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Cefiderocol. Summary and conclusions

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Antimicrobial treatment of most nosocomial infections includes the use of a β-lactam antibiotic. The antibacterial spectrum, tolerance and, in particular, clinical experience, justify the consideration of β-lactams as antibiotics of first choice, both in empirical treatment patterns and in targeted therapy.

Even assuming an ideal situation in which antibiotic prescription is appropriate and measures to prevent the acquisition of nosocomial infection are optimal, the consumption of B-lactam antibiotics in the hospital, especially in critical care and oncohematology units is inevitably high and is likely to remain so or even increase in the future with the progressive aging of the population and the increased complexity of some surgical procedures and the immunosuppression associated with many medical treatments. Under these conditions, even the rational prescription of β-lactams will end up selecting microorganisms with resistance mechanisms.

In gram-negative bacilli, resistance mechanisms can be classified into two large groups: 1) the production of β-lactamases, and 2) mechanisms that decrease the concentration of antibiotic in the periplasmic space. Research aimed at recovering the activity of β-lactams has been directed, on the one hand, to the search for inhibitors of β-lactamases with a broader spectrum or β-lactams with lower affinity or possibility of hydrolysis by β-lactamases and, on the other hand, to the development of antibiotics with a greater capacity for diffusion to the periplasmic space. Cefiderocol is a new cephalosporin that serves both purposes.

Cefiderocol has a C-7 side chain identical to ceftazidime and a C-3 side chain similar to cefepime, but with a chlorocatechol group at the end that makes it a siderophore. The natural siderophores enterobactin (*E. coli*) and pyoverdine (*P. aeruginosa*) contain similar catechol groups as an iron chelating moiety. During the infectious process, the innate immune response causes sequestration of intracellular iron to prevent bacteria from utilizing it. This leads to up-regulation of the bacterial iron transport system, which increases the uptake of extracellular iron or, in this case, the cefiderocol-iron complex. In the periplasmic space, iron is released and cefiderocol binds to PBPs, especially PBP3. The entry of cefiderocol into the periplasmic space simultaneously by facilitated diffusion (siderophore) and passive/facilitated diffusion (by porins), to some extent overwhelms the activity of β-lactamases [1].

Cefiderocol is not a substrate of the various efflux pumps, is stable against BLEEs and most carbapenemases (both class A, B and D) and has very low affinity for AmpC of *P. aeruginosa* and *Enterobacter*. In general, β-lactamases alone are not sufficient to raise the MIC of cefiderocol above the susceptibility cutoff point. Resistance usually results from coexpression of multiple β-lactamases and/or overexpression of β-lactamases, possibly in combination with changes in PBP3 and mutations associated with reduced permeability such as those affecting the expression/function of siderophore receptors and, to a lesser extent, porins and/or efflux pumps [2].

Cefiderocol is active with a MIC_{90} ≤ 2 mg/L, against aerobic gram-negative bacilli including Enterobacteriaceae, nonfermenting BGN (*P. aeruginosa, Acinetobacter, Stenotrophomonas, Burkholderia, Achromobacter* and *Chryseobacterium* spp.), *Vibrio, Aeromonas, Haemophilus* and *Neisseria* spp (except ceftriaxone-resistant *N. gonorrhoeae*). The activity is lower against anaerobic bacteria and Gram-positive bacteria. *Staphylococcus* and *Enterococcus* spp are resistant. Against *S. pneumoniae* the MIC_{90} is 2 mg/L [3].

The association of cefiderocol with β-lactamase inhibitors, particularly with avibactam, is synergistic against resistant *A. baumannii* by production of PER. Likewise, in vitro synergism has been observed with associations of cefiderocol with meropenem, amikacin, tigecycline and minocycline.

The administration of 2 g infused by iv in 1 hour generates

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a Cmax of 150 mg/L. Protein binding is 50%, volume of distribution is 0.26 L/kg and elimination half-life is 2.5 hours. It is almost completely eliminated by the renal route with almost no metabolism. In case of renal insufficiency, the dose should be reduced from a GFR < 60 mL/min, but it is not necessary to modify it in case of hepatic insufficiency.

Antimicrobial activity is related to the time that the fraction of free antibiotic remains above the MIC (%*f*T × MIC). Optimal efficacy can be expected when the concentration of cefiderocol remains 4 times above the MIC during the 80-100% interval between consecutive doses. The administration of 2 g/8 h in a 3 h extended infusion obtains a free antibiotic Cmin > 4 mg/L. In patients with GFR > 120 mL/min, the use of 2 g/6 doses should be considered. Once the vial has been reconstituted and diluted in 100 mL of glucose or physiological solution, it is stable for up to 6 hours at 25ºC.

No clinically significant interference has been observed between cefiderocol and substrates of different anion and cation organic transporters (OAT, OCT, MATE, OATP, BCRP). In vitro cefiderocol induces CYP3A4 activity and to a lesser extent CYP2C and g-Pp. If co-administered with CYP3A4 substrates, the efficacy of the concomitant drug should be monitored. Tolerability of the drug is like that of other cephalosporins Side effects observed in pivotal clinical trials classified as frequent include gastrointestinal disturbances (nausea (3.3%), vomiting (3.6%), diarrhea (8.2%)), increased liver enzymes (ASAT, ALAT), hypersensitivity reactions and perfusion site reactions (pain, erythema, phlebitis). Cases of candidiasis (oral, vulvovaginal, candiduria) and diarrhea due to *Clostridioides difficile* have been reported. Each vial of 1 g contains 7.64 mmol of sodium (approximately 176 mg). Two grams of cefiderocol, reconstituted with 100 mL of 0.9% sodium chloride solution for injection, contains 30.67 mmol (705 mg) of sodium. Reconstitution of 2 g with 100 mL of 5 % dextrose solution for injection contains 15.28 mmol (352 mg) of sodium [4].

The clinical efficacy of cefiderocol has been investigated in three double-blind, randomized controlled trials. A phase II study (APEKS-cUTI) included patients with complicated UTI, the comparator was imipenem/cilastatin and the endpoint was the sum of clinical and microbiological response 7 days after cessation of treatment. The result was an efficacy difference adjusted of 18.6% (95% CI: 8.2-28.9; p = 0.0004) in favor of cefiderocol, indicating that cefiderocol is not inferior to imipenem/cilastatin for treatment of complicated UTI. The Phase III study (APEKS-NP) included patients with nosocomial pneumonia (including that associated with mechanical ventilation) caused by gram-negative aerobic bacteria. The comparator was meropenem administered at a dose of 2 g/8 hours in a 3-hour infusion. No significant differences were observed in all-cause mortality (primary endpoint) at day 14. The third phase III study (CREDIBLE-CR) included patients with severe infections (nosocomial pneumonia, bacteremia or complicated urinary tract infection) caused by carbapenem-resistant gram-negative bacilli and the comparator was the best available therapy, mostly based on associations of colistin with other antibiotics. The most common pathogens were *Acinetobacter* spp (n = 56), *K. pneumoniae* (n = 39) and *P. aeruginosa* (n = 22). The clinical cure rate of nosocomial pneumonia or bacteremia and the microbiological eradication rate in complicated urinary tract infection were not numerically different between the two groups. However, the mortality of patients with *Acinetobacter* spp infection treated with cefiderocol was higher than that of the control group [5]. On the other hand, it has been observed that in vitro, when *A. baumannii* grows in the presence of human albumin or serum it undergoes down-regulation of genes involved in iron uptake. At the same time, genes for β-lactamases are expressed at higher levels. The result is an increase in MIC that could explain the lower clinical response observed in some infections produced by *A. baumannii* [6,7]. This data contrasts with clinical experience published of isolated cases or short series of patients with recalcitrant infections caused by *Acinetobacter* spp. MDR in which cefiderocol was used in rescue treatment or compassionate use due to colistin toxicity. It cannot be ruled out that the favorable results obtained in most of these cases are due to a possible selection and/or publication bias.

Treatment with cefiderocol, as with any other β-lactam, is not exempt from the risk of resistance development or failure, particularly when used in the therapy of infections in which one or more of the following circumstances usually coexist: (a) infections caused by multidrug-resistant microorganisms, which have shown a high capacity for mutation and/or incorporation of extrachromosomal genetic material after exposure to different antimicrobials, (b) microorganisms against which the MIC of cefiderocol is at the sensitivity limit (at or very close to the cut-off point), (c) infections with a high bacterial load and/or difficult control of the focus, or (c) infections in patients suffering from immunosuppression or significant comorbidities. In these circumstances, it is essential to optimize the PK/PD parameters (dose and administration schedule) of cefiderocol and the use of associations at least during the first 24-48 h of treatment.

In clinical practice the indications for use of cefiderocol include [8]:

(a) Targeted treatment of infection produced by a multidrug-resistant BGN against which cefiderocol is the only active β-lactam or the β-lactam that, because of its intrinsic activity, is most likely to achieve the optimal PK/PD parameter.

(b) Empirical treatment of severe (sepsis) or potentially severe infection (patient with Charlson index ≥ 4 and CRP ≥ 20) if present:

- History of infection or colonization in the last 3 months, by a carbapenem-resistant BGN and/or resistant to associations of a β-lactam with a carbapenemase-resistant β-lactamase inhibitor.

- History of having received in the last 3 months, treatment with a β-lactam associated with a carbapenemase-resistant β-lactamase inhibitor.

- Admission to a hospitalization unit in which there is a high pressure of colonization by carbapenem-resistant BGN

and/or associations of a β-lactam with a carbapenemase-resistant β-lactamase inhibitor.

CONFLICT OF INTEREST

JM has participated in scientific meetings and lectures organized or promoted by the companies Pfizer, and Shionogi. JB has participated in scientific meetings and lectures organized or promoted by the companies Pfizer, Menarini, and Shionogi.

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