

New antimicrobial alternatives in the treatment of pneumonia

María Cruz Soriano
Jessie Montufar
Aaron Blandino-Ortiz

Cefiderocol

Servicio Medicina Intensiva Hospital Universitario Ramón y Cajal, Madrid, Spain. Study group of infections in critically ill patients (GEIPC-SEIMC).

Revista Española de Quimioterapia
doi:10.37201/req/s01.07.2022

ABSTRACT

Cefiderocol is a new siderophore cephalosporin with potent in vitro activity against gram-negative bacilli including *Enterobacterales* that produce all kinds of carbapenemases and non-fermenting Gram-negative with difficult-to-treat resistance. As a β -lactam, its efficacy is optimized in extended-perfusion and requires dose adjustment in renal dysfunction and hyperclearance. Its efficacy has been validated in three clinical trials, one of them in the treatment of hospital-acquired pneumonia and ventilator-associated pneumonia. The clinical trial aimed at difficult-to-treat gram-negatives achieved the clinical and microbiological target, but the increase in mortality observed in the cefiderocol arm makes it necessary to demonstrate efficacy in real clinical practice. Cefiderocol is a good option among the new β -lactams for the treatment of pneumonia caused by Gram-negative bacilli carbapenem-resistant.

Keywords: Cefiderocol. Multiresistant bacterias. Carbapenemase. Difficult-to-treat resistance. *Acinetobacter baumannii*.

INTRODUCTION

In recent years, new β -lactam antibiotics have become available to us, essential for the treatment of infections by multi-drug resistant (MDR) Gram-negative bacteria. Cefiderocol is a novel siderophore cephalosporin, its main advantage lies in the breadth of its spectrum which includes Gram-negatives bacilli with difficult-to-treat resistance (DTR) and therapeutic gaps to be fulfilled, for instance carbapenem resistant as carbapenemase-metallo- β -lactamases producing Gram-negative bacilli, *Stenotrophomonas maltophilia*, carbapenem-resistant *Acinetobacter baumannii* and other non-fermenting MDR-bacilli with limited therapeutic choices.

Cefiderocol shares a chemical structure in the C-7 side chain with ceftazidime and in the C-3 side chain with cefepime, which gives it a profile for Gram-negative bacilli and stability against β -lactamases [1], although its main distinguishing feature is its chlorocatechol side chain that chelates ferric iron. Cefiderocol, in addition to its entry into bacteria through porin channels like other cephalosporins, its binding to iron allows to easily enter through active iron transport system [1], reaching high concentrations in the periplasmic space and thus exceeding most of the bacterial resistance mechanisms, such as efflux pumps, porins and β -lactamases. Once inside the cell binding to BPB-3 and PBP-2 of cellular wall, leading to cell death (Figure 1) [1,2].

MICROBIOLOGICAL PROFILE

Cefiderocol shows potent in vitro activity against Gram-negative pathogens, including *Enterobacterales* and MDR carbapenem-resistant non-fermenters, almost no activity against Gram-positive cocci and anaerobes organism [2].

To assess the susceptibility of cefiderocol, numerous studies have been conducted since 2014 in the SIDERO-WT [3] program, in which clinical samples of Gram-negative MDR Gram-negative bacilli from all over the world have been tested, comparing the in vitro activity of cefiderocol against other antibiotics including the newer β -lactam with β -lactamase inhibitors (BL-IBLs). These studies validate cefiderocol as a powerful option against *Enterobacterales*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Burkholderia* spp, *S. maltophilia* and *Elizabethkingia meningoseptica* resistant to carbapenems [3,4].

Candel et al. [4] conducted a European multicenter study where they obtained 20,911 clinical samples collected between 2013-2018 in which they describe the activity of cefiderocol compared with ceftazidime-avibactam, ceftolozane-tazobactam and against colistin. The authors categorized the results according to site of infection, microorganism and against samples with different breakpoints of susceptibility to carbapenems.

Correspondence:
María Cruz Soriano
Servicio Medicina Intensiva Hospital Universitario Ramón y Cajal, Madrid, Spain.
E-mail: cruzsorianocuesta@yahoo.es

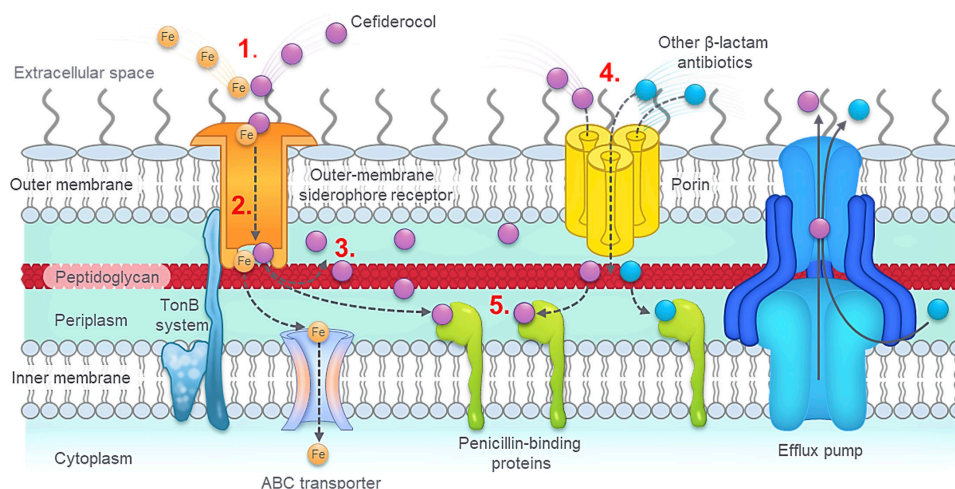


Figure 1 Mechanism of action of cefiderocol

Cefiderocol showed excellent activity against all Gram-negative species ($\geq 97\%$) regardless of key infection site and carbapenem MIC. In this study, 9,399 (34%) were respiratory samples from patients with hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP). In patients with this infection profile, cefiderocol maintained a high activity, sensitivity range of 93–100% for *Enterobacterales* samples, 92% for *Acinetobacter* spp, 99% for *P. aeruginosa*, 95% *Burkholderia* spp. and 100% of *S. maltophilia* strains [4].

PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES

In some subgroups of patients, with certain particularities, such as in critically ill patients, there is an increase in the volume of distribution, enhanced or reduced renal clearance, and hyperdynamic conditions, all factors that can produce inadequate plasma β -lactams antibiotic concentration [5]. In these patients, these considerations are essential to optimize their antimicrobial therapy, taking into account pharmacokinetics and pharmacodynamics (PK/PD) [5].

Cefiderocol exhibits a mean elimination half-life of 2–3 h, with a protein binding of 58% and is excreted mainly by the renal route without changes [6]. Administration of higher doses of cefiderocol and prolonged infusion times according to PK/PD principles have been identified as strategies to optimize the effectiveness of β -lactam antibiotics in this setting. The standard cefiderocol dose is 2000mg every 8h in extended perfusion over 3 h [6]. Cefiderocol shows physicochemical stability in syringes for 12 h, opening the possibility of continuous infusion [7]. The dose of cefiderocol requires dose adjustment based on renal function, either in dysfunction or in hyper-clearance states that require daily dose increase to 2000 mg every 6h with creatinine clearance $>120\text{ml/min}$ [6].

In an intrapulmonary pharmacokinetic study in patients with severe pneumonia on mechanical ventilation treated with cefiderocol, it was observed how the antibiotic penetrates the epithelial lining fluid at concentrations similar to other cephalosporins and sufficient to inhibit Gram-negative microorganisms with MICs of $\leq 4\text{ mg/L}$ [8].

CLINICAL EXPERIENCE. FROM PIVOTALS TO CASE SERIES

Cefiderocol has been approved since 2019 by the FDA for the treatment of infections caused by susceptible Gram-negative microorganisms, encompassing complicated urinary tract infections (cUTI) and HABP/VABP, and by the EMA in 2020 for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.

The efficacy of cefiderocol has been assessed in three randomized clinical trials (RCTs). In a 2018 first phase-2 RCT (APEKS-cUTI) [9] achieved its non-inferiority target against imipenem with a primary endpoint of composite of clinical and microbiological outcomes at test of cure for the treatment of cUTIs caused by Gram-negative. A total of 371 patients were enrolled on a modified intention-to-treat basis. The primary endpoint was attained by 73% (183/ 252) and 55% (65/119) of patients in the cefiderocol and imipenem-cilastatin arms respectively (adjusted difference: 18.6%; 95% confidence interval [CI]: 8.2 to 28.9). Microbiologic response was higher in patients treated with cefiderocol, with similar results in clinical response in both arms. Infections with carbapenem-resistant organisms were not admitted in this study. The most frequent uropathogens were *E. coli* and *K. pneumoniae*, while *P. aeruginosa* was isolated in less than 8%.

Subsequently, the EMA requested a new ECA to give its approval, which should include the infections with the greatest

need for this new antibiotic; carbapenem-resistant Gram-negative infections. With this objective, the CREDIBLE-CR [10] study was designed. CREDIBLE-CR trial was carried out to study the efficacy of cefiderocol for the treatment of life-threatening carbapenem-resistant Gram-negative infections (HABP; VABP; HCABP; cUTI, bloodstream infections or sepsis) with the best available therapy (BAT).

In this open-label multicentre RCT, 152 patients were enrolled in a 2:1 ratio to received cefiderocol ($n=101$) or BAT ($n=49$). The primary endpoint of this study was non-inferiority in terms of clinical cure and microbiological eradication in the test of cure. In the BAT arm, the combination of up to 3 antibiotics was allowed; in this arm the predominant antibiotic was colistin (66%). The addition of 1 antibiotic to cefiderocol, excluding colistin and BL-IBL, was allowed as well (20% of cases). The main endpoint of the study was achieved. However, when analyzing mortality, it was found that the group treated with cefiderocol had a higher mortality at days 14, 28 and end of study than those treated with BAT. This situation has led to a mortality warning from the FDA. Notwithstanding, it should be pointed out that this study had many limitations and design flaws that make it difficult to adequately interpret the excess mortality in cefiderocol arm. The first circumstance is that the study design was not programmed for a mortality endpoint. Hence, the small sample size and heterogeneous patient population limited the possible number of stratification factors for randomization, increasing the potential for imbalances in baseline factors that might have contributed to the difference in all-cause mortality. There is a great variability of treatments received and combinations. Heterogeneity was also observed in the microorganisms involved, with *Acinetobacter* spp. being the most represented microorganism ($n=54$ [46%]), the second microorganism was *Klebsiella* spp ($n=39$ [33%]), followed in a low number of cases by *P. aeruginosa* ($n=22$ [19%]), *S. maltophilia* ($n=5$ [6%]) and *E. coli* ($n=1$), therefore the interpretation of results according to microorganism is not possible. Moreover, this is a clinical trial carried out in critically ill patients, which by itself adds unavoidable confounding factors. Thereby, despite the higher mortality in this study, cefiderocol was approved by the EMA. for the treatment of infections due aerobic Gram-negative microorganism in adults with limited treatment options.

Last but not least, the APEKS-NP [11], is a multicentre double-blinded phase-3 RCT, in patients with HAP, VAP or health-care-associated Gram-negative pneumonia were randomly assigned in a proportion of 1:1 to receive cefiderocol or meropenem. All patients also received open-label intravenous linezolid for at least 5 days. Participants were stratified at randomization by infection type and Acute Physiology and Chronic Health Evaluation II (APACHE II) score (≤ 15 and ≥ 16). The primary endpoint was all-cause mortality at day 14 in the modified intention-to-treat (ITT) population. A total of 292 patients were recruited (148 to cefiderocol and 152 to meropenem). Among these 199 (68%) were in the ICU, 60% were mechanically ventilated. The primary endpoint of all-cause mortality at day 14 in the modified ITT population was 12.4% for the cefiderocol group (18/145) and 11.6% for the meropenem group (17

/146); adjusted treatment difference 0.8%, 95% CI -6.6 to 8.2; $p=0.002$). All-cause mortality was also similar between groups at day 28. The microbiological data showed that 86% in both groups (124 in the cefiderocol group and 127 in the meropenem group) had a culture documented Gram-negative infection; *K. pneumoniae* $n=92$ (32%), *P. aeruginosa* $n=48$ (16%), *A. baumannii* $n=47$ (16%), and *Escherichia coli* $n=41$ (14%). In this study 18.6% (27/145) in cefiderocol arm and 13.6% (20/147) in meropenem arm were Gram-negative carbapenemase producers. For 16 patients with *Acinetobacter* spp and meropenem MICs higher than 64 mg/L, all-cause mortality at day 14 was 0% (0/5) in the cefiderocol group and 46% (5/11) in the meropenem group. The results of this study in pneumonia reinforce cefiderocol in the safety aspect, because there were no differences in both groups in adverse events and without problems in unexpected mortality resulting in the primary endpoint at 14-day mortality were similar in both arms. In this trial safety profile is consistent with other cephalosporins or carbapenems.

Numerous publications with clinical experience data with cefiderocol have added evidence and information on this antibiotic in real life, most reports have been in the population of patients treated for carbapenem-resistant *Acinetobacter*. Falcone et al [12] have described their experience in the treatment of MDR *A. baumannii* or other carbapenem-resistant Gram-negatives infections in 10 critically ill patients in which *A. baumannii* was isolated in 80%. The authors report clinical success and 30-day survival of 70% and 90%, respectively. Bavaro et al. [13] reported their experience with cefiderocol-based combination therapies as rescue treatment in immunocompromised, critically ill patients or in patients with post-surgical infections. Cefiderocol was used in 13 patients with previous therapeutic failure. 10/13 infections were caused by carbapenem-resistant *A. baumannii*, 1/13 by *KPC-K. pneumoniae* and 2/13 by *P. aeruginosa* XDR. Microbiological eradication was achieved in 100%. The 30-day survival rate was 10/13. In an Italian multicentre observational study, Pascale et al. [14] analyzed the impact of cefiderocol use on outcome in patients admitted to the ICU for severe COVID-19 and further diagnosed with carbapenem-resistant *A. baumannii* infection. A total of 107 patients were included in the analysis. Among these, 42 were treated with cefiderocol as monotherapy, and the remaining patients were treated with colistin, mostly (82%) administered as combination therapy. Authors did not find differences between groups in 28-day mortality (57% mortality rate, cefiderocol 55% versus colistin 58% $P=0.70$).

In 2021 IDSA Guidelines [15] cefiderocol was recommended as alternative treatment in carbapenem-resistant *Enterobacteriales* infections outside of the urinary tract as pneumonia. In OXA-48 carbapenemase infections or unknown carbapenemase and as preferred treatment if metallo- β -lactamase is identified. In the treatment of *DTR-P. aeruginosa* cefiderocol is one of the possibilities recommended as treatment of choice in pyelonephritis or cUTI and as alternative in other focus. In other guidelines, cefiderocol is considered the treatment of choice in critical patients with pneumonia caused by carbapenem-resistant *A. baumannii* [16]. The need to use cefiderocol in combination

in the treatment of severe *Acinetobacter* carbapenem-resistant infections is still debated.

CONCLUSION

Cefiderocol provides a solution to DTR-infections. There is no doubt that the activity of cefiderocol against metallo- β -lactamases is of special interest, since to date there is no other β -lactam with activity against these carbapenemases produced by *Enterobacteriales* or non-fermenting microorganisms. Pending confirmation with clinical experience studies, the possibility of its use against other Gram-negative bacilli with few therapeutic options, such as *A. baumannii*, *Burkholderia cepacia*, and *S. maltophilia* [3,4] is encouraging. As a β -lactam, its performance in terms of PK/PD is predictable. Furthermore, although it has validated its efficacy in three RCTs, it needs more real-life experience to better approximate its effectiveness and safety profile on a case-by-case basis in the different MDR-microorganisms it covers in its broad spectrum.

CONFLICTS OF INTEREST

MCS has received honoraria for talks on behalf of Gilead Science, MSD, Pfizer and Shionogi. The other authors declare no conflicts of interest.

REFERENCES

- Ito A, Nishikawa T, Matsumoto S, Yoshizawa H, Sato T, Nakamura R, et al. Siderophore Cephalosporin Cefiderocol Utilizes Ferric Iron Transporter Systems for Antibacterial Activity against *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 2016 Nov 21;60(12):7396-7401. doi: 10.1128/AAC.01405-16.
- Ito A, Sato T, Ota M, Takemura M, Nishikawa T, Toba S, et al. Y. *In Vitro* Antibacterial Properties of Cefiderocol, a Novel Siderophore Cephalosporin, against Gram-Negative Bacteria. *Antimicrob Agents Chemother*. 2017 Dec 21;62(1):e01454-17. doi: 10.1128/AAC.01454-17.
- Yamano Y. *In Vitro* Activity of Cefiderocol Against a Broad Range of Clinically Important Gram-negative Bacteria. *Clin Infect Dis*. 2019 Nov 13;69(Suppl 7):S544-S551. doi: 10.1093/cid/ciz827.
- Candel FJ, Santerre Henriksen A, Longshaw C, Yamano Y, Oliver A. *In vitro* activity of the novel siderophore cephalosporin, cefiderocol, in Gram-negative pathogens in Europe by site of infection. *Clin Microbiol Infect*. 2022 Mar;28(3):447.e1-447.e6. doi: 10.1016/j.cmi.2021.07.018
- Osthoff M, Siegemund M, Balestra G, Abdul-Aziz MH, Roberts JA. Prolonged administration of β -lactam antibiotics - a comprehensive review and critical appraisal. *Swiss Med Wkly*. 2016 Oct 10;146:w14368. doi: 10.4414/sm.w.2016.14368.
- Katsube T, Echols R, Wajima T. Pharmacokinetic and Pharmacodynamic Profiles of Cefiderocol, a Novel Siderophore Cephalosporin. *Clin Infect Dis*. 2019 Nov 13;69(Suppl 7):S552-S558. doi: 10.1093/cid/ciz828.
- Loeuille G, Vigneron J, D'Huart E, Charmillon A, Demoré B. Physico-chemical stability of cefiderocol, a novel siderophore cephalosporin, in syringes at 62.5 mg/mL for continuous administration in intensive care units. *Eur J Hosp Pharm*. 2021 Aug 18;ejhpharm-2021-002935. doi: 10.1136/ejhpharm-2021-002935.
- Katsube T, Nicolau DP, Rodvold KA, Wunderink RG, Echols R, Matsunaga Y, et al. Intrapulmonary pharmacokinetic profile of cefiderocol in mechanically ventilated patients with pneumonia. *J Antimicrob Chemother*. 2021 Oct 11;76(11):2902-2905. doi: 10.1093/jac/dkab280.
- Portsmouth S, van Veenhuizen D, Echols R, Machida M, Ferreira JCA, Ariyasu M, 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 Dec;18(12):1319-1328. doi: 10.1016/S1473-3099(18)30554-1.
- Bassetti M, Echols R, Matsunaga Y, Ariyasu M, Doi Y, Ferrer R, 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 Feb;21(2):226-240. doi: 10.1016/S1473-3099(20)30796-9.
- Wunderink RG, Matsunaga Y, Ariyasu M, Clevenbergh P, Echols R, Kaye KS, 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 Feb;21(2):213-225. doi: 10.1016/S1473-3099(20)30731-3.
- Falcone M, Tiseo G, Nicastro M, Leonildi A, Vecchione A, Casella C, 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 Jun 1;72(11):2021-2024. doi: 10.1093/cid/ciaa1410.
- Bavaro DF, Belati A, Diella L, Stufano M, Romanelli F, Scalone L, et al. Cefiderocol-Based Combination Therapy for "Difficult-to-Treat" Gram-Negative Severe Infections: Real-Life Case Series and Future Perspectives. *Antibiotics (Basel)*. 2021 May 29;10(6):652. doi: 10.3390/antibiotics10060652
- Pascale R, Pasquini Z, Bartoletti M, Caiazza L, Fornaro G, Bussini L, 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 Nov 17;3(4):dlab174. doi: 10.1093/jacamr/dlab174.
- Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β -lactamase Producing *Enterobacteriales* (ESBL-E), Carbapenem-Resistant *Enterobacteriales* (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-P. *aeruginosa*). *Clin Infect Dis*. 2021 Apr 8;72(7):1109-1116. doi: 10.1093/cid/ciab295.
- Zaragoza R, Vidal-Cortés P, Aguilar G, Borges M, Diaz E, Ferrer R, et al Update of the treatment of nosocomial pneumonia in the ICU. *Crit Care*. 2020 Jun 29;24(1):383. doi: 10.1186/s13054-020-03091-2.