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The role of cefiderocol in clinical practice

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ABSTRACT

Cefiderocol is a new antimicrobial with a chemical structure similar to ceftazidime and cefepime. In this review we will focus on the role of cefiderocol in different clinical scenarios produced by resistant Gram-negative microorganisms, especially to carbapenems. In infections caused by Gram-negative microorganisms, inappropriate antibiotic treatment increased the risk of mortality almost fourfold.

In patients with hospital-acquired infection and septic shock; with sepsis and poor functional reserve due to fragility; in immunocompromised patients; and in those with local ecology, individual history of colonization or previous infection and risk factors for carbapenem-resistant *Enterobacteriaceae* (CRE) such as the presence of chronic multi-morbidities, the best option would be to start an active empirical treatment against gram-negative bacteria resistant to carbapenems and later in 24-36 h with the information obtained from the cultures we could decide on a definitive empirical or directed treatment and avoid unnecessary overuse of these antibiotics. Cefiderocol would be in these cases a good candidate due to its excellent in vitro activity against all classes of beta-lactamase-producing Gram-negatives (including carbapenemase class A, B and D producers), as well as against non-fermenting Gram-negatives such as *P. aeruginosa*, *Acinetobacter* spp. and *S. maltophilia*. It is necessary to optimize the use of new antibiotics such as cefiderocol, guaranteeing the best available treatment to patients while delaying the emergence and spread of resistance.

Keywords: cefiderocol, *Enterobacterales*, carbapenem-resistant, *Pseudomonas aeruginosa*, *Acinetobacter baumanniii*

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In 2017, the World Health Organization published the list of antibiotic-resistant bacteria that generated the greatest concern worldwide. Of the four microorganisms identified as priorities, three of them are carbapenem-resistant: carbapenem-resistant *Enterobacteriaceae* (CRE) or carbapenemase-producing *Enterobacteriaceae* (CPE), carbapenem-resistant *Pseudomonas aeruginosa* (CR-PS), and carbapenem-resistant *Acinetobacter baumannii* (CR-AB). These are microorganisms for which we lack effective antimicrobial treatment and which generate high mortality in the infectious processes they cause [1]

In this regard, the Infectious Diseases Society of America (IDSA), in view of the worldwide increase in antimicrobial resistance, has recently published a clinical guideline establishing the potential role of "new" and "old" antimicrobials in dealing with bacterial infections caused by resistant Gram-negative bacteria [2].

In this paper, we will review the role of cefiderocol, a new antimicrobial with a chemical structure similar to ceftazidime and cefepime, in different clinical scenarios produced by resistant Gram-negative microorganisms, especially to carbapenems. Most of the available clinical data on the role of cefiderocol come from the APEKS-cUTI, APEKS-NP, CREDIBLE-CR studies and publications with real-life case series [3-11].

In the clinical guidelines published by the IDSA [2], cefiderocol is recommended as one of the best therapeutic options for the treatment of patients with pyelonephritis and complicated urinary tract infections caused by CRE and by *P. aeruginosa* with difficult-to-treat resistance (DTR) (exhibiting non-susceptibility to all beta-lactams, including carbapenems, and to fluoroquinolones). Likewise, if the patient is infected by CPE producer of metallo-beta-lactamase or an unidentified carbapenemase, cefiderocol would be one of the best therapeutic options.

With the available data, we will give a personal view on the value of cefiderocol in clinical practice for patients with Gram-negative infections resistant especially to carbapenems.

WHEN SHOULD WE USE CEFIDEROCOL AS EMPIRICAL TREATMENT AGAINST POSSIBLE GRAM-NEGATIVE BACILLI RESISTANT TO CARBAPENEMS?

Different studies confirm the relationship between the delay in initiating appropriate antibiotic treatment and mortality [12-17]. In infections caused by Gram-negative microorganisms, inappropriate antibiotic treatment increased the risk of mortality almost fourfold [18]. Furthermore, the need for prompt antibiotic treatment becomes extremely important in patients with sepsis or septic shock, in whom even with treatment mortality can reach 27% to 40% [19-21], in patients with limited functional reserve due to frailty or multi-morbidity, and in patients with some degree of immunosuppression. Despite the importance of these data, the reality is that according to Vazquez-Guillamet et al. the rate of inappropriate antibiotic treatment continues to be almost 30% of patients with sepsis or septic shock, and according to these authors the number of patients needed for appropriate antimicrobial treatment to save a life would be 5 [22]. The most important factor predisposing to inappropriate antibiotic treatment is infection by resistant microorganisms [18,22].

Knowledge of the local epidemiology is essential in order to initiate appropriate empirical treatment. Knowing the total rate of carbapenem resistance among most of the epidemiologically important Gram-negatives in each department and hospital can be used as an indicator of patient risk for the presence of carbapenem-resistant Gram-negative microorganisms. A threshold of 10-20% carbapenem resistance is considered sufficient to initiate active antimicrobial treatment for carbapenem-resistant Gram-negatives.

But this alone is not sufficient. Most hospital-acquired infections are infections that originate from the endogenous microbiota of mucosal surfaces by translocation or invasion of predominant microorganisms depending on the density of the bacterial population. Therefore, knowing the colonizing flora and its antimicrobial susceptibility pattern may be important in the choice of initial empirical treatment. Therefore, it would seem reasonable to perform surveillance cultures on admission to the ICU and 1-2 times a week thereafter, although changes in the composition of the microbiota prior to the sepsis episode cannot be ruled out. An alternative strategy is to obtain a semiquantitative rectal, pharyngeal and nasal mucosa swab at the time of sepsis.

It is also important to assess the site of infection. In patients with risk factors for carbapenem-resistant Gram-negatives, we should evaluate the use of new antibiotics such as cefiderocol when the clinical efficacy of possible alternatives is expected to be suboptimal, as in the case of polymyxins and/or aminoglycosides in patients with pneumonia [23,24].

However, making decisions on the use of active empirical treatment against carbapenemase-producing Enterobacteriaceae can be difficult for the clinician. Scales that aim to predict the individual risk of developing bacteremia in patients colonized by these microorganisms have been published and validated [25-28]. These scales have their limitations, in the sense that they are validated in an epidemiological setting with a specific group of patients, and that they cannot necessarily be reproduced in different clinical situations.

In any case, it is crucial to initiate early empirical antibiotic treatment with no margin for error in patients with hospital-acquired infection and septic shock, with sepsis and poor functional reserve due to fragility, or in immunocompromised patients. In this type of patients and in those with local ecology, individual history of colonization or previous infection and risk factors for CRE such as the presence of chronic multi-morbidities [29], the best option would be to start an active empirical treatment against Gram-negative bacteria resistant to carbapenems and later in 24-36 h with the information obtained from the cultures we could decide on a definitive empirical or directed treatment and avoid unnecessary overuse of these antibiotics.

We need antibiotics that are active against the highest possible percentage of Gram-negative microorganisms involved with carbapenem resistance, with cefiderocol being, a priori, a good candidate due to its excellent in vitro activity against all classes of beta-lactamase-producing Gram-negatives (including carbapenemase class A, B and D producers), as well as against non-fermenting gram-negatives such as *P. aeruginosa*, *Acinetobacter* spp. and *S. maltophilia*. Depending on the infectious focus we should add antimicrobials with activity against Gram-positive bacteria (daptomycin, linezolid, vancomycin) and anaerobes as in the case of intra-abdominal infection (tigecycline or eravacycline). Figure 1 summarizes graphically the possible factors that determine the choice of new antibiotics such as cefiderocol in empirical antimicrobial treatment against carbapenem-resistant Gram-negatives.

CEFIDEROCOL AGAINST CARBAPENEM-RESISTANT *ENTEROBACTERALES*

Cefiderocol shows in vitro activity against different carbapenemase-producing CRE including KPC, OXA-48 and MBLs (NDM, IMP, VIM) [30]. According to clinical data from the CREDIBLE-CR study [5], clinical cure of cefiderocol was similar to the best available antimicrobial therapy (53% vs 50%). In patients with infections caused by CRE, 19 (66%) of 29 patients in the cefiderocol group and 5 (45%) of 11 patients in the best available antimicrobial treatment achieved clinical cure. Notably, in infections caused by MBL-producing bacteria, clinical cure was 75% in the cefiderocol group and 29% in the best available antimicrobial therapy group.

The clinical guidelines recently published by the IDSA for antimicrobial treatment against multidrug-resistant Gram-negative bacteria recommend the use of cefiderocol as one of the best options for infections caused by NDM-producing CRE and other MBLs, and it is also a therapeutic alternative against carbapenemase-producing CRE of the KPC and OXA-48 types [2].

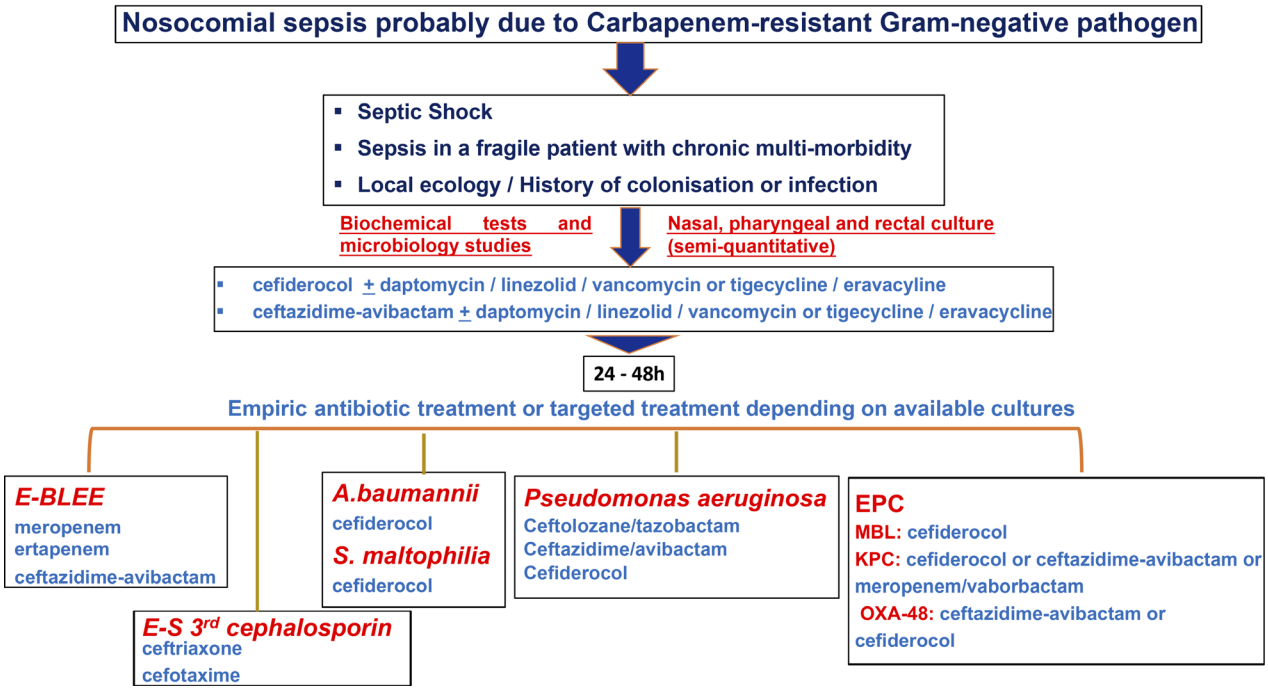

Figure 1 | **Clinical algorithm for using new antibiotics as an empirical treatment against carbapenem-resistant Gram-negative.**

ESBL-E: Extended-spectrum beta-lactamases producing *Enterobacterales* ; E-S 3rd cephalosporin: third-generation cephalosporin-susceptible *Enterobacterales*; CRE: carbapenem-resistant *Enterobacterales*; MBL: metallo-beta-lactamase; KPC: *Klebsiella pneumoniae* carbapenemase; OXA-48: OXA-48-like carbapenemase.

CEFIDEROCOL IN TARGETED ANTIBIOTIC TREATMENT AGAINST CARBAPENEM-RESISTANT *P. AERUGINOSA*, CARBAPENEM RESISTANT *A. BAUMANNII* AND *S. MALTOPHILIA*

Cefiderocol shows great *in vitro* activity against CR-PS. In a multicenter study conducted in Europe, cefiderocol showed activity against 97.5% of carbapenem-resistant *P. aeruginosa* strains [31]. In two randomized, controlled studies, cefiderocol was non-inferior to its comparators in patients with complicated urinary tract infections and in patients with nosocomial pneumonia including ventilator-associated pneumonia [3,4]. As previously mentioned, in the CREDIBLE-CR study, the clinical cure of patients treated with cefiderocol was similar to that of patients treated with the best available therapy for carbapenem-resistant Gram-negative infections [5]. In this study, 19 % of patients (22 of 118 patients included in the study) developed *P. aeruginosa* infections. Clinical cure in patients with pneumonia or bacteremia in this subgroup of patients was similar in both treatment groups.

We also have clinical evidence for patients who received cefiderocol in a compassionate use setting, with no alternative treatment options for DTR / CR-PS infections. Among 29 patients with *P. aeruginosa* isolates that had cefiderocol MICs up to 4 mg/L or susceptibility confirmed by disk zone diameter, 24 receiving cefiderocol responded to treatment (14 patients in combination therapy and 10 patients monotherapy) [10].

While the IDSA clinical guidelines [2] recommends cefiderocol as a primary treatment option exclusively for patients with DTR *P. aeruginosa* UTI (uncomplicated, complicated, and pyelonephritis), I believe that based on recent results [31] and complex clinical cases demonstrating its efficacy in real life [10], cefiderocol should be considered as one of the main options in the treatment of DTR *P. aeruginosa* in scenarios other than UTI such as pneumonia.

In the study by Candel et al. [31], cefiderocol showed in vitro activity against 91% of CR-AB isolates. According to clinical data provided by the APEKS-NP study [4], 16% of patients had *A. baumannii* pneumonia and the clinical response was similar in patients receiving cefiderocol (52%) or high dose meropenem (58%). In the CREDIBLE-CR study [5], although clinical cure of patients with pneumonia and bacteremia treated with cefiderocol versus best available therapy was similar in both treatment groups, crude all-cause mortality at 14, 28 and 49 days was higher in patients treated with cefiderocol [32]. This difference in mortality was observed mainly in patients with *A. baumannii* infections. The cause for this difference in mortality has not been fully established and we do not know if these results would be reproducible

in another study, if they could be due to chance considering the small sample size of the study, or if they are due to not achieving optimal PK/PD targets with the currently recommended dosing [33]. In any case, it would be important to know the true attributable mortality in both treatment groups to determine the effect of both therapeutic interventions on infection [34]. On the other hand, different real-life cases have been published in which cefiderocol has shown excellent results in complex infections produced by carbapenem-resistant, extremely resistant and pan-resistant *A. baumannii* [6,7,9]. An observational study including 124 patients with CR-AB infections (79 patients with bloodstream infection, 35 with a ventilator-associated pneumonia and 10 with other infections) compared cefiderocol- and colistin-containing regimens [11]. A total of 47 patients received cefiderocol, while 77 colistin-containing regimens. Thirty-day mortality in patients receiving colistin- compared to those who received cefiderocol-containing regimens was 55.8% versus 34% (p = 0.018). On multivariable analysis cefiderocol therapy was protective with 30-day mortality and nephrotoxicity was more common in the colistin group.

Cefiderocol should be considered as one of the best therapeutic options against CR-AB in patients with severe infections such as pneumonia, given the limited treatment alternatives available, either due to poor penetration or toxicity. Another aspect that should be analyzed, which is beyond the scope of this review, is whether it should be used in monotherapy or as combination therapy.

According to the study by Candel et al. cefiderocol has an in vitro activity against *S. maltophilia* of 99.6% [31]. It shows MIC_{90} values of 0.5 and 0.25 mg/L for isolates from North America and Europe, respectively, and no isolate with MIC > 4 mg/L [35]. Clinical experience is very limited. There were only five patients included in the CREDIBLE-CR study with *S. maltophilia* infections; all of them developed pneumonia and were randomized to the cefiderocol group. Four of these five patients did not survive [5]. However, with the small sample size and no patients with *S. maltophilia* in the best available antibiotic group, it is difficult to draw valid conclusions. Nevertheless, based on published experience in some real-life cases [9] cefiderocol should be considered as an option for severe *S. maltophilia* infections.

CONCLUSIONS

With this brief review, we have tried to highlight the use of cefiderocol in clinical practice for the treatment of resistant Gram-negative infections, especially against carbapenems. Taking into account that until very recently we did not have antimicrobial options that were completely effective and well tolerated against this type of infections, it is necessary to optimize the use of new antibiotics such as cefiderocol, guaranteeing the best available treatment to patients while delaying the emergence and spread of resistance.

CONFLICT OF INTEREST

E.M. reports personal fees from Shinogi. A.S.D.L.R. has nothing to declare

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