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Cefiderocol, the first catechol-cephalosporin

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Clinical experience of cefiderocol

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ABSTRACT

Infections by antibiotic-resistant microorganisms could be considered a "stealth pandemic" that we fight daily in most hospitals. Some estimates suggest that today 700,000 deaths per year can be attributed to antimicrobial resistance. By the year 2050, it is estimated that this will increase to ten million deaths per year as a result of infections by multidrug-resistant microorganisms. In this context, the availability of antimicrobial therapy that is effective against these pathogens is essential to be able to "save the lives" of our patients. Cefiderocol, a new cephalosporin with a different mechanism of action, will be an essential treatment in many infections caused by resistant aerobic gram-negative bacteria.

Cefiderocol has been used to treat patients with complicated urinary tract infections (cUTI); hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), healthcare-associated pneumonia (HAP); in patients with sepsis and bacteremia, some without an identified primary focus of infection.

Cefiderocol is indicated for the treatment of infections caused by Gram-negative aerobes with limited therapeutic options [1]. It has been used to treat patients with complicated urinary tract infections; nosocomial pneumonia in the non-ventilated and associated with mechanical ventilation, healthcare associated pneumonia; in patients with bacteremia and sepsis and in other infections as rescue therapy [2-19].

In the following, we will review the clinical experience in the different types of infections in which it has been used.

Keywords: cefiderocol; complicated urinary tract infections; hospital-acquired pneumonia; ventilator-associated pneumonia; healthcare-associated pneumonia; sepsis; bacteremia

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URINARY TRACT INFECTIONS

On November 14, 2019, the U.S. Food and Drug Administration (FDA) approved cefiderocol, for the treatment of adults with complicated urinary tract infections (cUTIs), including pyelonephritis caused by sensitive Gram-negative microorganisms, who have limited or no alternative treatment options. The approval was based on substantial preclinical and clinical data, including in vitro and in vivo work, as well as pharmacokinetic and pharmacodynamic studies that established that cefiderocol is an effective agent for the treatment of cUTIs [2].

One of the first clinical trials demonstrating the efficacy of cefiderocol in complicated urinary tract infections was the Phase 2 trial led by Portsmouth et al [3,4]. In this multicenter, double-blind study, cefiderocol demonstrated in patients at risk for multidrug-resistant Gram-negative infections (excluding those with known infection with carbapenemase-resistant bacteria at enrolment) noninferiority to imipenem-cilastatin in both microbiological eradication and clinical cure. A total of 448 patients were treated, 300 in the cefiderocol group and 148 in the imipenem-cilastatin group. The cUTI was caused by Gram-negative uropathogens in 252 in the cefiderocol group and 119 in the imipenem-cilastatin group, and 183 [73%] of the 252 patients in the cefiderocol group versus 65 [55%] of 119 in the imipenem-cilastatin group had clinical cure.

The CREDIBLE-CR clinical trial has recently been published (5). This is a randomized, open-label, multicenter, parallel-group, pathogen-focused, descriptive, phase 3 study in 95 hospitals in North America, South America, Europe and Asia. Patients ≥18 years admitted to hospital with nosocomial pneumonia, bacteremia or sepsis, or cUTI, and evidence of a carbapenem-resistant Gram-negative pathogen were included. Of the 150 patients who received treatment 101 received cefiderocol (85 [85%] received monotherapy) and 49 received best available therapy (30 [61%] received combination therapy). The most frequent carbapenem-resistant pathogens were *Acinetobacter baumannii* (in 54 patients

[46%]), *Klebsiella pneumoniae* (in 39 patients [33%]) and *Pseudomonas aeruginosa* (in 22 patients [19%]). Cefiderocol had similar clinical and microbiological efficacy to the best available therapy. However, despite the similarities in clinical and microbiological outcomes the all-cause mortality rate in the cefiderocol group was higher than in the best available therapy group, primarily in patients with *Acinetobacter* spp. infections. It is unclear whether the difference in all-cause mortality is a chance finding in this heterogeneous population or truly reflects a deficit in the activity of cefiderocol. There was no cefiderocol-related toxicity that could explain the difference in all-cause mortality rates. Nevertheless, the results of this study support cefiderocol as an option for the treatment of carbapenem-resistant infections in patients with limited treatment options.

HOSPITAL-ACQUIRED PNEUMONIA ASSOCIATED OR NOT TO MECHANICAL VENTILATION OR ASSOCIATED WITH HEALTH CARE

We are currently witnessing an increase in the incidence of nosocomial pneumonia caused by multidrug-resistant Gram-negative microorganisms. In addition to the results of the CREDIBLE-CR trial [5] in patients with nosocomial pneumonia, the APEKS-NP study [6] was conducted to compare the efficacy and safety of cefiderocol versus high doses of meropenem in prolonged infusion in adults with nosocomial pneumonia. A randomized, double-blind, parallel-group, phase 3, noninferiority trial at 76 centers in 17 countries in Asia, Europe, and the United States. Adults aged 18 years and older with hospital-acquired, mechanical ventilation-associated or healthcare-associated Gram-negative bacterial pneumonia were included.

The study concluded that treatment with cefiderocol was noninferior to treatment with prolonged infusion high-dose meropenem in terms of 14-day all-cause mortality. The results suggest that cefiderocol is a potential option for the treatment of patients with nosocomial pneumonia, including those caused by multidrug-resistant Gram-negative bacteria.

Other clinical cases of patients with pneumonia treated with cefiderocol have been published, such as that of Trecarichi et al [7] in which they describe the cure of an adult male patient with severe H1N1 influenza complicated with ventilator-associated pneumonia and bacteremia caused by carbapenemase-producing *K. pneumoniae* (KPC-Kp).

Recently, Falcone et al [8] described their experience of cefiderocol in the treatment of 10 patients admitted to the Intensive Care Unit with bacteremia or ventilator-associated pneumonia caused by carbapenem-resistant *A. baumannii*, *Stenotrophomonas maltophilia* or New Delhi metalloproteinase-producing *K. pneumoniae* who received cefiderocol. All strains had a minimum inhibitory concentration ≤2 mg/L. Clinical success and 30-day survival rates were 70% and 90%, respectively. Two patients had microbiological failure.

BLOOD STREAM INFECTIONS AND SEPSIS

In addition to the cases of bacteremia patients included in the CREDIBLE-CR trial [5], an *in vitro* study of 300 consecutive isolates of imipenem-resistant Pseudomonas aeruginosa (n=100), imipenem-resistant *A. baumannii* (n=100), and *S. maltophilia* (n=100), from patients with bacteremia treated at the National Taiwan University Hospital, cefiderocol showed more potent in vitro activity than ceftolozane/tazobactam and ceftazidime/avibactam [9].

OTHER SERIOUS MULTIDRUG-RESISTANT GRAM-NEGATIVE BACILLI INFECTIONS

Several clinical cases have been described in which cefiderocol has achieved clinical cure after use as a second or third treatment option, mainly in the treatment of multidrug-resistant Gram-negative bacilli.

Stevens et al [10] published a case of a 46-year-old man who developed an extremely resistant intra-abdominal *P. aeruginosa* infection, in which severe and life-threatening toxicities to aminoglycoside and polymyxin antibiotics led to the use of cefiderocol on compassionate use. The isolate was sensitive to cefiderocol, and the patient was treated for 28 days, with clinical and radiographic resolution of his infection.

Treatment options for *Achromobacter xylosoxidans* are very few. Warner et al (11) treated 8 cystic fibrosis patients with *A. xylosoxidans* isolates with 12 cycles of cefiderocol and observed a clinical response after 11/12 cycles of treatment. However, there was a microbiological relapse, although without emergence of resistance.

In immunosuppressed or critically ill patients, or in patients with post-surgical infections who have failed previous regimens, cefiderocol-based combination therapies have been used as "rescue" treatments. Bavaro et al [12] describe the evolution of 13 patients treated from September 1, 2020 to March 31, 2021. Overall, 5/13 (38%) patients were classified as critically ill, due to pulmonary failure secondary to COVID-19; 4/13 (31%) patients had post-surgical infections and 4/13 (31%) were patients with severe infections, immunocompromised after having received a solid organ transplant (2/4) or having a hematologic malignancy (2/4). Overall, 10/13 infections were caused by carbapenem-resistant *A. baumannii*, 1 by ceftazidime/avibactam-resistant *K. pneumoniae* and 2 by extremely resistant *P. aeruginosa*. Cefiderocol was associated with different accompanying drugs, in particular with high-dose fosfomycin and tigecycline and/or colistin. Microbiological eradication was achieved in all cases and the 30-day survival rate was 10/13; 2 patients died of pulmonary failure due to SARS-CoV-2, and 1 due to subsequent infections. No recurrent infections were recorded within 30 days of the end of treatment.

The same group [13] published a case of a 64-year-old male patient with a recurrent neurosurgical site infection in the right parietal bone due to extremely resistant *P. aeruginosa*, who had failed previous treatment based on combined

antimicrobial therapy plus surgical cleaning of the right parietal bone and who presented clinical cure after treatment with cefiderocol (6 g daily, divided into three doses, each administered as a three-hour infusion) plus fosfomycin (18 g daily, divided into three doses). The patient presented clinical cure after 14 days of treatment. He had no adverse effects to cefiderocol.

There are several reported cases of clinical cure of patients with osteoarticular infections caused by multidrug-resistant Gram-negative microorganisms treated with cefiderocol, suggesting its penetration into bone tissue in sufficient concentrations when administered 2 g/3 times a day.

Alamarat et al [14] published the case of a 15-year-old Nigerian adolescent with chronic osteomyelitis caused by an extremely resistant *P. aeruginosa* strain carrying bla NDM-1 and an extended-spectrum β-lactamase-producing *K. pneumoniae* strain. The patient developed neurologic side effects in the form of paresthesias with polymyxin B and asymptomatic elevation of transaminases with aztreonam (used in combination with ceftazidime-avibactam). Treatment with cefiderocol for 14 weeks plus bone grafting resulted in cure of the patient and prevented amputation.

Dagher et al [15] described the clinical cure of a patient with extremely resistant *A. baumannii* osteomyelitis with rescue therapy with cefiderocol combined with surgical debridement. The authors suggest that their case in addition to good bone penetration highlights the improved side effect profile of cefiderocol relative to alternative therapies for extremely resistant *A. baumannii*, such as polymyxins, especially with regard to nephrotoxicity.

Also in relation to osteoarticular infections, Simeone et al (16) published a case of a 67-year-old man with a right knee prosthetic joint infection caused by extremely drug-resistant *Enterobacter hormaechei*. The resistance phenotype was due to overproduction of intrinsic cephalosporinase (ACT-5) associated with the production of three acquired lactamases (CTX-M-15, TEM-1B and OXA-1), and decreased membrane permeability. He first received treatment with colistin-tigecycline and due to adverse reactions to the drug, the treatment was changed to cefiderocol for 12 weeks of antibiotic, with a favorable evolution.

Other clinical cases described in which cefiderocol has been successfully used as rescue treatment have been in a patient with left-sided endocarditis due to extremely resistant *P aeruginosa* [17]; treatment of 2 patients with osteomyelitis and 1 with pneumonia associated with mechanical ventilation [18]; 1 patient with renal transplant [19]; 3 patients with osteomyelitis, bacteremia and septic thrombophlebitis respectively due to extremely resistant *A. baumannii* [20].

CONFLICT OF INTEREST

Author declares no conflict of interest.

REFERENCES

1. Boletin mensual de la AEMPS sobre medicamentos de uso humano del mes de febrero de 2020. Fecha de publicación: 27/4/2020. https://www.aemps.gob.es/informa/boletines-aemps/boletinMensual/2020-3/boletin-mensual-de-la-aemps-sobre-medicamentos-de-uso-humano-del-mes-de-febrero-de-2020/?lang=en.
2. McCarthy MW. Cefiderocol to treat complicated urinary tract infection. Drugs Today (Barc). 2020 Mar;56(3):177-184. doi: 10.1358/dot.2020.56.3.3118466.
3. Portsmouth S, van Veenhuyzen 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;18(12):1319-1328. doi: 10.1016/S1473-3099(18)30554-1.
4. Portsmouth S, Echols R, Den Nagata T. Cefiderocol for treatment of complicated urinary tract infections. Lancet Infect Dis. 2019;19(1):23-24. doi: 10.1016/S1473-3099(18)30721-7.
5. 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;21(2):226-240. doi: 10.1016/S1473-3099(20)30796-9.
6. 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;21(2):213-225. doi: 10.1016/S1473-3099(20)30731-3.
7. Trecarichi EM, Quirino A, Scaglione V, Longhini F, Garofalo E, Bruni A, et al. Successful treatment with cefiderocol for compassionate use in a critically ill patient with XDR *Acinetobacter baumannii* and KPC-producing *Klebsiella pneumoniae*: a case report. J Antimicrob Chemother. 2019;74(11):3399-3401. doi: 10.1093/jac/dkz318.
8. 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;72(11):2021-2024. doi: 10.1093/cid/ciaa1410..
9. Hsueh SC, Lee YJ, Huang YT, Liao CH, Tsuji M, Hsueh PR. In vitro activities of cefiderocol, ceftolozane/tazobactam, ceftazidime/avibactam and other comparative drugs against imipenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*, all associated with bloodstream infections in Taiwan. J Antimicrob Chemother. 2019 Feb 1;74(2):380-386. doi: 10.1093/jac/dky425..
10. Stevens RW, Clancy M. Compassionate Use of Cefiderocol in the Treatment of an Intraabdominal Infection Due to Multidrug-Resistant *Pseudomonas aeruginosa*: A Case Report. Pharmacotherapy. 2019 Nov;39(11):1113-1118. doi: 10.1002/phar.2334.
11. Warner NC, Bartelt LA, Lachiewicz AM, Tompkins KM, Miller MB,

Alby K, et al. Cefiderocol for the Treatment of Adult and Pediatric Patients with Cystic Fibrosis and *Achromobacter xylosoxidans* Infections. Clin Infect Dis. 2020 Dec 13: ciaa1847. doi: 10.1093/cid/ciaa1847.

12. 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.
13. Bavaro DF, Romanelli F, Stolfa S, Belati A, Diella L, Ronga L, et al. Recurrent neurosurgical site infection by extensively drug-resistant *P. aeruginosa* treated with cefiderocol: a case report and literature review. Infect Dis (Lond). 2021 Mar;53(3):206-211. doi: 10.1080/23744235.2020.1856921.
14. Alamarat ZI, Babic J, Tran TT, Wootton SH, Dinh AQ, Miller WR, et al. Long-Term Compassionate Use of Cefiderocol to Treat Chronic Osteomyelitis Caused by Extensively Drug-Resistant *Pseudomonas aeruginosa* and Extended-Spectrum-β-Lactamase-Producing *Klebsiella pneum*oniae in a Pediatric Patient. Antimicrob Agents Chemother. 2020 Mar 24;64(4):e01872-19. doi: 10.1128/AAC.01872-19.
15. Dagher M, Ruffin F, Marshall S, Taracila M, Bonomo RA, Reilly R, et al. Case Report: Successful Rescue Therapy of Extensively Drug-Resistant *Acinetobacter baumannii* Osteomyelitis with Cefiderocol. Open Forum Infect Dis. 2020 May 5;7(5):ofaa150. doi: 10.1093/ofid/ofaa150.
16. Siméon S, Dortet L, Bouchand F, Roux AL, Bonnin RA, Duran C, et al. Compassionate Use of Cefiderocol to Treat a Case of Prosthetic Joint Infection Due to Extensively Drug-Resistant *Enterobacter hormaechei*. Microorganisms. 2020 Aug 13;8(8):1236. doi: 10.3390/microorganisms8081236.
17. Edgeworth JD, Merante D, Patel S, Young C, Jones P, Vithlani S, et al. Compassionate Use of Cefiderocol as Adjunctive Treatment of Native Aortic Valve Endocarditis Due to Extremely Drug-resistant Pseudomonas aeruginosa. Clin Infect Dis. 2019;68(11):1932-1934. doi: 10.1093/cid/ciy963.
18. Zingg S, Nicoletti GJ, Kuster S, Junker M, Widmer A, Egli A, et al. Cefiderocol for Extensively Drug-Resistant Gram-Negative Bacterial Infections: Real-world Experience From a Case Series and Review of the Literature. Open Forum Infect Dis. 2020 May 21;7(6):ofaa185. doi: 10.1093/ofid/ofaa185.
19. Contreras DA, Fitzwater SP, Nanayakkara DD, Schaenman J, Aldrovandi GM, Garner OB, et al. Coinfections of Two Strains of NDM-1- and OXA-232-Coproducing *Klebsiella pneumoniae* in a Kidney Transplant Patient. Antimicrob Agents Chemother. 2020;64(4):e00948-19. doi: 10.1128/AAC.00948-19.
20. Oliva A, Ceccarelli G, De Angelis M, Sacco F, Miele MC, Mastroianni CM, et al. Cefiderocol for compassionate use in the treatment of complicated infections caused by extensively and pan-resistant *Acinetobacter baumannii*. J Glob Antimicrob Resist. 2020;23:292-296. doi: 10.1016/j.jgar.2020.09.019.