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# Real-life experience with cefiderocol for the treatment of difficult-to-treat gram-negative infections

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***ABSTRACT:***

— ***Objective:*** The aim of this study was to report our real-life experience with cefiderocol for the treatment of difficult-to-treat gram-negative infections.

— ***Patients and Methods:*** Patients treated with cefiderocol for at least one day between October 2021 and November 2022 were included following them until 28 days after the end of treatment or death.

— ***Results:*** Seventeen treatment courses from 16 patients were analyzed (13 males, 3 females). The median age was 69.14 years (35-84). All had a documented gram-negative infection in which cefiderocol was the only treatment option. Nine patients were critical when treatment started (Sequential Organ Failure Assessment = 7.6). The isolated microorganisms were carbapenemase producers, particularly VIM producer *Pseudomonas aeruginosa* (11 cases) and *Serratia marcescens* (5 cases, one of them was also KPC producer) and NMD producer *Klebsiella oxytoca* (1 case). The median treatment duration was 12.4 days (5-27). Clinical cure was achieved in 10 patients, 5 died and 1 achieved clinical cure once its main infection was treated.

— ***Conclusions:*** The results of cefiderocol in real life are similar to those reported for the drug in clinical trials. This is one of the largest series of cases published in literature that includes different microorganisms and indications, which might help clinicians when treating this kind of patients.

— ***Keywords:*** *Cefiderocol, Gram-negative infection, Resistance, Real-world.*

## INTRODUCTION

The rise in antimicrobial resistance has become a worldwide problem. Carbapenem-resistant gram-negative bacteria are an emerging cause of healthcare-associated infections and have become a threat to public health, according to World Health Organization[1]. These pathogens are usually involved in difficult-to-treat infections, such as ventilator-associated pneumonia (VAP), bloodstream infections, or intra-abdominal infections, and are associated with high mortality[2] and substantial healthcare costs[3]. In this context, antibiotics with a novel mechanism of action, such as cefiderocol, become promising alternatives.

Cefiderocol is a new siderophore cephalosporin recently approved in Europe for the treatment of aerobic gram-negative infections with limited therapeutic options.

Its new mechanism of action allows it to bind to extracellular iron and penetrate the bacteria through the siderophore uptake systems. Once inside the cell, it binds to penicillin-binding proteins, inhibiting cell wall peptidoglycan synthesis and causing cell death[4].

According to some clinical trials[5,6] involving this new antibiotic, cefiderocol was found to have similar clinical and microbiological efficacy to the best available therapy in patients with infections caused by carbapenem-resistant Gram-negative bacteria, and was non-inferior to high-dose, extended-infusion meropen-



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em in terms of all-cause mortality on day 14 in patients with Gram-negative nosocomial pneumonia.

The 2021 Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales, Carbapenem-Resistant Enterobacterales, and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance[7], recommended cefiderocol as an alternative treatment for these pathogens.

Until the end of 2022, access to cefiderocol in Spain was controlled by the Spanish Medicines and Health Products Agency. Due to its recent commercialization, real-life evidence[8-10] is still scarce; however, published case series[8,9] and reviews[10] show promising results in difficult-to-treat pathogens such as *Pseudomonas aeruginosa* or *Acinetobacter baumannii* in monotherapy and combination treatment.

Therefore, the aim of this study is to report a real-life experience with cefiderocol for the treatment of difficult-to-treat gram-negative infections prior to its commercialization.

## PATIENTS AND METHODS

This is an observational, retrospective study. All patients treated for at least one day with cefiderocol, between October 2021 and November 2022, were included, following them until 28 days after the end of treatment or death. No patients were excluded. The main endpoint was the clinical cure, defined by the resolution of the symptoms by the end of the treatment.

The criteria for clinical cure depended on the initial diagnosis. In cases of tracheobronchitis and VAP: resolution of fever, decrease of purulent secretions, improvement of $PaO_2/FiO_2$ returning to pre-infection values or successful weaning from mechanical ventilation.

— Sepsis: the clinical cure was defined as complete resolution, substantial improvement (i.e., reduction in severity of all baseline signs and symptoms and worsening of none) or return to pre-infection signs and symptoms.
— Surgical site infection: the clinical cure was defined as the improvement or complete resolution of local signs and symptoms of infection, such as pain, redness, swelling, and drainage at the surgical site.

The endpoint used for the evaluation of the safety profile was the occurrence of adverse effects that could have been caused by cefiderocol.

The variables collected from each patient were: sex, age, comorbidities, cause of admission, infectious diagnosis for which cefiderocol was needed, previous use of any antibiotic since admission, previous use of carbapenems or ceftazidime-avibactam since admission, use of concomitant antibiotics for the same infection, days of treatment with cefiderocol, need for dose adjustment based on renal function, use of renal replacement techniques while cefiderocol treatment, procalcitonin (PCT) and C reactive protein (CRP) on the first and last day of treatment, clinical cure, Sequential Organ Failure Assessment (SOFA) on the first day of treatment (only in critical patients) and 14 and 28 days mortality.

In patients in whom arterial blood gasses were not performed, the $PaO_2/FIO_2$ for the calculation of SOFA was estimated using the Severinhause-Ellis equation from $SpO_2/FIO_2$.

## RESULTS

During the study period, 17 treatment courses from 16 patients were analyzed (13 males, 3 females). The median age was 69.14 years (35-84), mean 66. Cardiovascular comorbidity was the most frequent comorbidity (hypertension, dyslipidemia, diabetes mellitus, heart failure), 14 patients had at least one. One patient was HIV-positive, with undetectable viral load in the last controls, but CD4-positive T-lymphocyte count was low (17%). Another patient had received treatment with doxorubicin, vincristine, cyclophosphamide, prednisone and rituximab two weeks before the initiation of cefiderocol because of diffuse large B cell lymphoma.

All had a documented gram-negative infection in which cefiderocol was the only treatment option, either due to the resistance profile of the organism or due to contraindication or unavailability of other alternatives. Patients 3, 6, 7, 8, 9, 10, 11, 12, 13 and 15 were admitted to the ICU when treatment was started. The mean SOFA score on the first day of treatment was 7.6. CRP was under 2.9 mg/L in two patients on the first day of treatment. The median CRP for the rest of the patients on day 1 was 132 mg/L (<2.9-221). The median PCT on day 1 was 0.44 ng/ml (0.07-3.28). Patient characteristics are detailed in **Supplementary Table 1.**

All of the isolated microorganisms were carbapenemase producers, particularly VIM producer *Pseudomonas aeruginosa* in 11 cases, VIM producer *Serratia marcescens* in 4 cases, VIM and KPC producer *Serratia marcescens*, and NMD producer *Klebsiella oxytoca* in 1 case. The most frequent infectious diagnoses were VAP (8) and sepsis (3).

Only one patient had not received a previous course of antibiotics during admission, while 13 patients had received carbapenems or new antibiotics, such as ceftazidime/avibactam.

Most patients (14) received monotherapy. Cefiderocol was used in association with intravenous colistin in two patients.

The median CRP for the rest of the patients on the last day of treatment was 81 mg/L (0-246), and the median PCT was 0.45 ng/ml (0.1-7.3).

The median treatment duration was 12.4 days (range: 5-27). Clinical cure was achieved with cefiderocol treatment in 10 patients: 5 died and 1 achieved clinical cure once the main infection was treated (patient 9: tuberculosis). Dose adjustment for renal impairment was necessary for 8 patients, while 2 required the highest dose due to hyperfiltration. Six patients needed renal replacement therapy while undergoing cefiderocol treatment. Details of each patient's treatment are specified in **Supplementary Table 2.**

## DISCUSSION

No adverse events were reported during the study period. Mortality at 14- and 28-days rate in our population was 25%, and clinical cure was 58%. CRP decreased on average by 29 points, while PCT increased by 0.08 points on average, this might be because, in patients who progress favorably, PCT is less likely to be requested.

Our population median age was a little over the CREDIBLE-CR's clinical trial[5] population, and our percentage of critical patients admitted to the Intensive Care Unit while they were receiving cefiderocol was also a little higher in our population (66% vs 56%), mean SOFA on the first day of treatment was also higher in our critical patients (7.6 *vs.* 5.1).

VIM producer *Pseudomonas aeruginosa* was the most frequent microorganism, while on CREDIBLE-CR the most common pathogen was *Acinetobacter baumannii*. The most frequent infection in our population was nosocomial pneumonia, same as in CREDIBLE-CR.

Clinical cure was similar to CREDIBLE-CR's (58.8% *vs.* 53%).

While other real-life studies[11-13] found higher mortality rates (36.34 and 55%), in our population, mortality rate after 28 days since the end of treatment was the same as in CREDIBLE-CR while mortality by day 14 is 25%, the same as in APEKS[6] study.

Cefiderocol is a new antibiotic with a novel mechanism of action that has shown promising results in clinical trials against difficult-to-treat gram-negative organisms. Its adverse effect profile is similar to that of other beta-lactams according to clinical trials.

In our experience, the results of cefiderocol in real life, even with a higher percentage of critical patients and with a worse prognosis according to SOFA score, are similar to those reported for the drug in clinical trials, also coinciding with other published case series[8].

### Limitations

One limitation of the study is that cefiderocol was used in real-life conditions, not in a study setting, and therefore clinical samples were requested according to the patient's evolution and the clinician's criteria, not according to a protocol. Investigations for cultures were more frequent in patients who did not progress favourably. Therefore, it has not been possible to perform an analysis in terms of microbiological cure.

## CONCLUSIONS

Cefiderocol is a new antibiotic with a novel mechanism of action that has shown promising results in clinical trials against difficult-to-treat gram-negative organisms. Its adverse effect profile is similar to that of other beta-lactams according to clinical trials.

In our experience, the results of cefiderocol in real life, even with a higher percentage of critical patients and with a worse prognosis according to SOFA score, are similar to those reported for the drug in clinical trials, also coinciding with other published case series[8].

This study represents one of the largest series of cases published that includes different microorganisms and indications, which might help clinicians when treating this kind of patients.

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No specific funding has been received; data have been generated as part of the routine work of the hospital.

**Conflict of Interest:**
None to declare.

**Ethics Approval:**
The local Ethics Review Board (Hospital Clínico San Carlos), in minute 2.1/2023, approved the retrospective data collection for this study (code 23-009).

**Informed Consent:**
The Ethics Committee authorized the waiver of informed consent, as the study intervention did not interfere with standard care procedures and did not require additional exceptional activities.

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