emergence of numerous drug-resistant pathogens, such as MBL producers, represents an additional challenge in this scenario. Therefore, new antibiotics active against carbapenemase-producing microorganisms are urgently warranted.[1]

Cefiderocol is a novel siderophore cephalosporin with a unique mechanism of uptake into the bacterial cell; it is also relatively stable to most β-lactamases including serine- and metallo-carbapenemases. *In vitro* studies have shown excellent

activity against carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Acinetobacter* spp. (CRAB) and difficult-to-treat resistant (DTR) *Pseudomonas aeruginosa*.[2] Notably, cefiderocol maintains activity against several strains producing the most prevalent types of MBLs, such as New-Delhi MBL (NDM), imipenemase (IMP) and Verona integron-encoded MBL (VIM).[3]

However, information on the clinical use of cefiderocol in the treatment of MDR infections is limited so far. The randomized clinical trials leading to US FDA approval of the drug for complicated urinary tract infections (cUTIs) and pneumonias were APEKS-cUTI[4] and APEKS-NP,[5] respectively. The main limitation of both studies was that they were not focused on MDR pathogens. In Europe, the open-label CREDIBLE-CR study overcome this limitation, showing that cefiderocol had clinical and microbiological efficacy similar to best available therapy against infections caused by carbapenem-resistant Gram-negative bacteria.[6]

At the time of writing this manuscript, consistent real-life experiences of cefiderocol use are increasing but are still limited.[7–10] This study aimed to describe the early experience on cefiderocol post-marketing use at three tertiary care hospitals in Italy, to analyse the predictors of 30 day mortality among patients treated with cefiderocol due to infection with MDR pathogens, and to assess whether the use of cefiderocol-based combinations was associated with different outcomes compared with cefiderocol monotherapy.

Methods

Study population

The study retrospectively involved patients treated with cefiderocol at three Italian tertiary care hospitals [Azienda Ospedaliero-Universitaria Careggi (AOU-C), Firenze; Ospedali Riuniti, Ancona; Ospedale Cotugno, Napoli] from 1 March 2021 to 30 June 2022.

Eligibility criteria for enrollment in the analysis were: (i) age ≥18 years; (ii) microbiologically documented infections caused by Gram-negative MDR and DTR pathogens, including CRE, CRAB and DTR *P. aeruginosa*; and (iii) treatment with cefiderocol for ≥3 days (either monotherapy or combination therapy).

Exclusion criteria were: (i) death in the first 48 h; and (ii) empirical treatment with cefiderocol without infection with carbapenem-resistant pathogens, including CRE, CRAB and DTR *P. aeruginosa*, documented by positive cultures.

Cefiderocol treatment and outcome

Cefiderocol was administered to all patients with normal renal function at a dose of 2 g every 8 h; patients with impaired renal function received a dose adjusted according to the manufacturer's indications.[11] We defined 'combination therapy' as a regimen containing cefiderocol and at least one other antibiotic active against the involved pathogen or with potential synergistic activity *in vivo* (e.g. sulbactam or fosfomycin). The combination was considered valid if prolonged for ≥48 h.

Data were collected for the whole hospital stay and all patients were followed up until hospital discharge or death. Survival at Day 30 was assessed for all patients discharged before Day 30 from the beginning of cefiderocol treatment.

The primary outcome was 30 day mortality. Secondary outcomes were: microbiological cure, length of in-hospital stay and presence of major clinical events during the hospitalization [septic shock, acute kidney injury (AKI), acute respiratory distress syndrome (ARDS)]. Microbiological cure was defined as negative culture from the index specimen repeated after ≥72 h from the beginning of cefiderocol.

Data collection and variables

Demographic, clinical, laboratory, microbiological, treatment and outcome information were captured by reviewing medical records in each centre. Data were recorded in a secure electronic sheet and sent to the Coordinating Center for analysis.

Baseline patient's condition included the most important comorbidities and the Charlson Comorbidity Index (CCI).[12] Disease severity at presentation was assessed through APACHE-II score[13] and MEWS-2 score.[14]

Infections were classified into bloodstream infections (BSIs), in the presence of positive blood cultures for a carbapenem-resistant pathogen, and non-BSIs, in patients with one or more positive cultures from specimens other than blood (sputum, bronchoalveolar aspirate or lavage, urine, intra-abdominal fluids, biopsies) and consistent clinical and/or radiological signs of infection.

Microbiology

All isolates were identified by MALDI-TOF MS (MALDI-TOF Biotyper; Bruker Daltonics GmbH, Leipzig, Germany). When performed (61/142), susceptibility to cefiderocol was assessed through broth microdilution (BMD) using iron-depleted cation-adjusted Mueller–Hinton broth at AOU-C or disc diffusion (cefiderocol disc at 30 mg; Liofilchem, Roseto degli Abruzzi, Italy) at Cotugno Hospital and Ospedali Riuniti following EUCAST guidelines for Enterobacterales and *P. aeruginosa*. Breakpoints, when available, were considered according to EUCAST breakpoint tables.[15]

The presence of carbapenemase genes among Enterobacterales and *P. aeruginosa* isolates was investigated by immunochromatographic assay (Resist5, Coris Bioconcept, Belgium) or Xpert Carba-R assay (Cepheid, Sunnyvale, CA, USA), according to local standard procedures.

Concerning the definition of susceptibility to cefiderocol of *Acinetobacter baumannii* we considered resistant all isolates with MIC above 2 mg/L as for Enterobacterales (pharmacokinetic-pharmacodynamic breakpoints).

Statistical analysis

A convenience sample, including all patients meeting eligibility criteria in the three recruiting sites during the study period, was used. Continuous variables are expressed as medians and IQRs; categorical variables are expressed as percentages of the group to which they belong. The Mann–Whitney U test was used to compare non-normally distributed continuous variables; the Kruskal–Wallis test was used in case of comparison of three or more groups. Categorical variables were evaluated by the two-tailed Fisher exact test. The variables emerging from the univariate analysis with P values <0.05 were included in a multivariate Cox model; moreover, all possible confounders were tested with the likelihood ratio, and the final goodness of fit of the model was tested through the Hosmer–Lemeshow test. The Kaplan–Meier estimator was used for survival analysis, and the log-rank test for survival comparison. For each patient, we calculated the propensity score (PS) to receive a combination regimen. The covariates included to create the PS were chosen according to all potential risk factors for negative outcome that emerged from our analysis. A PS weighting was then performed using inverse probability of treatment weighting (IPTW) to estimate the average treatment effect of cefiderocol combination therapy versus cefiderocol monotherapy. The multivariate Cox model was performed on the weighted population to compare the outcome between the two treatment groups, and the HR with 95% CI was reported.

Table 1. Characteristics of survivors and deceased patients treated with cefiderocol

Variable	SurvivorsCSBARLINE (*N* = 90)	DeceasedCSBARLINE (*N* = 52)	*P* value
Age, median (IQR), years	65 (51–73)	68 (59–78)	0.06
Males, ***N*** (%)	68 (75.6)	35 (67.3)	0.33
Ward category, ***N*** (%)			
ICU	43 (47.8)	36 (69.2)	**<0.05**
Medical ward	33 (36.7)	15 (28.9)	
Surgical ward	14 (15.6)	1 (1.9)	
Hospital, ***N*** (%)			
AOU-C	38 (42.2)	19 (36.5)	0.44
Ospedali Riuniti di Ancona	43 (47.8)	24 (46.2)	
Ospedale Cotugno	9 (10)	9 (17.3)	
Underlying condition, ***N*** (%)			
Diabetes	16 (17.8)	20 (38.5)	**<0.05**
Heart failure	10 (11.1)	14 (26.9)	**<0.05**
COPD	15 (16.7)	11 (21.2)	0.51
Coronary heart disease	10 (11.1)	10 (19.2)	0.21
Chronic renal failure	10 (11.1)	14 (26.9)	**<0.05**
Cerebrovascular disease	13 (14.4)	11 (21.2)	0.4
Neoplasm			
Localized neoplasm	8 (8.9)	9 (17.3)	0.16
Metastatic neoplasm	6 (6.7)	6 (11.5)	
Obesity (missing 51)	11 (19.6)	9 (25.7)	0.6
Smoking (missing 64)			
Smoker	19 (41.3)	9 (28.1)	0.53
Former smoker	13 (28.3)	11 (34.4)	
Charlson Comorbidity Index, median (IQR)	3 (2–6)	6 (4–8)	**<0.001**
MEWS score, median (IQR)	2 (0–4)	3 (2–5)	**<0.05**
APACHE-II, median (IQR)	13 (8–18)	19 (14–25)	**<0.001**
Reason for hospidalization, ***N*** (%)			
Infection	14 (15.6)	12 (23.1)	0.12
Trauma	16 (17.8)	3 (5.8)	
COVID-19	21 (23.3)	9 (17.3)	
Respiratory failure	2 (2.2)	3 (5.8)	
Cardiovascular diseases	13 (14.4)	6 (11.5)	
Hepatic diseases	4 (4.4)	2 (3.9)	
Surgical intervention	14 (15.6)	7 (13.5)	
Others	6 (6.7)	10 (19.2)	
Type of infection, ***N*** (%)			
Bacteraemia	14 (15.6)	5 (9.6)	0.5
UTI	8 (8.9)	4 (7.7)	
IAI	9 (10)	4 (7.7)	
Pneumonia	46 (51.1)	35 (67.3)	
ABSSSI	6 (6.7)	3 (5.8)	
Others	7 (7.8)	1 (1.9)	
Positive blood cultures, *n* (%)	31 (34.4)	14 (26.9)	0.45
Resistance to cefiderocol,[a] *n* (%)	12 (32)	5 (20)	0.39
Type of bacterium, *n* (%)			
A. baumannii	56 (62.2)	33 (63.5)	
K. pneumoniae	13 (14.4)	9 (17.3)	
P. aeruginosa	19 (21.1)	8 (15.4)	0.76
Others	2 (2.2)	2 (3.9)	

Continued

Table 1. *Continued*

Variable	SurvivorsCSBARLINE (*N* = 90)	DeceasedCSBARLINE (*N* = 52)	*P* value
Coinfection, ***N*** (%)			
Overall	62 (68.9)	32 (61.5)	0.46
Gram-negative	16 (25.8)	11 (34.4)	<0.05
Gram-positive	23 (37.1)	8 (25)	
Mixed	14 (22.6)	2 (6.3)	
Fungal	9 (14.5)	11 (34.4)	
Therapy, ***N*** (%)			
>10 days of antibiotic treatment before cefiderocol[b]	26 (36.6)	21 (52.5)	0.11
>10 days of cefiderocol treatment	49 (54.4)	22 (42.3)	0.22
Combination therapy	43 (47.8)	29 (55.8)	0.39
One other active antimicrobial	36 (43.4)	27 (54)	0.28
Two other active antimicrobials	7 (7.8)	2 (3.9)	0.49
Outcomes			
In-hospital stay, days, median (IQR)	54 (30–81)	32 (22–50)	**<0.001**
Microbiological cure,[c] ***N*** (%)	35 (54.7)	10 (35.7)	0.12
Major events,[d] ***N*** (%)			
ARDS	43 (47.8)	46 (88.5)	**<0.001**
AKI	24 (26.7)	30 (57.7)	**<0.001**
Septic shock	30 (33.3)	40 (76.9)	**<0.001**

Numbers in bold are statistically significant.

[a]Susceptibility testing for cefiderocol was performed in only 28 isolates of *A. baumannii* (31.5%), 16 cases of *K. pneumoniae* (72.7%) and 16 isolates of *P. aeruginosa* (59.2%).

[b]Regardless of the antibiotics used.

[c]Microbiological cure available on 92/142 patients who had follow-up cultures available.

[d]After entering the observation period.

Ethics

Local Ethics Committees (registry number 23248) approved the data collection. Informed consent for medical record consultation was obtained from each patient. The study was conducted in agreement with the ethical principles of the Declaration of Helsinki.

Results

Population characteristics

Patients treated with cefiderocol during the study period in the three sites numbered 189. Among them, 142 adults (72.5% males) with a median age of 66 years (IQR 54–75), met the inclusion criteria (see Figure S1, available as Supplementary data at *JAC* Online). More than half of the cases received cefiderocol in the ICU (55.6%). Concerning pre-existing comorbidities, 57% of patients had a CCI >3, with a median value of 4 (IQR 2–7).

About one-third of patients (*n* = 45, 31.7%) had a positive blood culture, associated with cUTI (7%), lower respiratory tract infections (LRTIs, 38%), intra-abdominal infections (IAIs, 4%) or acute bacterial skin and skin structure infections (ABSSSIs, 9%). ABSSSIs (*n* = 9) included four traumatic wound infections, two cases of cellulitis and three post-surgical wounds. The remaining cases with positive blood culture (42%) were classified as primary bloodstream infections and included 11 who were likely central line related (58%). In the other two-thirds of cases (*n* = 97, 68%), MDR pathogens were obtained from respiratory specimens (*n* = 78, 58%), abscess drainage (*n* = 10, 7%), urine culture (*n* = 11, 8%) or tissue biopsy (*n* = 13, 9%). Complete demographic and clinical information is given in Table 1.

The most common pathogen observed was *A. baumannii* (*n* = 89, 63%) followed by *P. aeruginosa* (*n* = 27, 19%) and *Klebsiella pneumoniae* (*n* = 22, 16%). Four cases were caused by *Escherichia coli* (*n* = 2), *Enterobacter cloacae* (*n* = 1) and *Stenotrophomonas maltophilia* (*n* = 1). The presence of carbapenemase genes was detected in all isolates of *K. pneumoniae* (*n* = 10 KPC, 9 NDM, 3 VIM) and *E. coli* (*n* = 1 NDM, 1 VIM), and in 9/27 of *P. aeruginosa* (*n* = 8 VIM, 1 KPC). In two cases, co-expression of VIM and KPC was observed.

In 66% of cases there was a coinfection supported by other Gram-negative (29%), Gram-positive (32%), both Gram-negative and Gram-positive (17%), and fungal (21%) pathogens.

Treatment and outcomes

More than 40% of cases received >10 days of different therapy during their hospital stay before diagnosis of the index infection. The median duration of treatment with cefiderocol was 11 days (IQR 7–14 days). In 69% of cases cefiderocol was started within 4 days from culture sampling, and in 88% of cases within 7 days. About half of the cases were managed with a

Table 2. Subgroups of patients treated with cefiderocol monotherapy versus cefiderocol combination therapy

Variable	Total (*N* = 142)	Monotherapy (*N* = 70)	Combination therapy (*N* = 72)	*P* value
Age, median (IQR), years	66.5 (54–75)	66 (57–73)	67 (50–76)	0.96
Males, *n* (%)	103 (72.5)	54 (77.1)	49 (68.1)	0.26
Ward category, *n* (%)				
ICU	79 (55.6)	38 (54.3)	41 (56.9)	0.88
Medical ward	48 (33.8)	25 (35.7)	23 (31.9)	
Surgical ward	15 (10.6)	7 (10)	8 (11.1)	
Hospital, *n* (%)				
AOU-C	57 (40.1)	22 (31.4)	35 (48.6)	**<0.05**
Ospedali Riuniti di Ancona	67 (47.2)	35 (50)	32 (44.4)	
Ospedale Cotugno	18 (12.7)	13 (18.6)	5 (6.9)	
Underlying condition, *n* (%)				
Diabetes	36 (25.3)	15 (21.4)	21 (29.2)	0.34
Heart failure	24 (16.9)	10 (14.3)	14 (19.4)	0.5
COPD	26 (18.3)	9 (12.9)	17 (23.6)	0.13
Coronary heart disease	20 (14.1)	7 (10)	13 (18.1)	0.23
Chronic renal failure	24 (16.9)	9 (12.9)	15 (20.8)	0.23
Cerebrovascular disease	24 (16.9)	12 (17.1)	12 (16.7)	1
Neoplasm				
Localized neoplasm	17 (12)	14 (20)	3 (4.2)	**<0.05**
Metastatic neoplasm	12 (8.5)	6 (8.6)	6 (8.3)	
Obesity (missing 51)	20 (22)	7 (14.9)	13 (29.6)	0.13
Smoking (missing 64)				
Smoker	28 (35.9)	15 (39.5)	13 (32.5)	0.44
Former smoker	24 (30.8)	9 (23.7)	15 (37.5)	
Charlson Comorbidity Index, median (IQR)	4 (2–7)	4 (3–7)	4 (2–7)	0.79
MEWS score, median (IQR)	2 (1–4)	2 (1–4)	5 (2–6)	0.71
APACHE-II, median (IQR)	16 (10–20)	16 (9–20)	16 (11–20)	0.92
Reason for hospitalization, *n* (%)				
Infection	26 (18.3)	16 (22.9)	10 (14.4)	0.87
Trauma	19 (13.4)	8 (11.4)	11 (15.3)	
COVID-19	30 (21.1)	15 (21.4)	15 (20.8)	
Respiratory failure	5 (3.5)	2 (2.9)	3 (4.2)	
Cardiovascular diseases	19 (13.4)	8 (11.4)	11 (15.3)	
Hepatic diseases	6 (4.2)	3 (4.3)	3 (4.2)	
Surgical intervention	21 (14.8)	9 (12.9)	12 (16.7)	
Others	16 (11.2)	9 (12.9)	7 (9.7)	
Type of infection, *n* (%)				
Bacteraemia	19 (13.4)	11 (15.7)	8 (11.1)	<0.05
UTI	12 (8.5)	5 (7.1)	7 (9.7)	
IAI	13 (9.2)	7 (10)	6 (8.3)	
LRTI	81 (57)	44 (62.9)	37 (51.4)	
ABSSSI	9 (6.3)	0 (0)	9 (12.5)	
Others	3 (2.1)	3 (4.3)	5 (6.7)	
Positive blood cultures, *n* (%)	45 (31.7)	20 (28.6)	25 (34.7)	0.47
Resistance to cefiderocol,[a] *n* (%)	17 (27.9)	7 (25.9)	10 (29.4)	1
Type of bacterium, *n* (%)				
A. baumannii	89 (62.7)	42 (60)	47 (65.3)	0.76
K. pneumoniae	22 (15.5)	11 (15.7)	11 (15.3)	
P. aeruginosa	27 (19)	14 (20)	13 (18.1)	
Others	4 (2.8)	3 (4.3)	1 (1.4)	
Coinfection, *n* (%)				
Overall	94 (66.2)	45 (64.3)	49 (68.1)	0.38
Gram-negative	27 (28.7)	12 (26.7)	15 (30.6)	

Continued

Table 2. *Continued*

Variable	Total (*N* = 142)	Monotherapy (*N* = 70)	Combination therapy (*N* = 72)	*P* value
Gram-positive	31 (32.3)	17 (37.8)	14 (28.6)	
Mixed	16 (17)	6 (13.3)	10 (20.4)	
Fungal	20 (21.2)	10 (22.2)	10 (20.4)	
Therapy, *n* (%)				
>10 days of antibiotic treatment before cefiderocol[b]	47 (42.3)	18 (37.5)	29 (46)	0.44
>10 days of cefiderocol treatment	71 (50)	33 (47.1)	38 (52.8)	0.62
Outcome				
In-hospital stay (IQR), days	42 (26–65)	41 (24–64)	43 (28–70)	0.3
30-day mortality, *n* (%)	52 (36.6)	23 (32.9)	29 (40.3)	0.39
Microbiological cure,[c] *n* (%)	45 (48.9)	22 (45.8)	23 (52.3)	0.68
Major events,[d] *n* (%)				
ARDS	89 (62.7)	42 (60)	47 (65.3)	0.6
AKI	54 (38)	26 (37.1)	28 (38.9)	0.86
Septic shock	70 (49.3)	34 (48.6)	36 (50)	0.87

Numbers in bold are statistically significant.
[a]Susceptibility testing for cefiderocol was performed in only 61 isolates (43%).
[b]Regardless of the antibiotics used.
[c]Microbiological cure available on 92/142 patients who had follow-up cultures available.
[d]After entering in the observation period.

combination therapy consisting of cefiderocol plus at least one other drug active against the MDR isolate (Table 2). The 30 day mortality, calculated from the initiation of cefiderocol therapy, was 37% (52/142).

Notably, there were no significant differences in demographic and clinical characteristics between the group treated with cefiderocol monotherapy and those treated with the combination therapy. Patients treated with the combination therapy showed a slightly higher mortality rate (40% versus 33%) without statistical significance. Also, in the subgroup analysis by pathogen type, the outcome of cefiderocol monotherapy was comparable to combination therapy in the treatment of *A. baumannii*, *K. pneumoniae* or *P. aeruginosa* infections (Figure 1).

Microbiological cure rates, calculated among 92 patients with follow-up cultures available, were also comparable between the two groups, as shown in Table 2.

Stratifying by infection type, no statistical association was observed with 30 day mortality. However, a higher number of deaths was observed in the LRTI group (*n* = 35, 43%), followed by cUTIs (*n* = 4, 33%), ABSSSIs (*n* = 3, 33%) and IAIs (*n* = 4, 31%). BSIs showed the lowest proportion of deaths (*n* = 5, 26%).

Susceptibility testing for cefiderocol was performed in only 61 of 142 isolates (43%). Of these, 17 (27.9%) were resistant to cefiderocol, including 10 (35.7%) strains of *A. baumannii* and 7 (43.8%) of *K. pneumoniae*. Resistance to cefiderocol was not associated with 30 day mortality or a different microbiological cure rate, even if there were no differences in term of monotherapy or combination therapy between cefiderocol-susceptible and -resistant infections (54.5% and 58.8%, respectively, *P* = 1.00).

Eight patients (6%) had a clinical and microbiological relapse, a median of 11 days (IQR 9–25 days) after cefiderocol discontinuation, and received a second cycle of cefiderocol with a median duration of 12 days (IQR 9–18 days). Susceptibility testing was repeated in only one of these latter episodes, confirming susceptibility to cefiderocol.

Univariate and multivariate analysis for 30 day mortality prediction

Upon univariate analysis of ICU admission, 30 day mortality was associated with pre-existing diabetes, heart failure, chronic renal failure, higher CCI, and severity score at introduction of cefiderocol therapy (APACHE-II and MEWS), and major events occurring during hospital stay, such as AKI (according to KDIGO 2012 criteria[16]), ARDS (according to 2012 Berlin criteria[17]) or septic shock (according to Sepsis-3 definition[18]) (Table 1).

Conversely, no correlation was observed between mortality and pathogen type, source of infection, positive blood culture or coinfection.

In the multivariate Cox model (Table 3), 30 day mortality was independently associated with a CCI score ≥3 (HR 5.05, 95% CI 2.40–10.62, *P* < 0.001). At the same time, only the presence of a coinfection (HR 0.46, 95% CI 0.23–0.90, *P* < 0.05) was associated with lower rate of mortality. The complete results of the multivariable analysis are summarized in Figure 2.

IPTW using PS balanced the groups well. IPTW-adjusted Cox regression showed that combination treatment was not associated with lower 30 day mortality (HR 1.08, 95% CI 0.61–1.92, *P* = 0.78).

Discussion

To the best of our knowledge, this is the largest observational cohort study showing real-life postmarketing data on cefiderocol use for MDR Gram-negative infections.

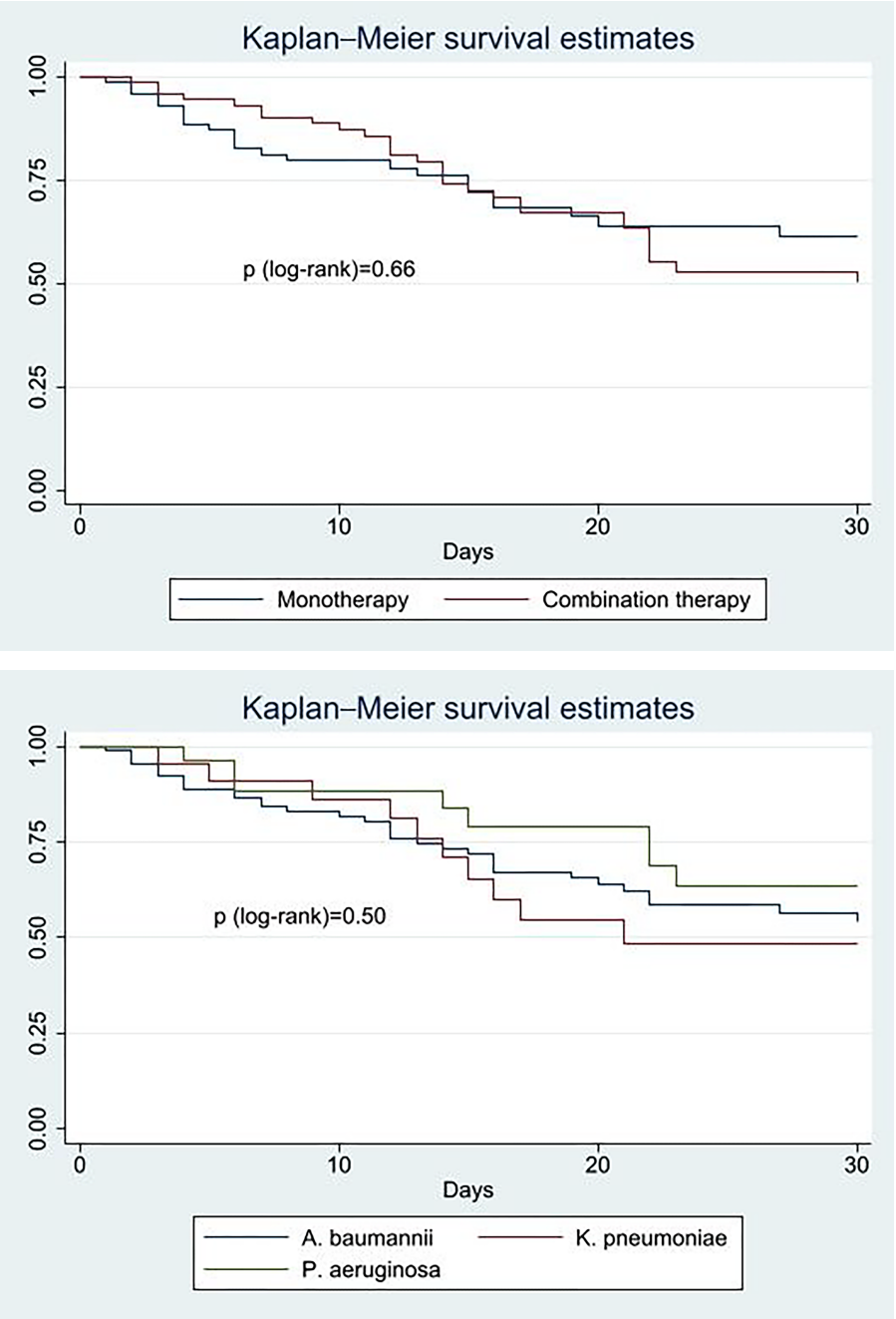

Figure 1. Kaplan–Meier estimator of the impact of combination treatment and pathogen type on 30 day mortality. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Our study showed an overall 30 day mortality rate of 37%, which was significantly higher than registration trials. APEKS-NP and APEKS-UTI studies were not based on MDR pathogens, preventing a meaningful comparison. The CREDIBLE trial showed an overall 28 day mortality of 25%.[6] Because the main prognostic factors were comparable at the time of enrollment (e.g. age, CCI, APACHE-II, ICU), a possible difference could be the distribution of MDR pathogens, which in our cohort was dominated by *A. baumannii* (63% versus 46% in the CREDIBLE trial).

Moreover, strains resistant to cefiderocol might have increased in the meantime. In our series, data on cefiderocol susceptibility were available for a minority of cases (61/142); however, we observed 28% of resistant isolates. Interestingly, resistance was concentrated in *A. baumannii* and *K. pneumoniae* strains, whereas no cases of resistant *P. aeruginosa* were identified. Epidemiological data from one of the participating centres (AOU-C) focusing on 52 NDM-producing *K. pneumoniae* isolated between January 2021 and June 2022 revealed that approximately 40% of these

Table 3. Multivariate Cox model for 30 day mortality in hospitalized patients with carbapenem-resistant pathogen infection treated with cefiderocol

Variables	HR	95% CI	*P* value
Combination therapy[a]	1.12	0.62–2.02	0.71
Age >65 years	0.89	0.46–1.76	0.75
Males	0.57	0.30–1.01	0.09
Ward category			
ICU	ref.		
Medical ward	0.63	0.28–1.41	0.26
Surgical ward	0.16	0.02–1.41	0.10
CCI >3	**5.05**	**2.40–10.62**	**<0.001**
APACHE-II >16	1.70	0.88–3.29	0.11
Coinfection	**0.46**	**0.23–0.90**	**<0.05**
Source control	0.69	0.34–1.41	0.30
Type of infection			
Bacteraemia	ref	ref	ref
UTI	2.02	0.49–8.04	0.33
IAI	1.31	0.33–5.24	0.70
LRTI	1.58	0.58–4.33	0.37
ABSSSI	1.37	0.28–6.64	0.70
Others	0.60	0.06–5.9	0.66
Type of bacterium			
A. baumannii	ref.	ref.	ref.
K. pneumoniae	1.02	0.44–2.34	0.95
P. aeruginosa	0.64	0.24–1.71	0.38
Others	0.95	0.20–4.56	0.95
Propensity score analysis			
Combination regimens (IPTW-adjusted)[a]	1.08	0.61–1.92	0.78

Numbers in bold are statistically significant.
[a]Monotherapy with cefiderocol as reference variable.

strains were resistant to cefiderocol. This outbreak was mostly sustained by clonal expansion of a mutant with the inactivated *cirA* siderophore receptor gene, which spread independently of cefiderocol exposure.[19] A recent comprehensive review of cefiderocol resistance mechanisms highlighted that the NDM enzyme is a proxy for the emergence of cefiderocol resistance through co-expression of additional mechanisms.[20,21] Overexpression of the bla_{NDM} gene following increased gene dosage was also reported to be linked to *in vivo* emergence of cefiderocol resistance under cefiderocol treatment.[22,23]

Stratifying by type of infection, no significant differences in mortality were observed. However, LRTIs had higher absolute rates of death (43%). Considering that pulmonary penetration of the drug appears to be sufficient, especially in patients with lung inflammation,[24–26] this excess mortality may depend on several underlying conditions (e.g. 69% of them were in ICU at the time of treatment with cefiderocol compared with the overall rate of 56%) and confirmed that nosocomial pneumonia and ventilator-associated pneumonia remain challenging entities to manage.

Focusing on *A. baumannii*, the mortality rate seen in our study was comparable with that observed for polymyxin-based regimens in the CREDIBLE-CR study and in more recent trials based on colistin[27] or sulbactam/durlobactam.[28] Interestingly, population characteristics were similar when stratified by the three main pathogens, and 30 day mortality for *A. baumannii* infections was comparable to that of *P. aeruginosa* and *K. pneumoniae*, supporting the efficacy of cefiderocol for CRAB. Falcone *et al.*[29] found a 30 day mortality rate of 34% among patients treated with cefiderocol for CRAB infections; in the study by Pascale *et al.*,[30] limited to ICU patients with CRAB infections treated with cefiderocol monotherapy, mortality was higher than in our ICU population (55% versus 46%). Pending further larger randomized trials, the results of real-life observational experiences, including the present study, may suggest reconsidering the role of cefiderocol in the management of CRAB infections with respect to the recommendation by the ESCMID guidelines.[31]

Limited data are available focusing on the efficacy of cefiderocol for DTR *P. aeruginosa*. A small study including 17 patients [of whom 14 received cefiderocol combination regimens (CCRs)] reported a 30 day mortality of 24% and a microbiological cure of 77%.[32] Bleibtreu *et al.*[33] found 9 out of 12 cases of XDR *P. aeruginosa*, which were associated with an all-cause mortality rate of 24%. These results were comparable to our experience with *P. aeruginosa*, as we observed a 30 day mortality of 30% and a microbiological cure rate of 55%. However, due to the small sample size it is not possible to draw a definitive conclusion about the role of cefiderocol against DTR *P. aeruginosa*.

Studies addressing the role of cefiderocol against MBL-producing Enterobacterales in a real-life setting are still lacking. In our experience we had 22 cases of MBL-producing *K. pneumoniae,* 2 cases of *E. coli* and 1 case of *E. cloacae*. Among them, 30 day mortality rate and microbiological cure were 44% and 47%, respectively.

Resistance to cefiderocol was not associated with poor outcome, suggesting that data obtained *in vitro* could disagree with *in vivo* performance. However, given the EUCAST warnings about cefiderocol susceptibility testing and the heterogeneity in methods between the sites, the interpretation of these results remains challenging.[34]

According to our results, there was no significant difference in 30 day mortality between groups receiving CCR and monotherapy. This finding contrasts with the recommendations included in the recent guidelines issued by ESCMID and the IDSA, which suggest a combination therapy including two *in vitro* active antibiotics for patients with moderate to severe and high-risk CRAB infections.[31,35] In particular, IDSA guidelines recommend the use of cefiderocol for CRAB only as part of a combination scheme.[35] Consistent with our findings, a small case series of ICU patients ($n=10$) with *A. baumannii* infections showed good efficacy of monotherapy (30 day mortality 10%).[36] Another small study ($n=18$) comparing monotherapy with combination therapy showed comparable results in patients treated with cefiderocol alone (30 day mortality was 29% in the combination therapy and 25% in the monotherapy group).[37]

The apparent protective role of the coinfection observed in the multivariate model may reflect a possible predominant role of a second, less virulent and 'easier-to-treat' pathogen.

Concerning microbiological cure, our results were in line with the CREDIBLE trial (48.9% versus 48%), but markedly different from other real-life studies, where microbiological eradication ranged from 28% to 82.6%.[29,30]

The main limitation of our study is related to the retrospective observational design. A control group comprising MDR infections

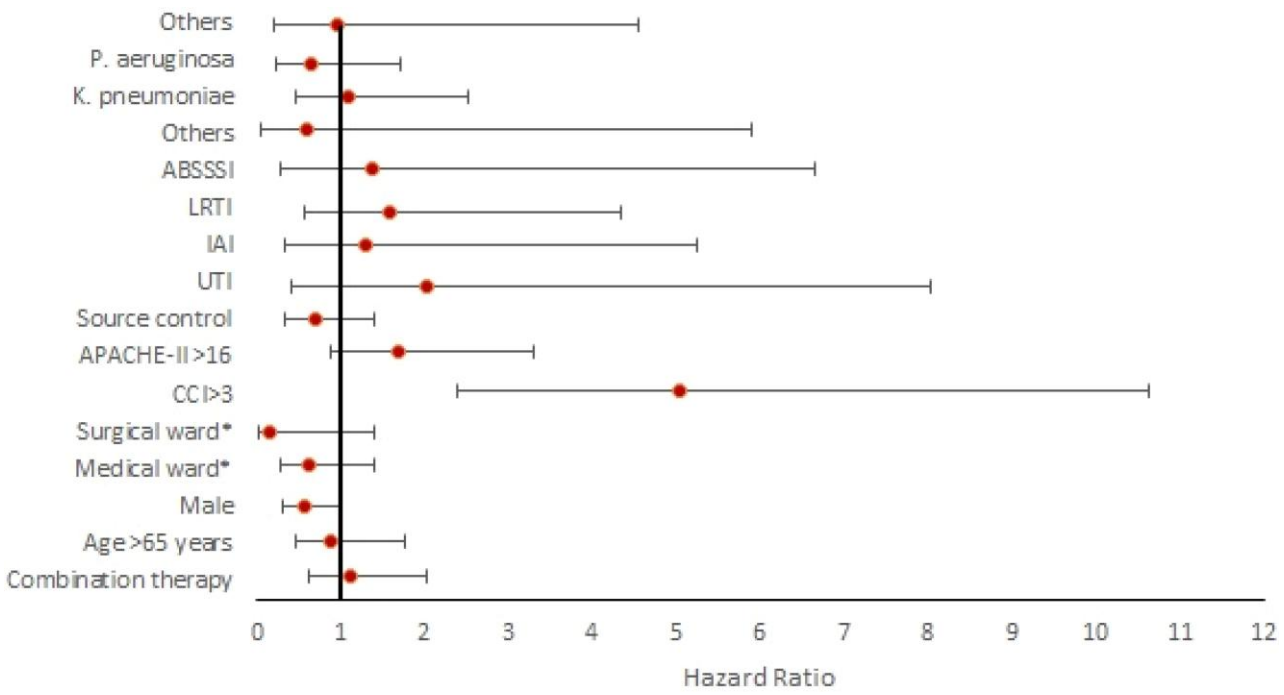

Figure 2. Multivariate Cox model for 30 day mortality in hospitalized patients infected with carbapenem-resistant pathogens treated with cefiderocol. Red spots represent the exact HR value, while horizontal bars represent the confidence interval. Multivariate analysis adjusted for inverse probability of treatment weighting (IPTW) confirmed that combination treatment was not associated with lower 30 day mortality (HR 1.08, 95% CI 0.61–1.92, $P = 0.78$). This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

treated with non-cefiderocol regimens was not provided; however, a comparison with different regimens against MDR was beyond the scope of this study. Moreover, most of the isolates were not tested for cefiderocol susceptibility, due to the well-known challenges in susceptibility testing during the first few months after cefiderocol is marketed.

Conclusions

Despite its limitations, cefiderocol has proven to be an important option for addressing emerging MDR pathogens, possibly even when the drug is used alone. The potential use in monotherapy deserves attention considering both the toxicity profile of common companion drugs (e.g. colistin), and the purpose of antimicrobial management. Randomized studies are urgently needed to reconsider the role of cefiderocol against *A. baumannii* infections and to compare its performance with aztreonam-based regimens against MBL Enterobacterales.

Funding

This work was supported by Shionogi & Co, which funded InformaPRO for the publication process by covering the language editing review and the article processing charge.

Transparency declarations

The authors have no conflicts of interest to declare. The lead author (M.P.) affirms that this manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Author contributions

Study conceptualization: M.P., M.S., A. Botta, A. Bartoloni. Data collection: M.P., A. Botta, A.F., V.B., L.G. Data elaboration and interpretation: M.P., M.S., F.L., G.M.R., T.G., A. Bartolini, M.B., G.M. Manuscript writing: M.P., M.S. Patient management and manuscript reviewing: M.P., M.S., G.M.R., T.G., F.L. Project supervision: A. Bartoloni, G.M.R., M.T., A.G., R.P.

Supplementary data

Figure S1 is available as Supplementary data at *JAC* Online.

References

1 WHO. *Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics*. World Health Organization, 2017. https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed

2 Tamma PD, Hsu AJ. Defining the role of novel β-lactam agents that target carbapenem-resistant Gram-negative organisms. *J Pediatric Infect Dis Soc* 2019; **8**: 251–60. https://doi.org/10.1093/jpids/piz002

3 Ito A, Sato T, Ota M *et al*. In vitro antibacterial properties of cefiderocol, a novel siderophore cephalosporin, against Gram-negative bacteria. *Antimicrob Agents Chemother* 2018; **62**: e01454-17. https://doi.org/10.1128/AAC.01454-17

4 Portsmouth S, van Veenhuyzen D, Echols R *et al*. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised,

double-blind, non-inferiority trial. *Lancet Infect Dis* 2018; **18**: 1319–28. https://doi.org/10.1016/S1473-3099(18)30554-1

5 Wunderink RG, Matsunaga Y, Ariyasu M *et al*. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis* 2021; **21**: 213–25. https://doi.org/10.1016/S1473-3099(20)30731-3

6 Bassetti M, Echols R, Matsunaga Y *et al*. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis* 2021; **21**: 226–40. https://doi.org/10.1016/S1473-3099(20)30796-9

7 Palermo G, Medaglia AA, Pipitò L *et al*. Cefiderocol efficacy in a real-life setting: single-centre retrospective study. *Antibiotics (Basel)* 2023; **12**: 746. https://doi.org/10.3390/antibiotics12040746

8 Sajib MI, Monteforte M, Go R. Clinical outcome of cefiderocol for infections with carbapenem-resistant organisms. *Antibiotics (Basel)* 2023; **12**: 936. https://doi.org/10.3390/antibiotics12050936

9 Satlin MJ, Simner PJ, Slover CM *et al*. Cefiderocol treatment for patients with multidrug- and carbapenem-resistant *Pseudomonas aeruginosa* infections in the compassionate use program. *Antimicrob Agents Chemother* 2023; **67**: e0019423. https://doi.org/10.1128/aac.00194-23

10 Rando E, Cutuli SL, Sangiorgi F *et al*. Cefiderocol-containing regimens for the treatment of carbapenem-resistant *A. baumannii* ventilator-associated pneumonia: a propensity-weighted cohort study. *JAC Antimicrob Resist* 2023; **5**: dlad085. https://doi.org/10.1093/jacamr/dlad085

11 Shionogi Inc. FETROJA (Cefiderocol) for injection, for intravenous use: US prescribing information. 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209445s002lbl.pdf

12 Charlson ME, Pompei P, Ales KL *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373–83. https://doi.org/10.1016/0021-9681(87)90171-8

13 Knaus WA, Draper EA, Wagner DP *et al*. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**: 818–29. https://doi.org/10.1097/00003246-198510000-00009

14 Subbe CB, Kruger M, Rutherford P *et al*. Validation of a modified Early Warning Score in medical admissions. *QJM* 2001; **94**: 521–6. https://doi.org/10.1093/qjmed/94.10.521

15 European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters. Version 02.01.2023. https://www.eucast.org/clinical_breakpoints

16 Stevens PE, Levin A, Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the Kidney Disease: Improving Global Outcomes 2012 clinical practice guideline. *Ann Intern Med* 2013; **158**: 825–30. https://doi.org/10.7326/0003-4819-158-11-201306040-00007

17 ARDS Definition Task Force, Ranieri VM, Rubenfeld GD *et al*. Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012; **307**: 2526–33. https://doi.org/10.1001/jama.2012.5669

18 Singer M, Deutschman CS, Seymour CW *et al*. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016; **315**: 801–10. https://doi.org/10.1001/jama.2016.0287

19 Coppi M, Antonelli A, Niccolai C *et al*. Nosocomial outbreak by NDM-1-producing *Klebsiella pneumoniae* highly resistant to cefiderocol, Florence, Italy, August 2021 to June 2022. *Euro Surveill* 2022; **27**: 2200795. https://doi.org/10.2807/1560-7917.ES.2022.27.43.2200795

20 Nurjadi D, Kocer K, Chanthalangsy Q *et al*. New Delhi metallo-beta-lactamase facilitates the emergence of cefiderocol resistance in *Enterobacter cloacae*. *Antimicrob Agents Chemother* 2022; **66**: e0201121. https://doi.org/10.1128/aac.02011-21

21 Karakonstantis S, Rousaki M, Kritsotakis EI. Cefiderocol: systematic review of mechanisms of resistance, heteroresistance and in vivo emergence of resistance. *Antibiotics (Basel)* 2022; **11**: 723. https://doi.org/10.3390/antibiotics11060723

22 Simner PJ, Patel R. Cefiderocol antimicrobial susceptibility testing considerations: the Achilles' heel of the Trojan horse? *J Clin Microbiol* 2021; **59**: e00951-20. https://doi.org/10.1128/JCM.00951-20

23 Choby JE, Ozturk T, Satola SW *et al*. Widespread cefiderocol heteroresistance in carbapenem-resistant Gram-negative pathogens. *Lancet Infect Dis* 2021; **21**: 597–8. https://doi.org/10.1016/S1473-3099(21)00194-8

24 Drwiega EN, Rodvold KA. Penetration of antibacterial agents into pulmonary epithelial lining fluid: an update. *Clin Pharmacokinet* 2021; **61**: 17–46. https://doi.org/10.1007/s40262-021-01061-7

25 Katsube T, Saisho Y, Shimada J *et al*. Intrapulmonary pharmacokinetics of cefiderocol, a novel siderophore cephalosporin, in healthy adult subjects. *J Antimicrob Chemother* 2019; **74**: 1971–4. https://doi.org/10.1093/jac/dkz123

26 Kawaguchi N, Katsube T, Echols R *et al*. Intrapulmonary pharmacokinetic modeling and simulation of cefiderocol, a parenteral siderophore cephalosporin, in patients with pneumonia and healthy subjects. *J Clin Pharmacol* 2022; **62**: 670–80. https://doi.org/10.1002/jcph.1986

27 Kaye KS, Marchaim D, Thamlikitkul V *et al*. Colistin monotherapy versus combination therapy for carbapenem-resistant organisms. *NEJM Evid* 2023; **2**: evidoa2200131. https://doi.org/10.1056/evidoa2200131

28 Watkins RR, Du B, Isaacs R *et al*. Pathogen-targeted clinical development to address unmet medical need: design, safety, and efficacy of the ATTACK trial. *Clin Infect Dis* 2023; **76**: S210–4. https://doi.org/10.1093/cid/ciad097

29 Falcone M, Tiseo G, Leonildi A *et al*. Cefiderocol- compared to colistin-based regimens for the treatment of severe infections caused by carbapenem-resistant *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 2022; **66**: e0214221. https://doi.org/10.1128/aac.02142-21

30 Pascale R, Pasquini Z, Bartoletti M *et al*. Cefiderocol treatment for carbapenem-resistant *Acinetobacter baumannii* infection in the ICU during the COVID-19 pandemic: a multicentre cohort study. *JAC Antimicrob Resist* 2021; **3**: dlab174. https://doi.org/10.1093/jacamr/dlab174

31 Paul M, Carrara E, Retamar P *et al*. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European Society of Intensive Care Medicine). *Clin Microbiol Infect* 2022; **28**: 521–47. https://doi.org/10.1016/j.cmi.2021.11.025

32 Meschiari M, Volpi S, Faltoni M *et al*. Real-life experience with compassionate use of cefiderocol for difficult-to-treat resistant *Pseudomonas aeruginosa* (DTR-P) infections. *JAC Antimicrob Resist* 2021; **3**: dlab188. https://doi.org/10.1093/jacamr/dlab188

33 Bleibtreu A, Dortet L, Bonnin RA *et al*. Susceptibility testing is key for the success of cefiderocol treatment: a retrospective cohort study. *Microorganisms* 2021; **9**: 282–8. https://doi.org/10.3390/microorganisms9020282

34 EUCAST. EUCAST warnings concerning antimicrobial susceptibility testing products or procedures. https://www.eucast.org/ast-of-bacteria/warnings

35 Tamma PD, Aitken SL, Bonomo RA *et al*. Infectious Diseases Society of America guidance on the treatment of AmpC β-lactamase-producing Enterobacterales, carbapenem-resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* infections. *Clin Infect Dis* 2022; **74**: 2089–114. https://doi.org/10.1093/cid/ciab1013

36 Falcone M, Tiseo G, Nicastro M *et al*. Cefiderocol as rescue therapy for *Acinetobacter baumannii* and other carbapenem-resistant Gram-negative infections in intensive care unit patients. *Clin Infect Dis* 2021; **72**: 2021–4. https://doi.org/10.1093/cid/ciaa1410

37 Corcione S, De Benedetto I, Pinna SM *et al*. Cefiderocol use in Gram negative infections with limited therapeutic options: is combination therapy the key? *J Infect Public Health* 2022; **15**: 975–9. https://doi.org/10.1016/j.jiph.2022.07.006