REVISTA ESPAÑOLA DE
Quimioterapia

SPANISH JOURNAL
OF CHEMOTHERAPY

ISSN: 0214-3429
Volume 35
Supplement number 2
September 2022
Pages: 01-47

Cefiderocol, the first catechol-cephalosporin

Guest editor:
Dr. José Barberán
Servicio de Medicina Interna y Enfermedades Infecciosas, Hospital Universitario HM Montepríncipe, Universidad San Pablo CEU. Madrid, Spain

Publicación Oficial
de la Sociedad Española
de Quimioterapia

REVISTA ESPAÑOLA DE
Quimioterapia

Revista Española de Quimioterapia tiene un carácter multidisciplinar y está dirigida a todos aquellos profesionales involucrados en la epidemiología, diagnóstico, clínica y tratamiento de las enfermedades infecciosas

Fundada en 1988 por la Sociedad Española de Quimioterapia

Indexada en
Science Citation Index Expanded (SCI),
Index Medicus (MEDLINE),
Excerpta Medica/EMBASE,
Índice Médico Español (IME),
Índice Bibliográfico en Ciencias de la Salud (IBECS)

Secretaría técnica
Dpto. de Microbiología
Facultad de Medicina
Avda. Complutense, s/n
28040 Madrid
revista@seq.es
Disponible en Internet:
www.seq.es

Sociedad Española de Quimioterapia

Publicidad y Suscripciones
Sociedad Española de Quimioterapia
Dpto. de Microbiología
Facultad de Medicina
Avda. Complutense, s/n
28040 Madrid

Atención al cliente
Teléfono 91 394 15 12
Correo electrónico
info@seq.es

Consulte nuestra página web
www.seq.es

Publicación que cumple los requisitos de soporte válido

ISSN
0214-3429

e-ISSN
1988-9518

Depósito Legal
M-32320-2012

Maquetación
Vic+DreamStudio

Impresión
España

Esta publicación se imprime en papel no ácido.
This publication is printed in acid free paper.

REVISTA ESPAÑOLA DE
Quimioterapia

Contents

REVISTA ESPAÑOLA DE Quimioterapia

Volume 35
Supplement number 2
September 2022

Cefiderocol , the first catechol-cephalosporin

Official journal of the Spanish Society of Chemotherapy

Víctor Garcia-Bustos
Marta Dafne Cabañero-Navalón
Miguel Salavert Lletí

Resistance to beta-lactams in Gram-negative bacilli: relevance and potential therapeutic alternatives

Unit of Infectious Diseases. Clinical Medical Area. University and Polytechnic Hospital La Fe, Valencia, Spain.

Revista Española de Quimioterapia
doi:10.37201/req/s02.01.2022

ABSTRACT

The indiscriminate and massive antibiotic use in the clinical practice and in agriculture or cattle during the past few decades has produced a serious world health problem that entails high morbidity and mortality: the antibiotic multi-drug resistance. In 2017 and 2019, the World Health Organization published a list of urgent threats and priorities in the context of drug resistance, which only included Gram-negative bacteria and specially focused on carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, as well as carbapenem and third generation cephalosporin-resistant *Enterobacteriaceae*. This scenario emphasizes the need of developing and testing new antibiotics from different families, such as new beta-lactams, highlighting cefiderocol and its original mechanism of action; new beta-lactamase inhibitors, with vaborbactam or relebactam among others; new quinolones such as delafloxacin, and also omadacycline or eravacycline, as members of the tetracycline family. The present work reviews the importance and impact of Gram-negative bacterial infections and their resistance mechanisms, and analyzes the current therapeutic paradigm as well as the role of new antibiotics with a promising future in the era of multi and pan-drug resistance.

Keywords: Gram-negative rods, multi-resistance, new antibiotics, cefiderocol

INTRODUCTION

Gram-negative bacterial infections are one of the major global public health problems. The high rate of antibiotic resistance and the increasing frequency of outbreaks of healthcare-associated infections lead to high morbidity and mortality [1-3]. Enterobacteriaceae (Enterobacteriaceae family) and non-fermenting Gram-negative bacilli are the two main groups of isolates with the highest pathogenicity and multidrug resistance causing hospital infections. In the case of the former, *Escherichia coli*, *Klebsiella spp*, *Enterobacter* spp, *Proteus* spp, *Citrobacter* spp, or others with frequently digestive involvement such as *Salmonella* spp, *Shigella* spp, or *Yersinia* spp. are among the most frequently isolated microorganisms, producing urinary tract infections, hospital-acquired bacterial pneumonia (HABP) and mechanical ventilation-related pneumonia (VAP), meningitis, intra-abdominal infections, bacteremia, and sepsis of various foci, among others. As for the latter, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia* or *Burkholderia cepacia* are of interest due to their role as opportunistic pathogens especially in critical care units and special hosts, and *Pseudomonas aeruginosa*, due to its high virulence and prevalence [1,4-6].

In 2017 and, later, in 2019, the World Health Organization (WHO) published a list of resistant pathogens stratified into different degrees of priority based on criteria such as mortality, socioeconomic burden, prevalence of resistance, transmissibility, preventability in the healthcare setting, and treatment options [7]. The critical priority multidrug-resistant (MDR) pathogens included only Gram-negative bacteria, namely carbapenem-resistant *A. baumannii* and *P. aeruginosa*, as well as enterobacteria resistant to carbapenems and third-generation cephalosporins. This multi-resistance results from the expression of drug inactivating enzymes or diverse non-enzymatic derivatives, being transmissible through the transfer of mobile genetic elements such as plasmid beta-lactamases or aminoglycoside-modifying enzymes; or they could be non-transmissible through chromosomal mutations, as happens with efflux pumps, alterations in membrane permeability or some inactivating enzymes, among others [5,8].

Therefore, the present work aims to review the importance and impact of Gram-negative bacterial infections and their resistance mechanisms, in addition to analyzing the cur-

Correspondence:
Miguel Salavert Lletí.
Unidad de Enfermedades Infecciosas. Área Clínica Médica.
Hospital Universitario y Politécnico La Fe, Valencia.
Av. Fernando Abril Martorell, nº 106. Valencia 46016.
E-mail: Salavert_mig@gva.es

rent therapeutic paradigm and the role of new antibiotics with a promising future in this era of multi- and pan-resistance, with special emphasis on cefiderocol.

INFECTIONS BY GRAM-NEGATIVE BACTERIA AT "BIRD'S EYE VIEW"

With great clinical importance and high morbimortality and prevalence, infections by Gram-negative bacteria have a high rate of antibiotic resistance that threatens healthcare systems worldwide, generating outbreaks of nosocomial infection of particular importance in critical care units and immunocompromised patients [1-3].

In contrast to Gram-positive microorganisms, Gram-negative bacteria have two membranes surrounding the peptidoglycan bacterial wall. While the membrane is involved in multifunctional processes, both structural and molecular transport and biosynthetic functions, one of the most potent major bacterial inducers of the immune response, lipopolysaccharide, or LPS, is found in the lipid bilayer that makes up the outer membrane [9]. Composed of a hydrophilic polysaccharide, antigen O and lipid A, the latter is responsible for the high endotoxic activity of Gram-negatives and is thus one of the most important determinants of pathogenicity [5, 6]. Moreover, this membrane structure is the main procurer of many of the mechanisms of resistance to a wide range of antibiotics that make Gram-negatives one of the major health threats. While hydrophobic drugs, such as aminoglycosides or macrolides, pass through passive diffusion, the highly hydrophilic beta-lactams cross the outer membrane through porins [10], so that their protein and lipid composition has a great impact on antibacterial susceptibility and the generation of high-grade resistance, to a greater extent than in Gram-positive bacteria [10,11].

With great clinical importance and high morbimortality and prevalence, infections by Gram-negative bacteria have a high rate of antibiotic resistance that threatens healthcare systems worldwide, generating outbreaks of nosocomial infection of particular importance in critical care units and immunocompromised patients [1-3].

Two main groups are responsible for most of the significant clinical isolates of high pathogenicity and multidrug-resistance, causing hospital infections: enterobacteria - *Enterobacteriaceae* family - and non-fermenting Gram-negative bacilli.

With more than 30 genera and 100 species, enterobacteria account for practically 80% of infections caused by Gram-negative bacteria in the hospital setting, including urinary tract infections, nosocomial and VAP, meningitis, intra-abdominal infections, bacteremia and sepsis of different foci, as well as endotoxic shock, among others. Among the most frequent are *E. coli*, *Klebsiella* spp, *Enterobacter* spp, *Proteus* spp, *Citrobacter* spp, or others with frequent digestive involvement such as *Salmonella* spp, *Shigella* spp, or Yersinia *spp*. On the other hand, the group of non-fermenting Gram-negative bacilli includes pathogens of high virulence, prevalence and antibiotic resistance such as *P. aeruginosa*, to microorganisms with a lower degree of pathogenicity and frequency, but of interest as originators of opportunistic infections or with high multidrug resistance in the hospital environment and, predominantly, in critical care units or in patients with comorbidities, high risk of colonization and frequent exposure to antibiotherapy, such as *A. baumannii*, *S. maltophilia* or *B. cepacia* [1,4-6].

THE ERA OF RESISTANCE

Since the discovery of penicillin by Alexander Fleming in 1929, a large number of antibiotic agents have been developed that have contributed to the global shift from infectious and contagious pathology as the main cause of morbidity and mortality to chronic non-communicable pathology. However, the massive and indiscriminate use of antibiotics in clinical practice and in agriculture or animal husbandry during the last decades has generated a problem that threatens, once again, the control that health systems had achieved over infectious pathology: antibiotic resistance [12]. In the USA, more than 2.8 million infections due to resistant microorganisms occur annually, causing more than 35,000 deaths per year and with an associated cost of more than 2 billion dollars [13].

In the last 15 years, the problem of antibiotic resistance to two or more drugs, or multidrug resistance, particularly in Gram-negative bacteria, has increased exponentially, challenging the management of severe nosocomial infections, increasing morbidity and mortality again, and generating strains with extreme resistance and even pan-resistance (PDR) [14,15].

In 2017, WHO published a list of resistant pathogens stratified into different degrees of priority (critical, high, and medium priority) based on the threat they pose to public health and the urgency of the need for new antibiotics or therapeutic tools with which to address them [7]. The critical priority multidrug-resistant (MDR) pathogens included only Gram-negative bacteria, namely carbapenem-resistant *A. baumannii* and *P. aeruginosa*, as well as carbapenem-resistant enterobacteria and third-generation cephalosporins. This classification, based on criteria such as mortality, socioeconomic and health system burden, resistance prevalence and 10-year trend, transmissibility, preventability in the health care setting, and treatment options, aims to prioritize research and development of new antimicrobial strategies [7].

The mechanisms of antimicrobial resistance in gram-negative bacteria result on the one hand from the expression of enzymes capable of inactivating the drug or, on the other hand, are derived from diverse non-enzymatic mechanisms. In turn, they may originate from non-transmissible mechanisms due to chromosomal mutations (inactivating enzymes, efflux pumps, alterations in the molecular target or in membrane permeability) or may be transmissible through the transfer of mobile genetic elements such as plasmid beta-lactamases, aminoglycoside-modifying enzymes, or plasmidic non-enzymatic mechanisms as part of quinolone resistance in enterobacteria [5,8].

Following the WHO's critical prioritization, we will now review the clinical importance and the main resistance mechanisms of the main Gram-negative bacterial threats in this new era of multidrug resistance.

Acinetobacter baumannii is an aerobic Gram-negative bacillus that frequently causes nosocomial infections in critical care patients, such as VAP. The treatment of severe *A. baumannii* infections resistant to all beta-lactams, their combinations with beta-lactamase inhibitors and fluoroquinolones has become a serious challenge in clinical practice. This fact has required recovering antimicrobial treatments of yesteryear with significant toxicity as rescue therapy, including among others polymyxins (colistin and polymyxin B) [16,17]. Carrier of an intrinsic AmpC-type cephalosporinase, its main mechanism of multidrug resistance consists in the production of beta-lactamases. Although efflux pumps can also be found (i.e. tigecycline efflux by overexpression of RND or AdeABC type pumps), aminoglycoside modifying enzymes (acetyltransferases, adenylyltransferases and phosphotransferases encoded by plasmids as well as integrons and transposons), alterations in membrane permeability (due to lower expression of porins associated with resistance to carbapenems or loss of LPS with decreased sensitivity to colistin), or alterations of molecular targets of antibiotherapy, such as the well-known PBPs and their diverse resistance associated with beta-lactams or DNA gyrase, in relation to decreased susceptibility to quinolones [5,18,19].

Emphasizing the main resistance mechanisms, the 4 classes of beta-lactamases have been described in *A. baumannii*. While some have a narrower spectrum (e.g., TEM-1, SCO-1 or CARB-4), the isolation of extended-spectrum beta-lactamases (ESBL)-producing strains, such as GES-11 or CTX-M, with reduced susceptibility to carbapenems is frequent [5]. In addition, class B beta-lactamases or metallo-beta-lactamases (MBL), which are a major problem worldwide, have potent carbapenemase activity and confer resistance to all beta-lactams except monobactams [18, 19]. It can also be a producer of class C beta-lactamases, defined by resistance to cephamycins and which can be identified in the antibiogram by their resistance to cefoxitin, with penicillinase and cephalosporinase activity. We cannot forget the class D beta-lactamases or OXA beta-lactamases, especially in our environment, capable of hydrolyzing a broad spectrum of cephalosporins and carbapenems and which, in the case of *A. baumannii,* OXA-23, OXA-24 and OXA-58 constitute emerging carbapenemases capable of generating serious outbreaks of nosocomial infection with difficult and complex therapeutic approach [18-20].

Pseudomonas aeruginosa is one of the most frequent nosocomial pathogens [21]. In addition to presenting intrinsic antibiotic resistance mechanisms (such as overexpression of efflux pumps or altered permeability, as previously described with *A. baumannii)*, it is capable of acquiring exogenous genetic material, resulting in the emergence of MDR strains with combined resistance to beta-lactams -including carbapenems-, aminoglycosides and fluoroquinolones [22].

Regarding endogenous mechanisms, the production of AmpC-type beta-lactamases induced by some beta-lactam antibiotics such as imipenem, or their overexpression produced by mutations in ampC, ampR, ampD or ampE genes [19] should be highlighted. In addition, we start from an intrinsic resistance to a wide range of antimicrobials product of the low intrinsic permeability of its outer membrane and the expression of efflux pumps, added to the inducible AmpC enzyme. In *P. aeruginosa*, class A, B, C and D beta-lactamases have also been identified, capable of conferring diverse resistance to the most commonly used antipseudomonal cephalosporins such as ceftazidime or cefepime [23], as well as piperacillin-tazobactam and carbapenems. The ease of acquiring resistance, both by chromosomal mutations and through horizontal acquisition of resistance determinants, has led to an increase in the prevalence of MDR or extremely resistant isolates (XDR). The production of IMP or VIM-type MBLs in *P. aeruginosa* strains with potent and broad carbapenemase activity has emerged as a serious emerging problem and is one of the reasons why WHO has considered these strains as a critical priority threat [7].

P. aeruginosa shares the mechanisms of aminoglycoside resistance previously discussed for *A. baumannii* through aminoglycoside-modifying enzymes, and resistance to fluoroquinolones is determined both by chromosomal mutations in genes encoding DNA gyrase or topoisomerase IV, as well as expulsion of the drug into the extracellular space by active transport [5].

***Enterobacterales* resistant** to third-generation cephalosporins and those resistant to carbapenems constitute the other two critical threats highlighted by the WHO to prioritize the development of new drugs and therapeutic strategies [7]. Resistance of the Enterobacteriaceae family to cephalosporins is determined by the production of beta-lactamases. New mutations can be added to some class A, lower spectrum, capable of hydrolyzing ampicillin, amoxicillin, and early generation cephalosporins such as TEM-1, TEM-2, or SHV-1, generating extended spectrum resistance to third generation cephalosporins, coexisting, on the other hand, with other ESBL such as CTX-M, capable of hydrolyzing cefotaxime more efficiently than ceftazidime [5].

However, resistance to carbapenems is an emerging problem of greater therapeutic complexity, of particular importance in critical care units. Since their description in the 1990s, their incidence has been increasing relatively homogeneously worldwide. Beyond those enterobacteria with intrinsic resistance to imipenem, such as *Proteus* spp, *Morganella morganii* or *Providencia* spp, the main problem is the production of carbapenemases [24,25]. There are 5 main types; the KPC or carbapenemases of *Klebsiella pneumoniae* (predominant, as their name indicates, in *K. pneumoniae* but not exclusive and also present in other enterobacteria), the New Delhi type MBL (or NDM), the VIM type MBL, both of global importance in the family, or the IMP type MBL -of importance, as has been mentioned, fundamentally in *P. aeruginosa*, as well

as the OXA-48 incidents, characteristic of *K. pneumoniae* and *E. coli* isolates, which exhibit varying degrees of hydrolytic activity and resistance to carbapenems [26].

FUNDAMENTALS OF THE TREATMENT OF INFECTIONS CAUSED BY MULTIDRUG RESISTANT GRAM-NEGATIVE BACTERIA

The selection of the appropriate antibiotic treatment for infections by resistant Gram-negative bacteria in complex patients depends on numerous highly interrelated factors, including characteristics of the pathogen and the origin of the infection, host-dependent factors, as well as factors related to antibiotherapy. In the factors related to the microorganism, it is essential to have data on the pharmacoepidemiology of resistance and the local epidemiological pattern, and it is necessary to consider not only the clinical focus, but also the community, healthcare-related or nosocomial context of the infection. In addition, in many cases, the choice of treatment is determined by the microbiological history of the patient, his clinical, immunological and comorbidity status, and by considerations that combine characteristics of the host and the drug or drugs chosen, such as pharmacokinetic or pharmacodynamic parameters, the safety profile and individualized toxicity, the ability to penetrate tissues or biofilms, as well as the spectrum, activity and post-antibiotic effect. We should not forget, also, in a public health system such as ours, the importance of taking into account the costs involved, the relevance of the use of some drugs or others, and the limitations of availability.

Multidrug-resistant Gram-negative pathogens present sometimes extremely limited therapeutic options, not only because of their sensitivity profile, but also because of the constellation of factors previously highlighted, which have led to a renewed interest in older drugs, previously discarded because of their high toxicity, such as colistin [17,27], and to use higher doses with new infusion regimens (prolonged or continuous infusion) or routes of administration (topical, nebulized inhalation, instillation) and combination treatments with a consequent increase in the risk of adverse effects.

Following the WHO critical threats approach, *A. baumannii* is one of the paradigms of extreme resistance to antibiotherapy. In sensitive strains, carbapenems are ideal agents for use. However, due to high-grade resistance, for more than a decade, treatment of severe *A. baumannii* infections has relied on the use of colistin, both in monotherapy and combination regimens [28,29]. However, in addition to nephrotoxicity and limitations in the knowledge of the drug that have forced its rediscovery in the strictly literal pharmacological sense, randomized clinical trials have shown that polymyxins generally present suboptimal efficacy [30]. Aminoglycosides may be useful, despite the obvious limitations, such as the high rate of resistance, nephrotoxicity, low pulmonary concentration in systemic treatments, and the scarce evidence of efficacy in inhaled treatments of both aminoglycoside and colistin [16]. The use of minocycline or tigecycline seems to be synergistic with colistin and they are better tolerated [31,32]. In cases with resistance to minocycline or colistin, their combination can be effective, as well as with trimethoprim-sulfamethoxazole or rifampicin [5]. On the other hand, sulbactam monotherapy or combined regimens with sulbactam have shown at least similar efficacy compared to other possibilities described [33].

Pseudomonas infections are more virulent than *A. baumannii* and those produced by MDR, XDR, and even PDR strains are of special concern. Although the therapeutic arsenal has recently expanded with the appearance of ceftolozane-tazobactam or ceftazidime-avibactam, polymyxins, in some cases, represent the only therapeutic option [34]. In this type of infections, not only the combination of drugs, especially with 2 or more, such as fosfomycin, aminoglycosides or quinolones, but also the increase of dosage and extended perfusion regimens with time-dependent antibiotics, such as carbapenems, which seek to optimize PK/PD parameters and time above the minimum inhibitory concentration (MIC) [34], has a special role [34]. In *P. aeruginosa* MDR isolates with AmpC production and mutation in porins, resistant to carbapenems but without carbapenemase production, ceftolozane-tazobactam in combination regimen with may be a valid alternative. On the other hand, with respect to the MBL problem, the role of possible new combinations, such as that of a monobactam (aztreonam) with a new beta-lactamase inhibitor from new molecular groups (for example, from the diaza-bicyclo-octanones, such as avibactam), formulated as aztreonam-avibactam, should also be highlighted [35].

Finally, with the increase in recent decades in the prevalence of infections by ESBL-producing Enterobacterales, carbapenems became the empirical therapy of first choice in areas with an unfavorable epidemiological situation, and in high-risk patients, which has made carbapenemase-producing Enterobacteriaceae an even greater problem [26,36], with very limited treatment options. While tigecycline and colistin have historically, and out of necessity in the absence of other options, been considered the first-choice treatment for infections caused by carbapenemase-producing *Enterobacteriaceae* [37,38], resistance to these drugs is now being added [38], forcing, as previously, the use of combinations with fosfomycin or aminoglycosides or, on the other hand, increasing the shock and maintenance doses of drugs such as tigecycline, given their safety profile [1,26,36]. However, dual therapy with carbapenems at higher doses, in extended perfusion, and/or in combination regimens may be useful in carbapenemase-producing Enterobacteriaceae with MICs lower than 8 mg/L of meropenem. The role of new drugs and combinations with beta-lactamase inhibitors, such as avibactam in combination with ceftazidime against beta-lactamases (carbapenemases) of groups A or D (OXA-48 type), should also be highlighted [39].

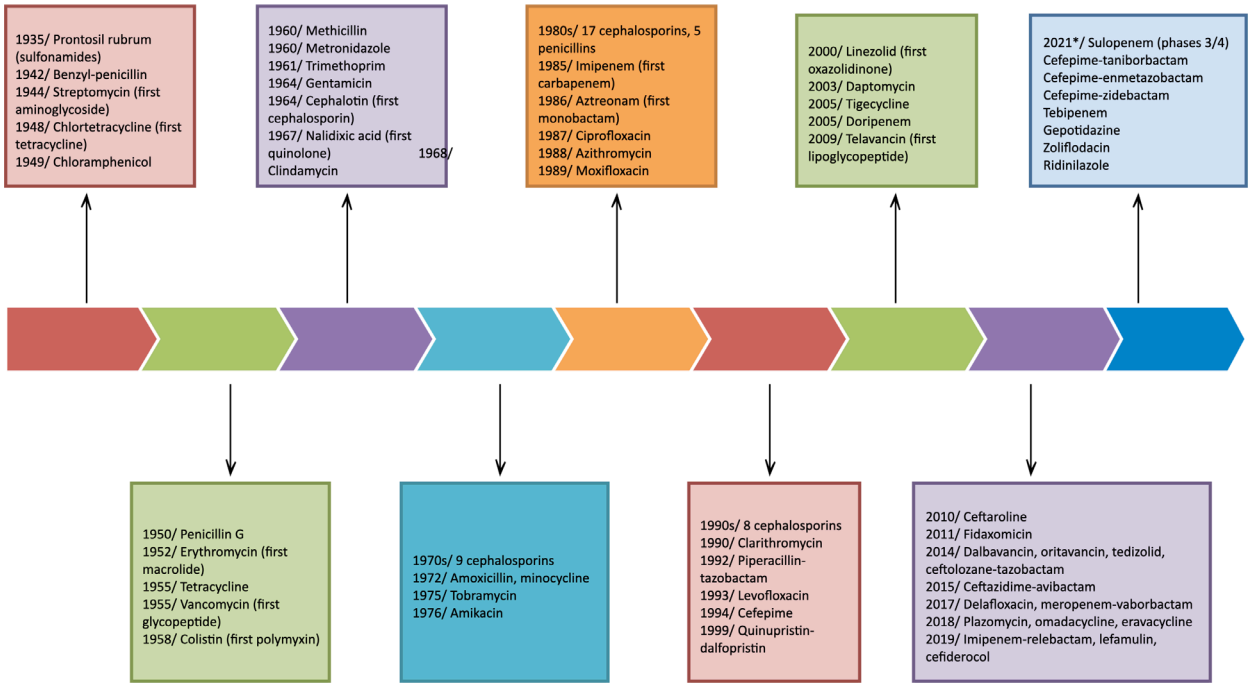


Figure 1 | **Chronological evolution of the investigation and development of antibiotics through time (antibiotic pipeline)**

Adapted and modified from: https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/03/tracking-the-global-pipeline-of-antibiotics-in-development

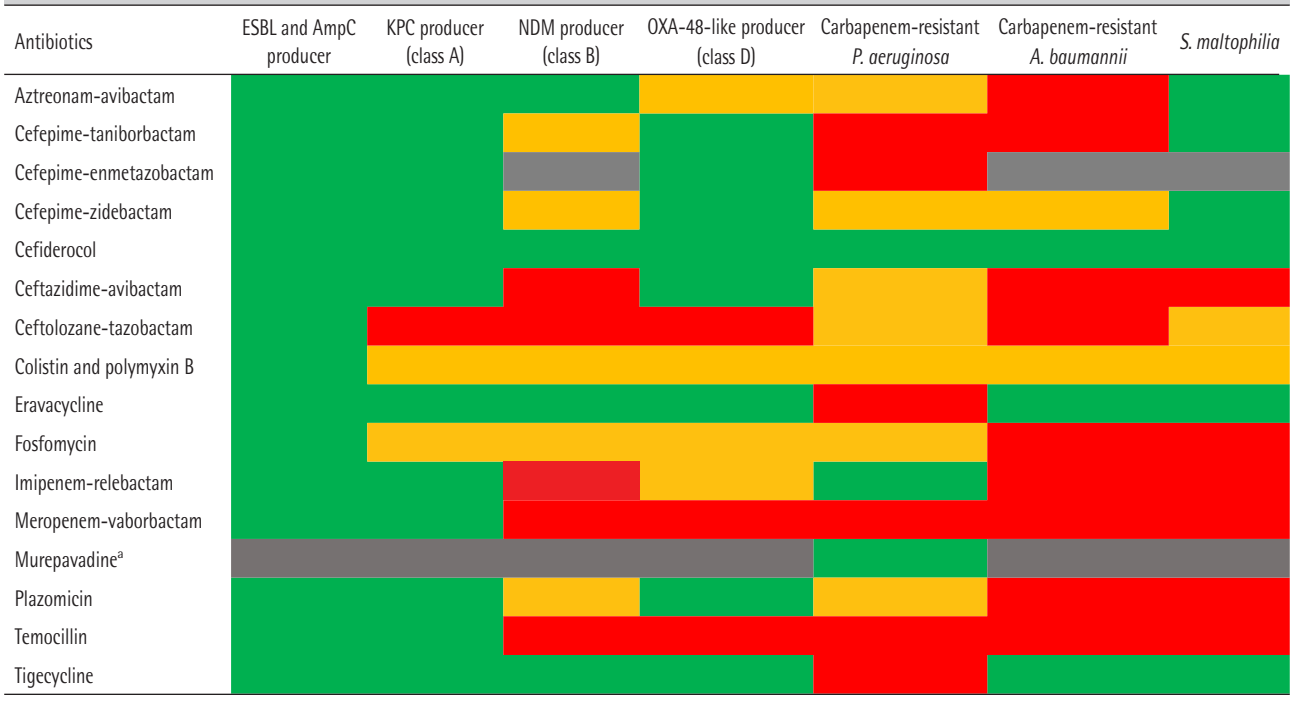
NEEDS IN ANTIBIOTIC THERAPY AGAINST GRAM-NEGATIVE BACILLI IN THE REAL WORLD SETTING: TOWARDS A NEW SCENARIO

Despite the fact that public health initiatives and preventive actions and optimization of antibiotic use, whether at the clinical, agricultural or veterinary level, constitute the most durable mechanisms to curb the development of new resistances, the creation of new antibiotics remains a critical and urgent need [2]. The history of the successive emergence of resistances is, in turn, the chronicle of the research and development of new antibiotics to overcome them, in a relentless but staggered chronological testimony over the decades of the antibiotic era (Figure 1).

Due to the costly, time-consuming and inefficient process involved in the development of new antibiotics, pharmaceutical companies decreased their involvement in the research of new antimicrobial agents in the 1990s and 2000s [40]. In recent years, new agents derived from the already known pharmacological categories, such as those discussed above (e.g. ceftazidime-avibactam), have come onto the market, although new mechanisms of resistance have emerged [41], exposing the need to search for novel mechanisms of action that are capable of functioning as rescue treatments in complex and extreme situations. The use and familiarity with these new antibiotics directed against resistant Gram-negative bacilli, in addition to the threat of multi- and pan-resistance, have once again stimulated research into novel agents capable of meeting future public health needs in terms of antimicrobial resistance [2,42].

We have commented throughout the review on the importance of combinations with new beta-lactamase inhibitors, such as ceftazidime-avibactam for its greater activity against KPC-type carbapenemases, and some D-type carbapenemases, together with a discrete potency against beta-lactamase-producing P. *aeruginosa* in combination with other antibiotic resistance mechanisms [39], ceftolozane-tazobactam and its role against non-metalloenzyme-producing *P. aeruginosa* not producing metalloenzymes, or even the emerging combination of aztreonam and avibactam, with an extended profile against carbapenemases type A (KPC), type B (NDM, VIM), activity also against *S. maltophilia* and partial potency against carbapenem-resistant *P. aeruginosa* isolates, but with limitations against class D carbapenemases (OXA) and no activity against carbapenem-resistant *A. baumannii*. The combination of traditional carbapenemics with new beta-lactamase inhibitors has also burst onto the new therapeutic scene against multidrug-resistant Gram-negative bacilli, together with new antibiotics from other pharmacological categories such as eravacycline (a fluorocycline) or plazomicin (a semisynthetic aminoglycoside), among others, directed against resistant Gram-negative infections, whose antimicrobial activity profile can be consulted in Table 1.

Table 1 **New and classic repositioned antibiotics with activity against multidrug resistant Gram-negative bacteria (beta-lactams and non-beta-lactams)**



Color code: Green: activity >80%; Yellow orange: activity 30-80%; red: activity <30%; Gray: not evaluated.

ESBL: extended-spectrum beta-lactamases. NDM: metallo-beta-lactamase (class B carbapenemase) of the New Delhi type. KPC: class A carbapenemase of *Klebsiella pneumoniae*. OXA-48-like: OXA-48-like oxacillininases with class D carbapenemase activity.

[a]Murepavadine is a cyclopeptide mimetic with high activity against *Pseudomonas aeruginosa*;

Adapted from: Tamma PD, Hsu AJ. Defining the Role of Novel β-Lactam Agents That Target Carbapenem-Resistant Gram-Negative Organisms. J Pediatric Infect Dis Soc. 2019 Jul 1;8(3):251-260. doi: 10.1093/jpids/piz002. PMID: 30793757; PMCID: PMC6601385.

a) New beta-lactams

On the table

Among the novelties of immediate incorporation into clinical practice, it is worth mentioning cefiderocol, a new siderophore cephalosporin -or sideromycin-, approved in 2020 for the treatment of infections caused by Gram-negative bacteria with limited treatment options, with a novel mechanism of action and broad antibacterial activity, including in the context of MDR and XDR [43]. This sideromycin will be discussed later and in great detail throughout this monographic issue.

Coming soon

Research efforts on new beta-lactams have focused on improving the activity profile of carbapenem agents, as well as their PK/PD parameters and, fundamentally, their oral bioavailability.

On the one hand, the first orally administered carbapenems, such as tebipenem, have been developed in recent years. Already approved in 2009 in Japan for pediatric use in combination with a pivoxyl ester, like cefditoren, its application in adult patients with ESBL- or AmpC enzyme-producing Gram-negative infections as sequential de-escalation therapy is recently being re-evaluated [44].

On the other hand, sulopenem, also with both parenteral and oral formulations, is currently under development for use in uncomplicated UTIs due to resistant Gram-negative bacilli, with an activity profile similar to that of ertapenem, without coverage against *P. aeruginosa* [45].

b) New beta-lactamase inhibitors

On the table

Vaborbactam is a new beta-lactamase inhibitor derived from boronic acid, whose combination with meropenem, approved in 2017 by the FDA for complicated urinary tract infections, has demonstrated very potent in vitro activity against 99% of KPC-producing K. pneumoniae isolates, but maintaining high MICs against OXA-48-like or MBL-type carbapenemases [46]. It highlights its lack of ability to increase the activity of meropenem in monotherapy against carbapenem-resistant *P. aeruginosa* or *A. baumannii* [47, 48]. Meropenem-vaborbactam thus shows potent in vitro activity against class A enzyme-producing enterobacteria (e.g., KPC-type car-

bapenemases), whereas activity against carbapenemase-producing strains belonging to other classes remains very limited. Meropenem-vaborbactam is approved by the FDA for the treatment of complicated UTIs and by the EMA for this and other indications such as the treatment of VAP, nosocomial pneumonia, complicated intra-abdominal infections and infections caused by aerobic Gram-negative bacilli in adult patients with limited treatment options.

On the other hand, the combination of **relebactam**, structurally related to avibactam, with imipenem-cilastatin presents a similar profile [49], targeting ESBL, AmpC-type beta-lactamases and class A carbapenemases (KPC), in addition to excellent activity against carbapenem-resistant *P. aeruginosa*, due to the ability of relebactam to hydrolyze AmpC-type enzymes characteristically produced by *Pseudomonas* [50]. It may have greater activity or specificity against KPC-2 and KPC-3 type enzymes than vaborbactam.

Imipenem-relebactam thus combines the classic carbapenem of the 1980s with relebactam, a diaza-bicyclo-octanone, non-beta-lactam beta-lactamase inhibitor, with the ability to inhibit class A, but not class B and D carbapenemases. Although this is in line with the inactivity of imipenem-relebactam against carbapenem-resistant A. baumannii and *P. aeruginosa* (in the case of the latter with production of MBL), the activity against carbapenem-resistant isolates of *P. aeruginosa* isolates resistant to carbapenems but not carbapenemase producers may be retained due to their activity against *P. aeruginosa* strains with carbapenem resistance due to loss of OprD porin combined with overexpression of AmpC, in addition to the fact that neither imipenem nor relebactam is affected by the MexAB-OprM efflux pump. Intrinsic resistance of *S. maltophilia* and *B. cepacia* complex to imipenem and reduced activity against A. baumannii may preclude the use of imipenem-relebactam for the treatment of infections caused by these nonfermenting Gram-negative bacilli.

Its combination with imipenem-cilastatin has recently been approved by the FDA for use in complicated UTI, complicated intra-abdominal infection, VAP and nosocomial pneumonia. It has also been approved by the EMA for the treatment of aerobic Gram-negative bacilli infections with limited treatment options in adult patients. In the RESTORE-IMI 2 randomized clinical trial (which demonstrated non-inferiority of imipenem-relebactam to piperacillin-tazobactam for the treatment of these nosocomial pneumonias and VAP), there was a favorable clinical response in patients with *P. aeruginosa* pneumonia in 47% (7/15) and 68% (17/25) of patients in the imipenem-relebactam and piperacillin-tazobactam arms, respectively (difference 21.3%, 95% CI 49.7 to 10.0). For 28-day all-cause mortality in patients with *P. aeruginosa*, it was 33.3% (5/15) and 12.0% (3/25) in the imipenem-relebactam and piperacillin-tazobactam arms, respectively (difference 21.3%, with 95% CI 4.5 to 48.9) [58]. The RESTORE-IMI 1 trial was a randomized double-blind clinical trial comparing imipenem-relebactam versus colistin plus imipenem for the treatment of complicated UTI, complicated intra-abdominal infection, nosocomial pneumonia, and VAP caused by imipenem-resistant bacteria, which in 77% of cases were carbapenem-resistant *P. aeruginosa* strains. An overall favorable response (primary endpoint, defined as 28-day all-cause mortality for pneumonias, clinical response for intra-abdominal infection, and a combination of clinical response and microbiological response for complicated UTI) in patients with carbapenem-resistant *P. aeruginosa* was 81% (13/16) and 63% (5/8) in the imipenem-relebactam and colistin plus imipenem arms, respectively. In particular, treatment-emergent nephrotoxicity was recorded overall in 10% (3/29) and 56% (9/16) of patients in the imipenem-relebactam group and the colistin plus imipenem group, respectively (difference of 45.9%, 95% CI 69.1 to 18.4). The probable nephroprotection traditionally offered by cilastatin due to inhibition of renal dehydropeptidases, in combination with imipenem, should not be forgotten.

Coming soon

Following the line of boronic acid derivatives, taniborbactam, a new beta-lactamase inhibitor similar to the already approved vaborbactam but with a broader spectrum, in combination with cefepime, is currently in Phase 3 clinical trials and has demonstrated good activity against KPC-producing enterobacteria, as well as A-type carbapenemases, some OXA-48 and OXA-48-like, VIM- and NDM-type, and combined ESBL- or AmpC-producing strains, including *S. maltophilia* (Table 1). However, MICs remain elevated against IMP-type class B carbapenemases and, in one third of the cases, against NDM-type enzyme-producing enterobacteria. Moreover, such potentiation is not observed against multidrug-resistant nonfermenting Gram-negative bacilli such as *P. aeruginosa* or MBL-producing *A. baumannii*, possibly due to lower drug incorporation or higher efflux pump activity [51].

Enmetazobactam is a tazobactam derivative that, combined with cefepime, has shown great activity against ESBL-producing Gram-negative bacteria, with greater potency than its predecessor and also being able to reduce MICs, not only with respect to cefepime, but also in combination with tazobactam. While it is active against ESBL enzymes, AmpC, and OXA-48, its potency is limited against KPC-producing K. pneumoniae isolates and VIM-type carbapenemases [52], as well as *P. aeruginosa*.

Finally, a new beta-lactamase inhibitor, zidebactam, is also combined with cefepime to increase its activity against MDR isolates of Enterobacteriaceae, *P. aeruginosa* and, even, *A. baumannii*, being able to inhibit type A, B and D carbapenemases, as well as *P. aeruginosa* strains with multiple mechanisms of resistance, including hyperexpression of efflux pumps, AmpC enzymes or non-functioning or decreased OprD-type porins [53].

c) Other pharmacological categories

Delafloxacin. Among the new quinolones, delafloxacin stands out because, unlike the other available fluoroquinolones, it has the particularity of being an acidic anionic molecule which gives it a greater tropism towards acidotic regions, with a microenvironment rich in reactive

oxygen species (ROS), all of which in turn gives it greater antimicrobial activity and a high degree of penetration into infected tissues [54]. The fact that it is active against acidic pH environments makes it very interesting in the clinical role it could have in the context of special situations (cystic fibrosis, abscesses or skin necrosis), highlighting in addition its penetration in biofilms. On the other hand, the activity of fluoroquinolones against Gram-positive and Gram-negative bacteria is due to the preferential inhibition of topoisomerase IV or DNA gyrase, respectively. With a low in vitro mutation rate that decreases the risk of resistance and maintaining activity even in isolates with resistance to levofloxacin and moxifloxacin, delafloxacin is equipotent in such inhibition and has action against both Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and high potency against *Streptococcus pneumoniae*, and against enterobacteria and nonfermenting bacilli such as *P. aeruginosa* [55, 56]. It is FDA approved for use in skin and soft tissue infections (STBI) and community-acquired pneumonia (CAP).

Eravacycline is a new synthetic fluorocycline with activity against ESBL-producing and carbapenemase-producing enterobacteria, but also against MRSA and vancomycin-resistant enterococci. However, it lacks activity against *P. aeruginosa*, although it shows activity against carbapenem-resistant strains of *A. baumannii*. Eravacycline has also been shown to be active in vitro against *S. maltophilia*, but not against *B. cepacia* complex. This novel fluorocycline can circumvent some resistance mechanisms affecting tetracyclines and has been shown to be able to evade common resistance mechanisms such as ribosomal protection, common in Gram-positive bacilli, and also mechanisms present in Gram-negative bacilli, such as efflux pumps [57].

Eravacycline has been approved by the FDA and EMA for the treatment of complicated intra-abdominal infections. In the randomized clinical trial IGNITE 1 (showing non-inferiority of eravacycline versus ertapenem for the treatment of these complicated intra-abdominal infections requiring surgical or percutaneous intervention), clinical cure in patients with *P. aeruginosa* infection was recorded in 83% (15/18) and 90% (18/20) of patients in the eravacycline and ertapenem arms, respectively, while in patients with infection due to Acinetobacter spp. clinical cure was observed in 100% (8/8) and 100% (6/6) of patients in the eravacycline and ertapenem arms, respectively. In the IGNITE 4 trial (showing non-inferiority of eravacycline to meropenem for the treatment of identical intra-abdominal infections), clinical cure in patients with *P. aeruginosa* infection was recorded in 95% (18/19) and 90% (18/20) of patients in the eravacycline and meropenem arms, respectively, while in patients with infection due to *Acinetobacter baumannii*, clinical cure was observed in 100% (5/5) and 100% (2/2) of patients in the eravacycline and meropenem arms, respectively.

Omadacycline. Similar in category to eravacycline, omadacycline is a novel aminomethylcycline with good oral bioavailability, exhibits activity against a multitude of both Gram-positive and Gram-negative pathogens, including methicillin-sensitive *S. aureus* and MRSA, *Streptococcus* spp, *Enterobacteriaceae*, *Clostridioides difficile*, and vancomycin-resistant enterococci, among others [57]. It was approved in 2018 for use in IPTB and CAP.

Plazomicin is a new semisynthetic aminoglycoside derived from sisomycin that shows a broad spectrum of potent *in vitro* activity against Gram-negative bacteria, including ESBL- and carbapenemase-producing enterobacteria, particularly with KPC-type enzymes, as well as aminoglycoside-modifying enzyme-producing strains, exhibiting a lower rate of cross-resistance (although methyltransferases have already been described that could inactivate it). However, it has less activity against NDM-type metallo-beta-lactamases, as well as carbapenem-resistant *P. aeruginosa* and *A. baumannii*. In contrast to its predecessors, its broad spectrum and minimal renal toxicity make it an optimal alternative against MDR and XDR Gram-negative bacilli infections, even in monotherapy [57,58]. Plazomicin is FDA-approved for the treatment of complicated UTIs caused by enterobacteria, while the EMA application for approval has recently been withdrawn.

CEFIDEROCOL, AN IRON TROJAN HORSE

Next, after the novel antibiotics discussed, the description of the main characteristics, peculiarities and contributions that cefiderocol can offer is introduced in the list of those included, in a brief and practical way, since the rest of this monographic work will go in depth into each and every one of its aspects in the different chapters.

Mechanism of action. Cefiderocol, like other cephalosporins, produces a disruption of the bacterial wall, albeit with a unique mechanism that attempts to mimic the natural process that bacteria undergo when in an iron-depleted environment. The chlorocatechol group at the end of the C3 side chain of cefiderocol acts as a siderophore that forms a complex with insoluble iron, allowing the antibiotic to cross the outer membrane of Gram-negative bacteria via specific iron transporters, allowing for an additional mechanism of cell entry, combined with passive transport through outer membrane porins [59]. Upon entering the periplasmic space, iron dissociates from the siderophore and the cephalosporin ring of cefiderocol covalently binds to penicillin-binding proteins (PUPs or PBP), especially PBP3, blocking peptidoglycan synthesis.

In addition, the C7 side chain mimics the mechanism of ceftazidime with respect to the aminothiazole ring, increasing the affinity for PBP and increasing antibacterial activity. The carboxypropyl group increases the permeability of the outer membrane [60]. Also, the quaternary ammonium of the C3 side chain, thanks to its positive charge, orients the antibiotic appropriately with respect to the negative charge of the bacterial inner membrane, in a manner similar to what happens with

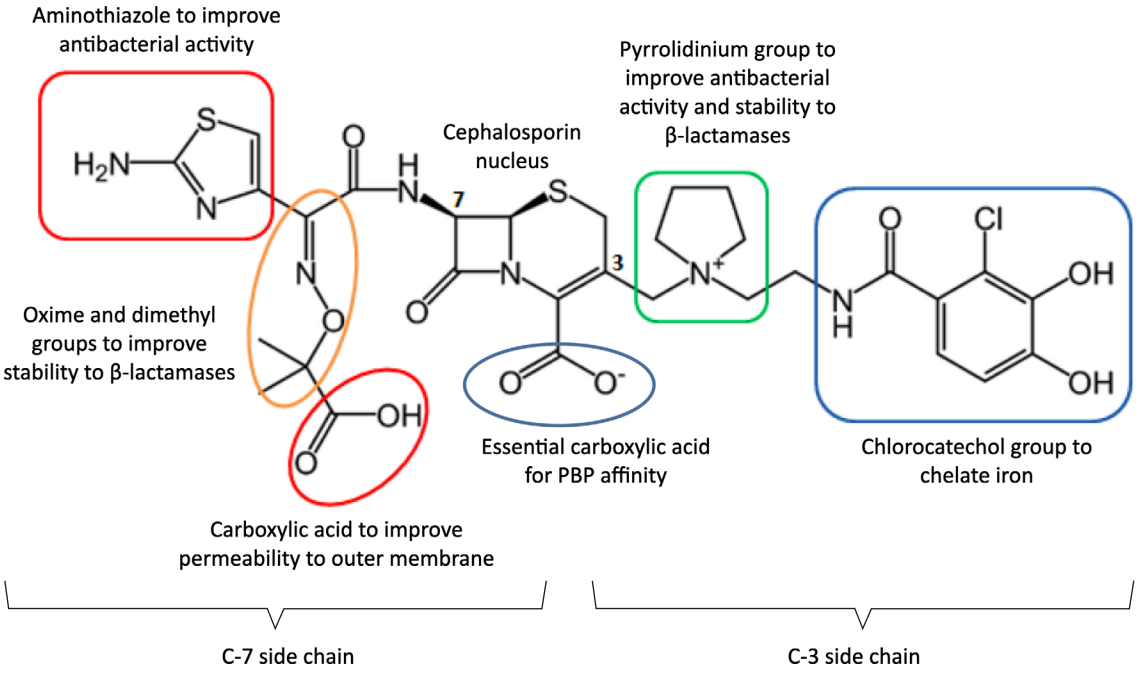


Figure 2 | **Relationship between structure and activity of cefiderocol**

cefepime [60]. These multiple complementary structure-activity relationships of cefiderocol are shown in Figure 2.

Antibacterial spectrum and the role of cefiderocol in multidrug-resistance. Cefiderocol is effective against Gram-negative bacilli of the Enterobacteriaceae family and also against nonfermenting bacilli such as *P. aeruginosa*, *A. baumannii*, and *S. maltophilia*, including carbapenem-resistant strains and multidrug-resistant strains [61]. Cefiderocol showed MIC ≤ 2 mg/L against a wide range of enterobacterial species (*Enterobacter spp., E. coli, Klebsiella spp., Proteus* spp., *Providencia* spp., *Samonella* spp., *Yersinia* spp.,), in addition to *Acinetobacter* spp, *Pseudomonas* spp, *Burkholderia* spp, *Vibrio* spp, *Haemophilus* spp. and *Neisseria* spp [61]. However, it has very low activity against Gram-positive and anaerobic bacteria due to the different structural characteristics of the bacterial wall and the absence of active ferric transport through the target of action of cefiderocol in these bacteria [62].

In the new era of multidrug resistance, with coexistence of multiple molecular mechanisms of resistance [8], the unique mechanism of entry and action of cefiderocol represents an innovative advantage over other drugs, capable of "by-passing" the resistance mechanisms by alterations of the secondary membrane permeability through porins, and through expulsion pumps. Also, thanks to the pyrridoline ring attached to the catechol group of the C3 chain, cefiderocol is stable against the hydrolytic action of a wide variety of beta-lactamases, including carbapenemases. The dimethyl group on the C7 side chain also acts against enzyme binding to the antibiotic core. In particular, cefiderocol remained stable on exposure to purified enzyme extracts KPC-3, IMP-1, VIM-2, NDM-1, L1, OXA-48, OXA-40 and OXA-23 [59, 63]. In fact, its antibacterial activity against ESBL and carbapenemases such as those mentioned is well documented [64]. Cefiderocol also showed antibacterial activity against AmpC-producing strains of *P. aeruginosa* and Enterobacter cloacae, as well as low affinity for chromosomal and inducible AmpC-type beta-lactamases [65].

All this contributes to a very special characteristic of cefiderocol, which is the low or lower risk of cross-resistance with other beta-lactams.

Pharmacokinetics and pharmacodynamics. Cefiderocol presents linear pharmacokinetics after infusion, by perfusion for 3h (EMA) of single or repeated doses both at standard doses of 2g -to be administered every 8h or every 6h- and half doses of 1g in healthy subjects, with a half-life between 1.98 to 2.74h [43]. Unlike other cephalosporins, it hardly binds to plasma proteins and unchanged cefiderocol is the predominant fraction in plasma, in more than 92% of the administered dose [66]. Given its water-soluble nature, which also explains its mechanism of action, the main route of excretion of the drug is renal, with more than 98% eliminated through urine, of which 90.6% is unchanged [66]. Because of this, and after confirmation in phase I and phase II studies, dose adjustment is required in patients with renal insufficiency. It has been shown that in a conventional hemodialysis session lasting 3

to 4h, 60% of the administered dose is eliminated, so that the adjusted dose in these patients (0.75g every 12h), should be administered immediately after the session and, in case of dialysis after administration, requires infusion of a supplementary dose to achieve adequate plasma concentrations [43,67].

Like the other beta-lactams, cefiderocol is a time-dependent drug. Thus, the pharmacodynamic parameter with the highest correlation with antimicrobial activity is the percentage of time above MIC (t>CMI) which, at a standard dose of 2g every 8h through a 3h infusion according to the technical data sheet, reaches percentages of 100% for MIC values less than or equal to 4 mg/L [68]. In animal models of infection by *E. coli, K. pneumoniae*, *P. aeruginosa, A. baumannii* and *S. maltophilia* it has been shown that with t>CMI around 75% adequate therapeutic efficacy is achieved with 1-2 log elimination of the bacterial inoculum [69, 70], with the highest values being found in the case of *A. baumannii* in the pneumonic infection model, which required t>CMI of approximately 88% [70]. In addition, pharmacodynamic studies in murine models confirm that prolonged infusion has greater efficacy against carbapenem-resistant *P. aeruginosa*, *A. baumannii* and *K. pneumoniae* and suggest an MIC of 4 mg/L as the cut-off point for cefiderocol [71].

From bench to bedside: From efficacy to effectiveness. Two in vitro studies demonstrated the effectiveness of cefiderocol against a wide variety of Gram-negative bacilli with different degrees of antimicrobial sensitivity. The first one was SIDERO-WT-2014-2016 with Gram-negative isolates from the United States and Europe, including some strains not sensitive to carbapenems. It showed that the activity of cefiderocol against enterobacteria (MIC_{90} 1 mg/L) was comparable to that of ceftazidime/avibactam (MIC_{90} 0.5 mg/L), improving the activity demonstrated by ceftolozane/tazobactam (MIC_{90} 4 mg/L) and by colistin (MIC_{90} >8 mg/L). In addition, cefiderocol maintained potent activity (MIC_{90} ≤4 mg/L) against strains not sensitive to carbapenems and was twice as potent as its comparators according to MIC_{90}. As for *P. aeruginosa*, and based on MIC_{90} values, cefiderocol (MIC_{90} 0.5 mg/L) was 4 times more potent than colistin and more than 8 times more potent than any other comparator tested. Similarly, its activity against *A. baumannii* (MIC_{90} 2 mg/L) was ≥32-fold greater than cefepime, ceftazidime/avibactam, ceftolozane/tazobactam, and meropenem, and 4-fold greater than colistin [72].

The second study was SIDERO-CR-2014-2016, which analyzed the in vitro bacterial activity of cefiderocol against carbapenem-resistant and MDR (defined as resistant to carbapenems, fluoroquinolones and aminoglycosides) nonfermenting strains of different international isolates. For European isolates of *K. pneumoniae*, the activity of cefiderocol was similar to that of colistin but superior to that of other comparators (>16-fold more potent than cefepime, ceftazidime/avibactam and ceftolozane/tazobactam). Specifically, cefiderocol (MIC_{90} 1 mg/L) was >64-fold more potent than the aforementioned comparators against *P. aeruginosa* MDR, and comparable to colistin, and also demonstrated activity against *A. baumannii* (MIC_{90} 8 mg/L) >8-fold more potent than the others, although 8-fold less potent than colistin [72].

Subsequently, several studies were developed that aimed to analyze the activity of cefiderocol in vivo to corroborate its effectiveness. The 2018 APEKS-cUTI non-inferiority, multicenter, double-blind, parallel, randomized, non-inferiority study aimed to compare the clinical and microbiological outcomes of cefiderocol versus imipenem/cilastatin administration in patients hospitalized for UTI, with or without pyelonephritis, or acute uncomplicated pyelonephritis (APNPE), caused by Gram-negative pathogens in 452 subjects. Cefiderocol achieved microbiological eradication and clinical cure in the test of cure (TOC) in 73% of patients (n=183/252), a result superior to that achieved by imipenem/cilastatin of 55% (n=65/119) (95% CI: 8.23, 28.92; p=0.0004), concluding its non-inferiority. It also showed a group-adjusted difference of 17.25%, suggesting superiority of cefiderocol over imipenem/cilastatin treatment [73].

The 2019 APEKS-NP trial, also a multicenter, double-blind, parallel, randomized, controlled trial, also aimed to analyze the non-inferiority of cefiderocol to high-dose meropenem in patients with nosocomial pneumonia or VAP in 300 patients. Cefiderocol achieved non-inferiority at 14 days of treatment in all-cause mortality (ACM) (95% CI -6.6-8.2%, p=0.002). It was also similar to high-dose meropenem at 28 days of treatment in ACM (95% CI -8.7-9.8%) and in terms of microbiological eradication and clinical cure [74], which postulates it as a suitable treatment alternative for nosocomial pneumonias in patients at risk of MDR Gram-negative bacilli infection.

The CREDIBLE-CR trial, from 2020, presented a multicenter, open-label, parallel, randomized design. Patients over 18 years of age with nosocomial pneumonia, complicated urinary tract infections, bacteremia or sepsis with isolation of Gram-negative bacteria with resistance to carbapenems were included. The aim was to compare the effectiveness of cefiderocol with respect to the best available treatment (BAT), for 7 to 14 days, in a total of 152 patients with a 2:1 allocation. Results in TOC were comparable to BAT in patients with pneumonia (20/40 in the cefiderocol group and 10/19 in the BAT group), complicated urinary tract infections (12/17 in cefiderocol and 2/5 in BAT) and in patients with bacteremia or sepsis (10/23 in cefiderocol and 6/14 in BAT), regardless of the microorganism found. The results, in terms of microbiological eradication, were also similar to those of BAT, and favor cefiderocol numerically, although with a very small sample size [75].

However, more deaths were documented in the cefiderocol group (18.8% of ACM at day 14, and 12.2% in the BAT; and 24.8% at day 28 in the cefiderocol group with respect to 18.4% in the BAT) especially in the subgroup of patients in whom *Acinetobacter spp.* isolation was found. However, an imbalance was found in the baseline and comorbid characteristics of the patients treated with cefiderocol with respect to the BAT group, despite randomization. The former, presented a higher proportion of severe-to-moderate renal function impairment (GFR of 69.4mL/min for the BAT and 59.2mL/min

for the cefiderocol-treated group) and also, there were more patients older than 65 years (44.9% in the BAT and 63.4% in the cefiderocol group). As for the design, the trial was open-label and purely descriptive, without performing uniform statistical analyses. For all these reasons, and after disaggregating all causes of mortality and analyzing them exhaustively, the observed mortality was not related to the administration of cefiderocol per se [75].

It should be taken into account that the CREDIBLE-CR study included patients with significant comorbidity in extreme clinical situations where cefiderocol could constitute the last resort in their treatment, and whose effectiveness in rescue could be limited in such circumstances.

Although the increase in mortality was uncertain due to these data limitations, the FDA has approved the use of cefiderocol for complicated UTI as well as HABP/VAP, and also allowing its dispensation also in compassionate use programs in which there is no other therapeutic alternative (EMA). There are a number of published cases that prove the possible effectiveness of cefiderocol in these situations. Administration of cefiderocol in a patient with *P. aeruginosa* XDR together with colistin and meropenem allowed her aortic valve replacement after controlling bacteremia [76]. Another case, published in 2019, showed the efficacy and safety of cefiderocol in monotherapy for the treatment of VAP with bacteremia due to *A. baumannii* XDR and KPC-producing *K. pneumoniae* [77]. It was also used effectively for the treatment of an intra-abdominal *P. aeruginosa* MDR infection in a patient with numerous comorbidities [78].

In order to obtain approval for other indications, further studies with a more controlled design and a larger sample size than the CREDIBLE-CR mentioned above are needed to evaluate safety in an exhaustive manner, in order to confirm or refute the doubts regarding mortality published in this study.

All these studies and the novelties contributed by other clinical trials already completed or under development will be extensively described in the corresponding chapter.

Safety. The FDA and EMA approved cefiderocol in 2019 for use in complicated UTIs [43], including pyelonephritis, caused by the following sensitive Gram-negative bacteria: *E. coli, K. pneumoniae, P. mirabilis*, *P. aeruginosa*, and *E. cloacae* complex. There are other published phase 3 trials using cefiderocol effectively for the treatment of other infections, such as VAP or bacteremia [74]. However, the multicenter, open-label, randomized CREDIBLE-CR study [75] documented higher mortality in the cefiderocol group compared to BAT group in the treatment of carbapenem-resistant Gram-negative bacterial infections. As indicated in the previous subsection of this article, this increased mortality has not yet been well established and may be due to methodological limitations of the study, but it entails greater vigilance in patients treated off-label. This increased mortality has not been documented in the other phase 3 trials conducted [73,74]. Phase 1 studies have ruled out a possible effect of cefiderocol on cardiac repolarization, with normal QTc interval and other electrocardiographic parameters despite dose increases [79].

On the other hand, adverse effects similar to those related to the administration of other cephalosporins have been described, such as seizures, C. difficile diarrhea or hypersensitivity reactions. The most frequently encountered adverse effect in the APEKS-cUTI clinical trial evaluating the non-inferiority of cefiderocol versus imipenem/cilastatin [73] was diarrhea (4% of 300 patients vs. 6% in impinem/cilastatin), followed by skin reaction at the infusion site (4% vs. 5%). In the APEKS-NP clinical trial, which compared the non-inferiority of cefiderocol versus high-dose meropenem in nosocomial or ventilator-associated pneumonias [74], transient elevation of liver enzymes (16% cefiderocol vs 16% meropenem), followed by hypokalemia (11% vs 15%) and diarrhea (9% vs 9%) were detected as the most frequent adverse effects. All these adverse reactions are more frequent in patients with renal insufficiency, so dose adjustment is required according to the estimated glomerular filtration rate [67].

On the other hand, it should be remembered that cefiderocol can produce false-positive results in the detection of protein, occult blood, or ketone bodies by test strip systems [43].

As a rough balance, it can be recapitulated that cefiderocol is a very useful addition to the therapeutic options available for these difficult-to-treat resistant infections, largely based on recent studies in which it has shown excellent in vitro activity against all species of Gram-negative microorganisms, regardless of the key focus of infection and the MIC of carbapenem [80]. The European study shows how cefiderocol maintained high activity in carbapenem-resistant isolates, and the difference in activity between carbapenem-resistant and carbapenem-sensitive isolates was lower for cefiderocol than for other comparative agents (ceftazidime-avibactam, ceftolozane-tazobactam, colistin, and meropenem).

CONCLUSIONS

In the new era of resistance, patients with multidrug-resistant Gram-negative bacteria infections constitute a complex therapeutic challenge that requires going beyond the evidence, reusing old drugs with numerous limitations in terms of activity and safety, using combination treatments at high doses or new perfusion strategies. Beta-lactams are still, at present, one of the most efficient pharmacological classes against MDR microorganisms. The recent discovery of new drugs, motivated by the urgency of public health and the growing morbimortality associated with infections by MDR bacteria, such as cefiderocol, the new beta-lactamase inhibitors, and other antibiotics belonging to other categories or families (such as plazomicin, eravacycline or delafloxacin), among several of the most novel ones, opens an expectant door to the future in the more favorable management of these patients. There are also new futuristic perspectives with non-antibiotic treatments, such as phage therapy, immunotherapy or biological treatments, gene therapy with gene editing techniques such as CRISPR-Cas9 or nanoantibiotics, which, without forgetting anti-virulence factor drugs and vaccines, augur hopeful and paradigmatic new strategies in the field of infectious diseases and bacterial multidrug resistance.

CONFLICT OF INTEREST

MS has participated in scientific meetings and lectures organized or promoted by the companies MSD, Pfizer, Shionogi, Menarini, and Angelini.

REFERENCES

1. Rodriguez-Baño J, Gutierrez-Gutierrez B, Machuca I, Pascual A. Treatment of Infections Caused by Extended-Spectrum-Beta-Lactamase-, AmpC-, and Carbapenemase-Producing Enterobacteriaceae. Clin Microbiol Rev. 2018;31(2). DOI: 10.1128/CMR.00079-17
2. Fitzpatrick MA. Real-world antibiotic needs for resistant Gram-negative infections. Lancet Infect Dis. 2020;20(10):1108-9. DOI: 10.1016/S1473-3099(20)30178-X
3. Timsit JF, Bassetti M, Cremer O, Daikos G, de Waele J, Kallil A, et al. Rationalizing antimicrobial therapy in the ICU: a narrative review. Intensive Care Med. 2019;45(2):172-89. DOI: 10.1007/s00134-019-05520-5
4. Hsu LY, Apisarnthanarak A, Khan E, Suwantarat N, Ghafur A, Tambyah PA. Carbapenem-Resistant Acinetobacter baumannii and Enterobacteriaceae in South and Southeast Asia. Clin Microbiol Rev. 2017;30(1):1-22. DOI: 10.1128/CMR.masthead.30-1
5. Breijyeh Z, Jubeh B, Karaman R. Resistance of Gram-Negative Bacteria to Current Antibacterial Agents and Approaches to Resolve It. Molecules. 2020;25(6). DOI: 10.3390/molecules25061340
6. Oliveira J, Reygaert WC. Gram Negative Bacteria. StatPearls. Treasure Island (FL)2021.
7. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318-27. DOI: 10.1016/S1473-3099(17)30753-3
8. Ruppe E, Woerther PL, Barbier F. Mechanisms of antimicrobial resistance in Gram-negative bacilli. Ann Intensive Care. 2015;5(1):61. DOI: 10.1186/s13613-015-0061-0
9. Silhavy TJ, Kahne D, Walker S. The bacterial cell envelope. Cold Spring Harb Perspect Biol. 2010;2(5):a000414. DOI: 10.1101/cshperspect.a000414
10. Delcour AH. Outer membrane permeability and antibiotic resistance. Biochim Biophys Acta. 2009;1794(5):808-16. DOI: 10.1016/j.bbapap.2008.11.005
11. Miller SI. Antibiotic Resistance and Regulation of the Gram-Negative Bacterial Outer Membrane Barrier by Host Innate Immune Molecules. mBio. 2016;7(5). DOI: 10.1128/mBio.01541-16
12. Munita JM, Arias CA. Mechanisms of Antibiotic Resistance. Microbiol Spectr. 2016;4(2). DOI: 10.1128/microbiolspec.VMBF-0016-2015
13. Thorpe KE, Joski P, Johnston KJ. Antibiotic-Resistant Infection Treatment Costs Have Doubled Since 2002, Now Exceeding $2 Billion Annually. Health Aff (Millwood). 2018;37(4):662-9. DOI: 10.1377/hlthaff.2017.1153
14. Hofer U. The cost of antimicrobial resistance. Nat Rev Microbiol. 2019;17(1):3. DOI: 10.1038/s41579-018-0125-x
15. Karakonstantis S, Kritsotakis EI, Gikas A. Pandrug-resistant Gram-negative bacteria: a systematic review of current epidemiology, prognosis and treatment options. J Antimicrob Chemother. 2020;75(2):271-82. DOI: 10.1093/jac/dkz401
16. Bassetti M, Labate L, Russo C, Vena A, Giacobbe DR. Therapeutic options for difficult-to-treat Acinetobacter baumannii infections: a 2020 perspective. Expert Opin Pharmacother. 2021;22(2):167-77. DOI: 10.1080/14656566.2020.1817386
17. Soman R, Bakthavatchalam YD, Nadarajan A, Dwarakanathan HT, Venkatasubramanian R, Veeraraghavan B. Is it time to move away from polymyxins?: evidence and alternatives. Eur J Clin Microbiol Infect Dis. 2021;40(3):461-75. DOI: 10.1007/s10096-020-04053-w
18. Lee CR, Lee JH, Park M, Park KS, Bae IK, Kim YB, et al. Biology of Acinetobacter baumannii: Pathogenesis, Antibiotic Resistance Mechanisms, and Prospective Treatment Options. Front Cell Infect Microbiol. 2017;7:55. DOI: 10.3389/fcimb.2017.00055
19. Lupo A, Haenni M, Madec JY. Antimicrobial Resistance in Acinetobacter spp. and Pseudomonas spp. Microbiol Spectr. 2018;6(3). DOI: 10.1128/microbiolspec.ARBA-0007-2017
20. Tafreshi N, Babaeekhou L, Ghane M. Antibiotic resistance pattern of Acinetobacter baumannii from burns patients: increase in prevalence of bla OXA-24-like and bla OXA-58-like genes. Iran J Microbiol. 2019;11(6):502-9. PMC7048957
21. Miyoshi-Akiyama T, Tada T, Ohmagari N, Viet Hung N, Tharavichitkul P, Pokhrel BM, et al. Emergence and Spread of Epidemic Multidrug-Resistant Pseudomonas aeruginosa. Genome Biol Evol. 2017;9(12):3238-45. DOI: 10.1093/gbe/evx243
22. Viedma E, Juan C, Acosta J, Zamorano L, Otero JR, Sanz F, et al. Nosocomial spread of colistin-only-sensitive sequence type 235 Pseudomonas aeruginosa isolates producing the extended-spectrum beta-lactamases GES-1 and GES-5 in Spain. Antimicrob Agents Chemother. 2009;53(11):4930-3. DOI: 10.1128/AAC.00900-09
23. Ruiz-Garbajosa P, Canton R. Epidemiology of antibiotic resistance in Pseudomonas aeruginosa. Implications for empiric and definitive therapy. Rev Esp Quimioter. 2017;30 Suppl 1:8-12.
24. van Duin D. Carbapenem-resistant Enterobacteriaceae: What we know and what we need to know. Virulence. 2017;8(4):379-82. DOI: 10.1080/21505594.2017.1306621
25. Lutgring JD. Carbapenem-resistant Enterobacteriaceae: An emerging bacterial threat. Semin Diagn Pathol. 2019;36(3):182-6. DOI: 10.1053/j.semdp.2019.04.011
26. Sheu CC, Chang YT, Lin SY, Chen YH, Hsueh PR. Infections Caused by Carbapenem-Resistant Enterobacteriaceae: An Update on Therapeutic Options. Front Microbiol. 2019;10:80. DOI: 10.3389/fmicb.2019.00080
27. El-Sayed Ahmed MAE, Zhong LL, Shen C, Yang Y, Doi Y, Tian GB. Colistin and its role in the Era of antibiotic resistance: an extended review (2000-2019). Emerg Microbes Infect. 2020;9(1):868-85. DOI: 10.1080/22221751.2020.1754133
28. Russo A, Bassetti M, Ceccarelli G, Carannante N, Losito AR, Bartoletti M, et al. Bloodstream infections caused by carbapenem-resistant Acinetobacter baumannii: Clinical features, therapy and

outcome from a multicenter study. J Infect. 2019;79(2):130-8. DOI: 10.1016/j.jinf.2019.05.017

29. Giacobbe DR, Saffioti C, Losito AR, Rinaldi M, Aurilio C, Bolla C, et al. Use of colistin in adult patients: A cross-sectional study. J Glob Antimicrob Resist. 2020;20:43-9. DOI: 10.1016/j.jgar.2019.06.009
30. Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. Lancet Infect Dis. 2018;18(4):391-400. DOI: 10.1016/S1473-3099(18)30099-9
31. Fragkou PC, Poulakou G, Blizou A, Blizou M, Rapti V, Karageorgopoulos DE, et al. The Role of Minocycline in the Treatment of Nosocomial Infections Caused by Multidrug, Extensively Drug and Pandrug Resistant Acinetobacter baumannii: A Systematic Review of Clinical Evidence. Microorganisms. 2019;7(6). DOI: 10.3390/microorganisms7060159
32. Ni W, Han Y, Zhao J, Wei C, Cui J, Wang R, et al. Tigecycline treatment experience against multidrug-resistant Acinetobacter baumannii infections: a systematic review and meta-analysis. Int J Antimicrob Agents. 2016;47(2):107-16. DOI: 10.1016/j.ijantimicag.2015.11.011
33. Kengkla K, Kongpakwattana K, Saokaew S, Apisarnthanarak A, Chaiyakunapruk N. Comparative efficacy and safety of treatment options for MDR and XDR Acinetobacter baumannii infections: a systematic review and network meta-analysis. J Antimicrob Chemother. 2018;73(1):22-32. DOI: 10.1093/jac/dkx368
34. Horcajada JP, Montero M, Oliver A, Sorli L, Luque S, Gomez-Zorrilla S, et al. Epidemiology and Treatment of Multidrug-Resistant and Extensively Drug-Resistant Pseudomonas aeruginosa Infections. Clin Microbiol Rev. 2019;32(4). DOI: 10.1128/CMR.00031-19
35. Yahav D, Giske CG, Gramatniece A, Abodakpi H, Tam VH, Leibovici L. New beta-Lactam-beta-Lactamase Inhibitor Combinations. Clin Microbiol Rev. 2020;34(1). DOI: 10.1128/CMR.00115-20
36. Sheu CC, Lin SY, Chang YT, Lee CY, Chen YH, Hsueh PR. Management of infections caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae: current evidence and future prospects. Expert Rev Anti Infect Ther. 2018;16(3):205-18. DOI: 10.1080/14787210.2018.1436966
37. Yang H, Chen G, Hu L, Liu Y, Cheng J, Ye Y, et al. Enhanced efficacy of imipenem-colistin combination therapy against multiple-drug-resistant Enterobacter cloacae: in vitro activity and a Galleria mellonella model. J Microbiol Immunol Infect. 2018;51(1):70-5. DOI: 10.1016/j.jmii.2016.01.003
38. Giacobbe DR, Del Bono V, Trecarichi EM, De Rosa FG, Giannella M, Bassetti M, et al. Risk factors for bloodstream infections due to colistin-resistant KPC-producing Klebsiella pneumoniae: results from a multicenter case-control-control study. Clin Microbiol Infect. 2015;21(12):1106 e1-8. DOI: 10.1016/j.cmi.2015.08.001
39. Zasowski EJ, Rybak JM, Rybak MJ. The beta-Lactams Strike Back: Ceftazidime-Avibactam. Pharmacotherapy. 2015;35(8):755-70. DOI: 10.1002/phar.1622
40. Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. Nat Biotechnol. 2014;32(1):40-51. DOI: 10.1038/nbt.2786
41. Shields RK, Chen L, Cheng S, Chavda KD, Press EG, Snyder A, et al. Emergence of Ceftazidime-Avibactam Resistance Due to Plasmid-Borne blaKPC-3 Mutations during Treatment of Carbapenem-Resistant Klebsiella pneumoniae Infections. Antimicrob Agents Chemother. 2017;61(3). DOI: 10.1128/AAC.02097-16
42. Strich JR, Warner S, Lai YL, Demirkale CY, Powers JH, 3rd, Danner RL, et al. Needs assessment for novel Gram-negative antibiotics in US hospitals: a retrospective cohort study. Lancet Infect Dis. 2020;20(10):1172-81. DOI: 10.1016/S1473-3099(20)30153-5
43. European Medicines Agency (EMA). Ficha técnica del cefiderocol: Fetroja 1g. 2021 [Available from: https://www.ema.europa.eu/en/documents/product-information/fetcroja-epar-product-information_es.pdf.
44. Jain A, Utley L, Parr TR, Zabawa T, Pucci MJ. Tebipenem, the first oral carbapenem antibiotic. Expert Rev Anti Infect Ther. 2018;16(7):513-22. DOI: 10.1080/14787210.2018.1496821
45. Bader MS, Loeb M, Leto D, Brooks AA. Treatment of urinary tract infections in the era of antimicrobial resistance and new antimicrobial agents. Postgrad Med. 2020;132(3):234-50. DOI: 10.1080/00325481.2019.1680052
46. Plazak ME, Tamma PD, Heil EL. The antibiotic arms race: current and emerging therapy for Klebsiella pneumoniae carbapenemase (KPC) - producing bacteria. Expert Opin Pharmacother. 2018;19(18):2019-31. DOI: 10.1080/14656566.2018.1538354
47. Lapuebla A, Abdallah M, Olafisoye O, Cortes C, Urban C, Quale J, et al. Activity of Meropenem Combined with RPX7009, a Novel beta-Lactamase Inhibitor, against Gram-Negative Clinical Isolates in New York City. Antimicrob Agents Chemother. 2015;59(8):4856-60. DOI: 10.1128/AAC.00843-15
48. Pogue JM, Bonomo RA, Kaye KS. Ceftazidime/Avibactam, Meropenem/Vaborbactam, or Both? Clinical and Formulary Considerations. Clin Infect Dis. 2019;68(3):519-24. DOI: 10.1093/cid/ciy576
49. Lapuebla A, Abdallah M, Olafisoye O, Cortes C, Urban C, Landman D, et al. Activity of Imipenem with Relebactam against Gram-Negative Pathogens from New York City. Antimicrob Agents Chemother. 2015;59(8):5029-31. DOI: 10.1128/AAC.00830-15
50. Livermore DM, Warner M, Mushtaq S. Activity of MK-7655 combined with imipenem against Enterobacteriaceae and Pseudomonas aeruginosa. J Antimicrob Chemother. 2013;68(10):2286-90. DOI: 10.1093/jac/dkt178
51. Mushtaq S, Vickers A, Doumith M, Ellington MJ, Woodford N, Livermore DM. Activity of beta-lactam/taniborbactam (VNRX-5133) combinations against carbapenem-resistant Gram-negative bacteria. J Antimicrob Chemother. 2021;76(1):160-70. DOI: 10.1093/jac/dkaa391
52. Morrissey I, Magnet S, Hawser S, Shapiro S, Knechtle P. In Vitro Activity of Cefepime-Enmetazobactam against Gram-Negative Isolates Collected from U.S. and European Hospitals during 2014-2015. Antimicrob Agents Chemother. 2019;63(7). DOI: 10.1128/AAC.00514-19
53. Thomson KS, AbdelGhani S, Snyder JW, Thomson GK. Activi-

ty of Cefepime-Zidebactam against Multidrug-Resistant (MDR) Gram-Negative Pathogens. Antibiotics (Basel). 2019;8(1). DOI: 10.3390/antibiotics8010032

54. Lemaire S, Tulkens PM, Van Bambeke F. Contrasting effects of acidic pH on the extracellular and intracellular activities of the anti-gram-positive fluoroquinolones moxifloxacin and delafloxacin against Staphylococcus aureus. Antimicrob Agents Chemother. 2011;55(2):649-58. DOI: 10.1128/AAC.01201-10
55. Ocheretyaner ER, Park TE. Delafloxacin: a novel fluoroquinolone with activity against methicillin-resistant Staphylococcus aureus (MRSA) and Pseudomonas aeruginosa. Expert Rev Anti Infect Ther. 2018;16(7):523-30. DOI: 10.1080/14787210.2018.1489721
56. Jorgensen SCJ, Mercuro NJ, Davis SL, Rybak MJ. Delafloxacin: Place in Therapy and Review of Microbiologic, Clinical and Pharmacologic Properties. Infect Dis Ther. 2018;7(2):197-217. DOI: 10.1007/s40121-018-0198-x
57. Vrancianu CO, Dobre EG, Gheorghe I, Barbu I, Cristian RE, Chifiriuc MC. Present and Future Perspectives on Therapeutic Options for Carbapenemase-Producing Enterobacterales Infections. Microorganisms. 2021;9(4). DOI: 10.3390/microorganisms9040730
58. Shaeer KM, Zmarlicka MT, Chahine EB, Piccicacco N, Cho JC. Plazomicin: A Next-Generation Aminoglycoside. Pharmacotherapy. 2019;39(1):77-93. DOI: 10.1002/phar.2203
59. 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;60(12):7396-401. DOI: 10.1128/AAC.01405-16
60. Sato T, Yamawaki K. Cefiderocol: Discovery, Chemistry, and In Vivo Profiles of a Novel Siderophore Cephalosporin. Clin Infect Dis. 2019;69(Suppl 7):S538-S43. DOI: 10.1093/cid/ciz826
61. Zhanel GG, Golden AR, Zelenitsky S, Wiebe K, Lawrence CK, Adam HJ, et al. Cefiderocol: A Siderophore Cephalosporin with Activity Against Carbapenem-Resistant and Multidrug-Resistant Gram-Negative Bacilli. Drugs. 2019;79(3):271-89. DOI: 10.1007/s40265-019-1055-2
62. Ito A, Sato T, Ota M, Takemura M, Nishikawa T, Toba S, et al. In Vitro Antibacterial Properties of Cefiderocol, a Novel Siderophore Cephalosporin, against Gram-Negative Bacteria. Antimicrob Agents Chemother. 2018;62(1). DOI: 10.1128/AAC.01454-17
63. Poirel L, Kieffer N, Nordmann P. Stability of cefiderocol against clinically significant broad-spectrum oxacillinases. Int J Antimicrob Agents. 2018;52(6):866-7. DOI: 10.1016/j.ijantimicag.2018.11.005
64. Wu JY, Srinivas P, Pogue JM. Cefiderocol: A Novel Agent for the Management of Multidrug-Resistant Gram-Negative Organisms. Infect Dis Ther. 2020;9(1):17-40. DOI: 10.1007/s40121-020-00286-6
65. Ito A, Nishikawa T, Ota M, Ito-Horiyama T, Ishibashi N, Sato T, et al. Stability and low induction propensity of cefiderocol against chromosomal AmpC beta-lactamases of Pseudomonas aeruginosa and Enterobacter cloacae. J Antimicrob Chemother. 2018;73(11):3049-52. DOI: 10.1093/jac/dky317
66. Miyazaki S, Katsube T, Shen H, Tomek C, Narukawa Y. Metabolism, Excretion, and Pharmacokinetics of [(14) C]-Cefiderocol (S-649266), a Siderophore Cephalosporin, in Healthy Subjects Following Intravenous Administration. J Clin Pharmacol. 2019;59(7):958-67. DOI: 10.1002/jcph.1386
67. Katsube T, Echols R, Arjona Ferreira JC, Krenz HK, Berg JK, Galloway C. Cefiderocol, a Siderophore Cephalosporin for Gram-Negative Bacterial Infections: Pharmacokinetics and Safety in Subjects With Renal Impairment. J Clin Pharmacol. 2017;57(5):584-91. DOI: 10.1002/jcph.841
68. Taheri Y, Jokovic N, Vitorovic J, Grundmann O, Maroyi A, Calina D. The Burden of the Serious and Difficult-to-Treat Infections and a New Antibiotic Available: Cefiderocol. Front Pharmacol. 2020;11:578823. DOI: 10.3389/fphar.2020.578823
69. Ghazi IM, Monogue ML, Tsuji M, Nicolau DP. Pharmacodynamics of cefiderocol, a novel siderophore cephalosporin, in a Pseudomonas aeruginosa neutropenic murine thigh model. Int J Antimicrob Agents. 2018;51(2):206-12. DOI: 10.1016/j.ijantimicag.2017.10.008
70. Nakamura R, Ito-Horiyama T, Takemura M, Toba S, Matsumoto S, Ikehara T, et al. In Vivo Pharmacodynamic Study of Cefiderocol, a Novel Parenteral Siderophore Cephalosporin, in Murine Thigh and Lung Infection Models. Antimicrob Agents Chemother. 2019;63(9). DOI: 10.1128/AAC.02031-18
71. Matsumoto S, Singley CM, Hoover J, Nakamura R, Echols R, Rittenhouse S, et al. Efficacy of Cefiderocol against Carbapenem-Resistant Gram-Negative Bacilli in Immunocompetent-Rat Respiratory Tract Infection Models Recreating Human Plasma Pharmacokinetics. Antimicrob Agents Chemother. 2017;61(9). DOI: 10.1128/AAC.00700-17
72. Tsuji M. Cefiderocol In vitro activity against Gram-negative clinical isolates collected in Europe: Results from SIDERO-CR-2014/2016. ECCMID 2019; 13-16 April 2019; Amsterdam2019.
73. 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):1319-28. DOI: 10.1016/S1473-3099(18)30554-1
74. Wunderink G. Efficacy and Safety of Cefiderocol versus High-Dose Meropenem in Patients with Nosocomial Pneumonia – Results of a Phase 3 Randomized, Multicenter, Double-Blind, Non-Inferiority Study. ID-Week; 2-6 October; Washington2019.
75. 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):226-40. DOI: 10.1016/S1473-3099(20)30796-9
76. 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):1932-4. DOI: 10.1093/cid/ciy963

77. 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):3399-401. DOI: 10.1093/jac/dkz318

78. 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;39(11):1113-8. DOI: 10.1002/phar.2334

79. Sanabria C, Migoya E, Mason JW, Stanworth SH, Katsube T, Machida M, et al. Effect of Cefiderocol, a Siderophore Cephalosporin, on QT/QTc Interval in Healthy Adult Subjects. Clin Ther. 2019;41(9):1724-36 e4. DOI: 10.1016/j.clinthera.2019.07.006

80. Candel FJ, Henriksen AS, 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. 2021: S1198-743X(21)00410-9. doi: 10.1016/j.cmi.2021.07.018.

Official journal of the Spanish Society of Chemotherapy

Cefiderocol, the first catechol-cephalosporin

Alex Soriano
Josep Mensa

Mechanism of action of cefiderocol

Servicio de Enfermedades Infecciosas, Hospital Clínic de Barcelona, Universidad de Barcelona. IDIBAPS

Revista Española de Quimioterapia
doi:10.37201/req/s02.02.2022

ABSTRACT

Gram-negative bacilli are intrinsically resistant to many antibiotics due to the low permeability of their outer membrane. The most effective strategy to solve this problem has been the design of antibiotics that cross the membrane using specific transport systems. This is the case of cefiderocol, which, unlike cefepime or ceftazidime, has a chlorocatechol group at the end of the C-3 side chain. This group is recognized by transporters located in the outer membrane that allow cefiderocol to accumulate in the periplasmic space. Furthermore, cefiderocol is not a substrate for efflux pumps and the configuration of the side chains at C-7 and in particular at C-3 confer it a high stability against hydrolysis by most beta-lactamases of clinical interest including class A (KPC, BLEEs), C (ampC) or D (OXA-48) serine beta-lactamases and metallo-betalactamases (NDM, VIM. IMP). In order to better understand the mechanism of action of cefiderocol, the importance of iron in bacterial metabolism and the competition for iron between bacteria and host are reviewed.

Keywords: cefiderocol, mechanism of action, Gram-negative, siderophore

INTRODUCTION

Gram-negative bacilli are intrinsically resistant to many antibiotics due to the low permeability of their outer membrane that slows the passive diffusion of hydrophobic compounds of high molecular weight, which are active against Gram-positive microorganisms. The outer membrane is an asymmetric lipid bilayer formed, in its superficial layer, by lipopolysaccharides (LPS) and, in its deeper or inner layer, by phospholipids of similar composition to those of the cytoplasmic membrane. The outer layer is less fluid (more rigid) than the inner layer because, unlike the phospholipid molecules that can move freely through the membrane, the negatively charged lipopolysaccharide molecules are neutralized and held together by divalent cations such as Mg2+. The outer membrane also contains two main classes of proteins, the lipoproteins and the proteins known as OMP (outer membrane proteins). The former bind the inner layer of phospholipids to the peptidoglycan and the OMPs can form channels (pores) that allow the passage of small hydrophilic molecules into the periplasmic space.

In addition to the difficulties of diffusion through the outer membrane, there are active transporters (ejector pumps) that can extract antibiotics from the periplasmic space or from the bacterial cytoplasm (Acrb-TolC in E. coli or MexAB-OprM in *Pseudomonas aeruginosa*). In *Enterobacteriaceae*, the structure of the most frequent porins (OmpF, OmpC) allows access to molecules with a molecular weight of 600-700 Da. On the other hand, the most frequent porins in *P. aeruginosa* (OprF, OprD), *B. cepacia* (OpcP1/OpcP2) or *Acinetobacter baumannii* (OmpA-AB), have a significantly lower permeability than that observed in *Escherichia coli*, which prevents the passage of molecules weighing more than 200 Da (the size of a monosaccharide) and are therefore called "slow" porins. This reduced permeability is compensated by: i) the secretion of nutrient-degrading enzymes, ii) the expression of a high number of nutrient-specific porins (OprB for glucose or OprD for basic amino acids) and iii) the expression of specific transporter proteins [1]. OprD is the main channel for entry of carbapenems through the outer membrane, and reduced expression or loss of OprD is frequently observed in carbapenem-resistant clinical isolates.

The slow penetration of the β-lactams through the porins, together with the removal from the periplasmic space by efflux pumps, allows the trapping and hydrolysis of the antibiotic molecules by the β-lactamases, before they reach the PBPs.

Different strategies aimed at increasing the concentration

Correspondence:
Alex Soriano
Servicio de Enfermedades Infecciosas, Hospital Clínic de Barcelona, Universidad de Barcelona
E-mail: asoriano@clinic.cat

of antibiotic in the periplasmic space include i) the use of outer membrane sensitizing compounds, ii) the use of inhibitors of efflux pump activity, iii) modification of the structure or electrical charge of the antibiotic, and iv) the design of antibiotics that cross the membrane using specific transport systems such as siderophore-Fe3+ complex receptors.

To date, several outer membrane sensitizers have been studied. None of these sensitizers, with the exception of SPR206, has shown promising antipseudomonal activity. SPR206 is active against *P. aeruginosa* with potency similar to polymyxin B and is currently in clinical trial [2].

Inhibitors of efflux pumps include Phe-Arg-b-naphthylamide, D13-9001, polyamines and bacteriophage OMKO1. Phe-Arg-b-naphthylamide (PAbN) is a broad-spectrum peptidomimetic compound capable of interfering with the four clinically relevant RND (resistance nodulation division) efflux pumps of *P. aeruginosa*. It probably functions as a substrate for these pumps. However, both PAbN and derivatives of this compound have not been approved, as toxic effects have been reported during Phase 1 clinical trials. The pyridopyrimidine derivative D13-9001 is active against the MexAB-OprM efflux pump [3]. Specificity against a single pump limits its use to coadministration with antibiotics cleared exclusively by it. Polyamines are aliphatic carbon chains containing several amino groups. A polyamine structure has been identified as a strong efflux pump inhibitor without direct antimicrobial activity. Association with aztreonam, chloramphenicol or a tetracycline decreased the MIC_{90} by 5- to 8-fold [4]. Finally, the lytic bacteriophage (of the family *Myoviridae*), OMKO1 ("Outer membrance porin OprM Knockout dependent phage 1"), utilizes OprM of the MexAB and MexXY efflux systems as a binding site. Selection to resist attack by bacteriophage OMKO1 creates an evolutionary compensation in *P. aeruginosa* consisting of reduced OprM expression, leading to increased susceptibility to ciprofloxacin, tetracycline, ceftazidime, and erythromycin [5].

The passage of an antibiotic through a porin occurs by facilitated diffusion. The protein that forms the porin has a loop towards the middle of the channel that decreases its span. The amino acids in this region have electrical charges that cause an electrostatic interaction between the antibiotic or substrate and the channel wall. This explains the specificity of a given porin for a particular antibiotic, as is the case with OprD and carbapenems, whose structure and electrical organization are very similar to the natural substrate of the porin (basic amino acids such as arginine). Selective modification of an electrical charge in meropenem has shown improved passage through an alternative porin to OprM. However, this change reduces its ability to acylate with PBP and thus its antibacterial activity, although it retains some efficacy against *P. aeruginosa* OprD- strains [6]. In the future, the design of new antibiotics could incorporate the analysis of passage through one or more porins.

The most effective strategy to solve the problem of diffusion through the external wall has so far been the design of antibiotics that cross the membrane using specific transport systems such as the receptors of the siderophore-Fe3+ complex. This is the case of cefiderocol and to better understand its mechanism of action we will review the importance of iron in bacterial metabolism and the competition for it between bacteria and host.

RELEVANCE OF IRON IN BACTERIAL METABOLISM AND THE BATTLE FOR ITS ACQUISITION WITH THE HOST'S PROTEINS

Iron is an essential element for aerobic respiration. The respiratory chain in bacteria is located on the cytoplasmic side of the inner membrane and is composed of a set of proteins (complexes) that aim to create an electrochemical proton gradient by transporting electrons between molecules capable of donating and/or accepting 1 or 2 electrons (oxide-reduction reactions) to a final acceptor (oxygen) that allows the synthesis of ATP. The ferrous ion (Fe2+) is a good electron donor and therefore an essential element of the respiratory chain of eukaryotic and prokaryotic cells, which is transported through the chain attached to a cytochrome.

The intracellular concentration of iron necessary to guarantee the viability of a bacterium is 10-6M, this is a very high concentration if we take into account that the concentration of free iron in serum or in any tissue of the host is of the order of 10-24M. Under physiological conditions iron is bound to hemoglobin, in intracellular deposits such as ferritin or to extracellular proteins such as transferrin. At physiological pH transferrin has a high affinity for Fe3+, as pH decreases the affinity decreases and ferric ions are released into the medium. This circumstance occurs in a septic focus where the presence of organic acids reduces the pH. To counteract this situation and prevent bacteria from obtaining free iron, neutrophils synthesize lactoferrin, which has an affinity for Fe3+ 300 times higher than transferrin, and this affinity increases in an acidic medium [7].

HOW DOES A GRAM-NEGATIVE BACILLUS ACQUIRE IRON FROM THE INVADED TISSUE?

To reach the intracellular iron concentration necessary for their metabolism, bacteria synthesize molecules capable of binding iron with high affinity (association constants of 1020 to 1030 M-1) known as siderophores (e.g. enterobactin, pioverdin, salmochelins). These molecules are dumped into the medium to bind scarce free iron (Fe3+) for which they compete efficiently with host proteins [8]. The siderophore-Fe3+ complex is recognized by receptors located on the outer membrane that are able to move it to the periplasmic space with the help of protein complexes of the cytoplasmic membrane (TonB and ExbB/ExbD family proteins) that generate the energy necessary for active transport. Once inside the bacterium, the iron will be incorporated into the respiratory chain.

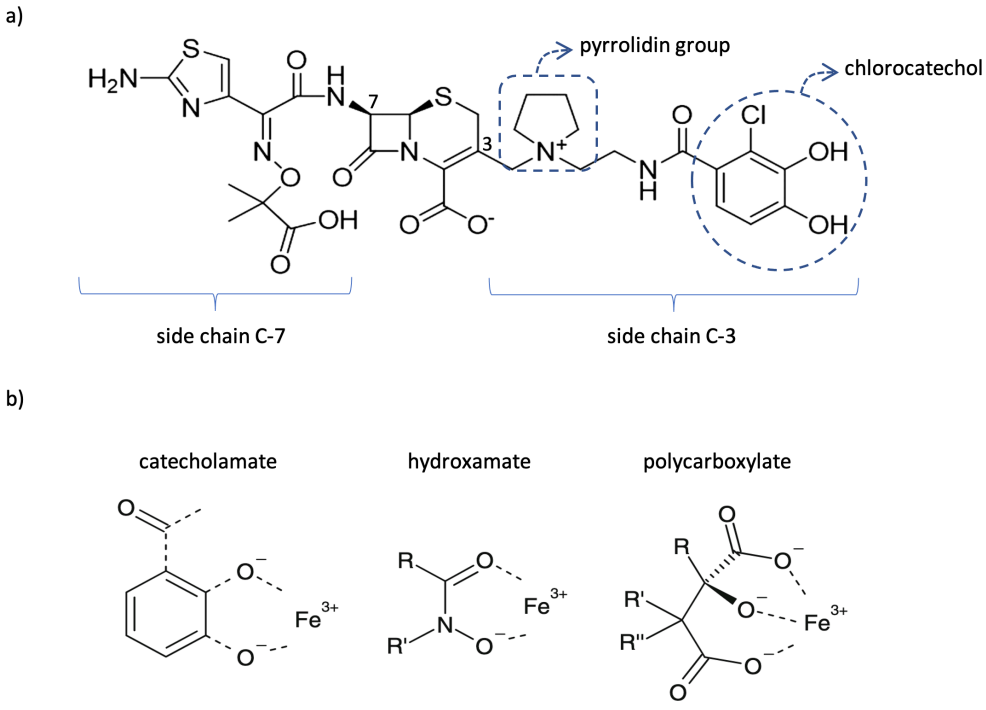


Figure 1 | **Molecular structure of cefiderocol (a). Structure of the group that fixes iron in different siderophores (b).**

MECHANISM OF ACTION OF CEFIDEROCOL

Cefiderocol is a cephalosporin with high affinity mainly for PBP 3 and a structure similar to that of cefepime due to the presence of a pyrrolidin group in the C-3 side chain, which confers potent antibacterial activity and greater stability against beta-lactamases. In addition, it possesses a carboxypropanoxymino group in the C-7 side chain similar to that of ceftazidime which improves transport across the outer membrane [9]. But unlike cefepime or ceftazidime, cefiderocol possesses a chlorocatechol group at the end of the C-3 side chain (Figure 1a) that confers siderophore activity. Siderophores can be grouped according to the structure fixing the iron atom into catecholamates, hydroxamates or polycarboxylates (Figure 1b). This catechol group is recognized by transporters such as CirA and Fiu in *E. coli* or PiuA in *P. aeruginosa* and allow cefiderocol to accumulate in the periplasmic space ("Trojan horse") avoiding resistance mechanisms such as loss of porins, Furthermore, cefiderocol is not a substrate for efflux pumps and the configuration of the side chains at C-7 and in particular at C-3 confers low affinity and/or high stability against hydrolysis of most beta-lactamases of clinical interest including class A (KPC, ESBLs), C (ampC) or D (OXA-48) serine beta-lactamases and metallo-betalactamases (NDM, VIM, IMP) [10].

CONFLICT OF INTEREST

AS has participated in scientific meetings and lectures organized or promoted by the companies Pfizer, MSD, Angelini, Shionogi, and Gilead.

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

REFERENCES

1. Zgurskaya HI, López CA, Gnanakaran S. Permeability Barrier of Gram-Negative Cell Envelopes and Approaches To Bypass It. ACS Infect Dis. 2015;1(11):512-522. doi: 10.1021/acsinfecdis.5b00097
2. Zhang Y, Zhao C, Wang Q, et al. Evaluation of the in vitro activity of new polymyxin B analogue SPR206 against clinical MDR, colistin-resistant and tigecycline-resistant Gram-negative bacilli. J Antimicrob Chemother 2020; 75:2609–2615.
3. Mahmood HY, Jamshidi S, Sutton JM, Rahman KM. Current Advances in Developing Inhibitors of Bacterial Multidrug Efflux Pumps. Curr Med Chem 2016; 23:1062–1081.
4. Fleeman RM, Debevec G, Antonen K, et al. Identification of a Novel Polyamine Scaffold With Potent Efflux Pump Inhibition Activity Toward Multi-Drug Resistant Bacterial Pathogens. Front Microbiol 2018; 9:1301.

5. Chan BK, Sistrom M, Wertz JE, Kortright KE, Narayan D, Turner PE. Phage selection restores antibiotic sensitivity in MDR Pseudomonas aeruginosa. Sci Rep-uk 2016; 6:26717.

6. Isabella VM, Campbell AJ, Manchester J, et al. Toward the Rational Design of Carbapenem Uptake in *Pseudomonas aeruginosa*. Chem Biol 2015; 22:535–547.

7. Page MGP. The Role of Iron and Siderophores in Infection, and the Development of Siderophore Antibiotics. Clin Infect Dis Official Publ Infect Dis Soc Am 2019; 69:S529–S537.

8. Möllmann U, Heinisch L, Bauernfeind A, Köhler T, Ankel-Fuchs D. Siderophores as drug delivery agents: application of the "Trojan Horse" strategy. Biometals. 2009;22(4):615-24. doi: 10.1007/s10534-009-9219-2

9. Sato T, Yamawaki K. Cefiderocol: Discovery, Chemistry, and In Vivo Profiles of a Novel Siderophore Cephalosporin. Clin Infect Dis 2019; 69:S538–S543.

10. Ito-Horiyama T, Ishii Y, Ito A, et al. Stability of Novel Siderophore Cephalosporin S-649266 against Clinically Relevant Carbapenemases. Antimicrob Agent Chemother 2016; 60:4384–4386.

Official journal of the Spanish Society of Chemotherapy

Cefiderocol, the first catechol-cephalosporin

Desirée Gijón Cordero[1,2]
Juan Antonio Castillo-Polo[1,2]
Patricia Ruiz-Garbajosa[1,2,3]
Rafael Canton[1,2,3]

Antibacterial spectrum of cefiderocol

[1]Servicio de Microbiología. Hospital Universitario Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS). Madrid, Spain
[2]Red Española de Enfermedades Infecciosas (REIPI). Instituto de Salud Carlos III. Madrid, Spain.
[3]CIBER de Enfermedades Infecciosas. Instituto de Salud Carlos III. Madrid, Spain.

Revista Española de Quimioterapia
doi:10.37201/req/s02.03.2022

ABSTRACT

Cefiderocol, a siderophore catechol cephalosporin, recently introduced in the market has been developed to enhance the *in vitro* activity of extended spectrum cephalosporins and to avoid resistance mechanisms affecting cephalosporins and carbapenems. The *in vitro* study of cefiderocol in the laboratory requires iron depleted media when MIC values are determined by broth microdilution. Disk diffusion presents good correlation with MIC values. In surveillance studies and in clinical trials it has been demonstrated excellent activity against Gram-negatives, including carbapenemase producers and non-fermenters such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Stenotrophomonas maltophilia*. Few cefiderocol resistant isolates have been found in surveillance studies. Resistance mechanisms are not directly associated with porin deficiency and or efflux pumps. On the contrary, they are related with gene mutations affecting iron transporters, AmpC mutations in the omega loop and with certain beta-lactamases such us KPC-variants determining also ceftazidime-avibactam resistance, certain infrequent extended-spectrum betalactamases (PER, BEL) and metallo-beta-lactamases (certain NDM variants and SPM enzyme).

Keywords: Cefiderocol, antimicrobial activity, surveillance, breakpoints

INTRODUCTION

The World Health Organisation has warned that antimicrobial resistance is one of the most important threats to humanity. It has also indicated that several actions are urgently needed to address the problem of bacterial resistance and that new antimicrobials need to be developed [1,2]. In recent years, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have granted marketing authorisation for several antimicrobials [3]. The latter include beta-lactam combinations with beta-lactamase inhibitors and a new class of cephalosporins, represented by cefiderocol. The originality of this cephalosporin is that it has a catechol group in its structure that favours its penetration into the bacteria, as it competes with the transport of iron. This unique mechanism of entry into the bacterial cell has been described as "Trojan horse" [4,5]. Cefiderocol also contains in its structure radicals present in ceftazidime and cefepime cephalosporins which make this drug particularly active against Gram-negative bacilli, including non-fermenters. These radicals doubly favour its enhanced intrinsic activity compared to other extended-spectrum cephalosporins by facilitating penetration through porins and its resistance to a large number of beta-lactamases [6,7]. Due to these characteristics, the arrival at PBPs, the site of action of beta-lactams, is very efficient, which makes it active even in most of the carbapenem resistant and carbapenemase-producing microorganisms.

In this paper we review the activity of cefiderocol on Gram-negative microorganisms with information obtained from isolates obtained in cefiderocol clinical trials and epidemiological surveillance studies. We also include methodological aspects in the determination of cefiderocol susceptibility, including clinical breakpoints interpretation and published data related to the potential mechanisms of resistance to this antimicrobial.

TECHNICAL ASPECT IN THE STUDY OF *IN VITRO* ACTIVITY OF CEFIDEROCOL

Cefiderocol, as a siderophore cephalosporin, needs active iron transporters to enter the periplasm and access to the PBPs. These transporters are upregulated under iron-depleted conditions as it would happen *in vivo*, which is considered advantageous for the antibiotic activity [8]. Because of this, iron

Correspondence:
Rafael Cantón.
Servicio de Microbiología. Hospital Universitario Ramón y Cajal. Carretera de Colmenar Km 91. 28034-Madrid. Spain
E-mail: rafael.canton@salud.madrid.org

concentrations in antimicrobial susceptibility testing media need special consideration when cefiderocol is tested in order to mimic *in vivo* conditions and accurately predict clinical efficacy [4]. Moreover, resistance to cefiderocol has been already described [10-13] and should be accurately detected in the laboratory.

Broth microdilution and disk diffusion techniques have been used to determine the *in vitro* activity of cefiderocol. MIC obtained by agar dilution method do not match with those obtained by broth microdilution and it is not a recommended technique for this compound [14]. Other techniques, such as gradient diffusion strips, are also now available but experience is limited and manufactures only recommend it for *Pseudomonas aeruginosa* isolates and no other non-fermentative rods or *Enterobacterales* [4]. Nevertheless, a recent study used cefiderocol MIC strips (Liofilchem, IT) in comparison with MIC obtained in iron-depleted broth (reference method) and disk diffusion in a collection of carbapenemase producing *Enterobacterales* [15]. The conclusion was that MIC strip should be avoided in these isolates due to the high number of discrepancies (only 64% of categorical agreement and 94.9% of very major errors due to critical underestimation of MICs), which were highly reproducible.

The inclusion of cefiderocol in panels used in automatic system is still waiting due to the fact of technical challenges of cefiderocol testing.

Broth microdilution. Standard cation-adjusted Mueller-Hinton broth (CAMHB) is not a medium controlled for iron concentration and this may vary among the different manufacturers. Some studies referred by the Clinical and Laboratory Standards Institute (CLSI) guidelines already demonstrated that MICs were higher when standard CAMHB was used, compared to those obtained with iron-depleted CAMHB (ID-CAMHB) [16]. These results are supported by the idea that iron transport, as well as the uptake of cefiderocol, are increased in low iron-concentration conditions.

A study demonstrated reproducibility of the ID-CAMHB in broth microdilution technique by testing 19 clinical isolates of Gram-negative bacilli (including 9 *Acinetobacter baumannii* isolates) over 10 replicates in CAMHB from 3 different manufacturers. More than 95% of MIC results were within one doubling dilution when analysed by individual medium lot. Besides this, when all medium lots were combined, 92.2% of MIC results were within one doubling dilution and 99.8% within two dilutions [17]. Thus, iron depletion is necessary to accurately perform MIC testing and to use this data to predict *in vivo* efficacy of cefiderocol. Moreover, MICs determined under these conditions have been proved to be reproducible and correlate with *in vivo* activity in animal models [18].

Following CLSI guidelines, the solvent and diluent required to prepare the medium for broth microdilution is a solution of 0.85% to 0.9% NaCl. To prepare the ID-CAMHB, both the European Committee of Antimicrobial Susceptibility testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI) recommendations use chelation with a resin to remove the polyvalent metal cations in the medium with a final iron content below 0.03 mg/L. After that, the resin is filtered out and the non-iron cations are re-added to concentrations of 20–25 mg/L of calcium, 10–12.5 mg/L of magnesium, and 0.5–1.0 mg/L of zinc; all the reagents should have a low content of iron. The pH should be checked after the chelation and the addition of cations and adjusted if required. The rest of the procedure is like the susceptibility testing of other cephalosporins [16,19].

To read the MIC values, the MIC of cefiderocol corresponds to the first well in which a button of <1 mm or a faint turbidity can be observed, with the positive control showing a strong growth (button of >2 mm or heavy turbidity) [19]. In some organisms such as *Acinetobacter* spp., a trailing has been reported, where up to 30% of isolates demonstrated such effect [4]. The MIC should then be read as the first well with a significant reduction of growth, ignoring buttons <1 mm and faint turbidity comparted with the control growth [17].

Disk diffusion. To determine the susceptibility by the disk diffusion technique, standard recommendations for non-fastidious organisms should be followed using a cefiderocol 30-mg disk. In contrast to broth microdilution, this method has been developed to be performed on regular unsupplemented Mueller-Hinton agar (MHA), since only small variations in the zone diameters were found when MHA with different concentrations of iron (0.03 to 10 mg/L) were tested [4]. Although it may vary among different manufacturers, the medium usually contains around 0.5 mg/L of iron. It is thought iron to be bound in the agar, simulating iron-depleted conditions without interfering with the results [20]. Regarding reading of inhibition zones and the interpretation of the results, some colonies may be found within inhibition zone and need to be taken into consideration. Zone diameters should be measured, therefore, as the inner zone without bacterial growth. [4]

BREAKPOINTS AND EPIDEMIOLOGICAL CUT-OFF VALUES OF CEFIDEROCOL

The clinical breakpoints for cefiderocol have been established by both EUCAST and CLSI [15,21]. In the first case, they are those listed in the summary of product characteristics of the EMA (SmPC) [21]. In the United States, the FDA and the United States Committee on Antimicrobial Susceptibility Testing (USCAST) have also published clinical breakpoints that differ in some cases from those defined by CLSI (Table 1) [23,24]. In the case of EUCAST, the susceptible breakpoints are one dilution lower than CLSI. This decision was based on the PK/PD analysis which is explained in their rational document [25]. EUCAST also does not recognize a "susceptible, increased exposure" (I) ("intermediate" in CLSI terms) category as the marketing authorization only includes a single dose (2 g/8 h over 3 hours of infusion). Moreover, EUCAST, unlike CLSI, have not yet stablished clinical breakpoint for *Acinetobacter* spp. and *Stenotrophomonas malthophilia* due to the lack of clinical data to correlate outcomes with MIC values. In the future, real life

Table 1 **Clinical breakpoints for cefiderocol published by breakpoint committees and/or regulatory agencies in 2022**

Microorganisms and non-species related PK/PD breakpoints	EUCAST - EMA					USCAST				CLSI				FDA			
	MIC, mg/L		Inhibition zone diameter, mm[a]			MIC, mg/L		Inhibition zone diameter, mm[a]		MIC, mg/L		inhibition zone diameter, mm		MIC, mg/L		inhibition zone diameter, mm[a]	
	≤S	>R	≥S	<R	ATU[b]	≤S	≥R	≥S	≤R	≤S	≥R	≥S	≤R	≤S	≥R	≥S	≤R
Enterobacterales	2	2	22	22	18-22	2[c] (4)[d]	4[c] (8)[d]	-	-	4	16	16	8	4	16	16	8
Pseudomonas aeruginosa	2	2	22	22	14-22	2[c] (4)[d]	4[c] (8)[d]	-	-	4	16	18	12	1	4	22	12
Acinetobacter spp.	IE[e]	IE	-[f]	-[f]	-	IE	IE			4	16	15	-[g]	1	4	19	11
Stenotrophomonas maltophilia	IE	IE	-[h]	-[h]	-	IE	IE	-	-	1[i]	-	15[i]	-	-	-	-	-
PK/PD	2	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

[a]30-µg disk content; [b]ATU: area of technical uncertainty; [c]breakpoints for pneumonia; [d]breakpoints for non-pneumonia; [e]IE: insufficient evidence; [f]Zone diameters of ≥17 mm for the cefiderocol 30-µg disk correspond to MIC values below the PK-PD breakpoint of S ≤ 2 mg/L; [g]Disk diffusion diameters ≤14 mm should not be interpreted or reported because zone diameters ≤14 mm occur with resistant, intermediate and susceptible isolates. For isolates with zone diameters ≤14 mm, do not report cefiderocol without performing an MIC test; [h]Zone diameters of ≥20 mm for the cefiderocol 30-µg disk correspond to MIC values below the PK-PD breakpoint of S ≤ 2 mg/L; [i]Breakpoints are based on PK/PD properties, and limited clinical data.

studies will help to define these breakpoints. In the absence of them, PK/PD breakpoints have been defined, which can help to take decisions of the use of this drug when other therapeutic alternatives are not available [21]. To note that, USCAST is the only breakpoint committee that discriminates breakpoints for pneumonia and non-pneumonia infections being one-fold dilution lower in the former than in the later.

The epidemiological cut off values (ECOFF) of cefiderocol have been recently published but to a low number of species due to the technical particularities that arise when MIC values are determined [25]. These values have been established following EUCAST guidelines. Tentative ECOFFs (TECOFF, based in 3-4 MIC distributions) for *Escherichia coli*, *Klebsiella pneumoniae* and *P. aeruginosa* are 0.25 mg/L, 0.125 mg/L and 0.5 mg/L, respectively. For *A. baumannii* and *S. maltophilia* ECOFFs (based in at least 5 MIC distributions) are 0.25 mg/L and 0.06 mg/L, respectively.

Disk diffusion breakpoints are also included in table 1. EUCAST includes for *Enterobacterales* and *Pseudomonas* spp. an area of technical uncertainty (ATU) when interpreting disk diffusion susceptibility due to difficulties in correlating inhibition zones with MIC values at the wild-type end of the population. In this case, it is recommended to establish susceptibility to cefiderocol by calculating and interpreting MIC values.

IN VITRO ACTIVITY OF CEFIDEROCOL IN SURVEILLANCE STUDIES

The *in vitro* activity of cefiderocol has been studied both nationally and internationally. Among the international studies, we highlight SIDERO-WT-2014, SIDERO-WT-2015 and the studies carried out by different investigators [27-29].

The SIDERO-WT-2014 [28] study includes meropenem- and colistin-resistant *Enterobacterales* isolates and meropenem-resistant *P. aeruginosa* and *A. baumannii* isolates from both the United States and Europe. These isolates were also screened for the presence of genes encoding beta-lactamases, loss of porins and resistance to colistin mediated by plasmids, in order to later define the spectrum of cefiderocol activity against these challenging Gram-negative isolates. Most meropenem-resistant *Enterobacterales* carried carbapenemases, being KPC-type the most frequent enzyme. *P. aeruginosa* isolates from the United States did not carry acquired beta-lactamases, while 16% of the isolates from Europe carried VIM-, IMP- or GES-carbapenemase. Regarding *A. baumannii* isolates, the most common carbapenemase in both regions was OXA-23 followed by OXA-24, however, OXA-58 was only detected in Europe. In the collection of meropenem-resistant isolates, the MIC of cefiderocol ranged between 0.002 mg/L and 64 mg/L. A total of 97.7% of isolates tested had cefiderocol MIC values ≤4 mg/L, including isolates producing KPC, IMP, VIM and OXA-48 enzymes. In these carbapenemases producing isolates, 99.6% of them were inhibited with MIC values of cefiderocol ≤8 mg/L. In meropenem-resistant *Enterobacterales* isolates, the MIC_{90} value was 4 mg/L compared to MIC_{90} values ≥64 mg/L for meropenem, ceftazidime, ceftolozane-tazobactam and ceftazidime-avibactam, and ≥8 mg/L for ciprofloxacin and colistin. Ceftazidime-avibactam showed MIC values equal to or slightly better than cefiderocol in isolates producing KPC-, OXA-types, and those meropenem-resistant without carbapenemase, however, unlike cefiderocol, ceftazidime-avibactam was not active against isolates producing VIM and IMP-enzymes. On the other hand, no correlation was observed between cefiderocol MICs and the presence of different combinations of intact and disrupted porin genes. Regarding *P. aeruginosa* isolates, the MIC_{90} value was 1 mg/L compared with MIC_{90} values of ≥32 mg/L for meropenem, cefepime, ceftazidime-avibactam, and ceftolozane-tazobactam and >8 mg/L for ciprofloxacin. With the exception of colistin, the comparator agents showed

reduced activity against the GES and MBL producing isolates. Finally, the MIC_{90} value in meropenem-resistant *A. baumannii* isolates was 1 mg/L. As in *P. aeruginosa*, in *A. baumannii* isolates, both carbapenemase-producers and non-producers, meropenem, cefepime and ciprofloxacin showed reduced activity in comparison with cefiderocol. In addition, a total of 136 colistin-resistant *Enterobacterales* were screened for the presence of the transmissible colistin resistance determinant *mcr*-1 gene. Most of these isolates (n = 101) were susceptible to meropenem and 35 of them produced different carbapenemases. The MIC_{90} value of cefiderocol for these isolates was 2 mg/L. In summary, results of the SIDERO-WT-2014 surveillance program demonstrate the potent *in vitro* activity of cefiderocol against meropenem-resistant *Enterobacterales*, *P. aeruginosa* and *A. baumannii* isolates. Cefiderocol activity was comparable to that of ceftazidime-avibactam against MBL-negative *Enterobacterales* isolates but superior to all the comparator agents against NDM- and VIM-positive isolates. Furthermore, cefiderocol was also active against colistin-resistant *Enterobacterales*, including those carrying the transmissible colistin resistance determinant *mcr*-1.

Data generated during the second year of this global surveillance initiative for cefiderocol is included in the SIDERO-WT-2015 study [29]. During this period, isolates of *Enterobacterales*, *P. aeruginosa*, *A. baumannii*, *S. maltophilia* and *Burkholderia cepacia* complex were collected. Results of this study support those obtained in the previous year demonstrating an *in vitro* activity of cefiderocol superior to ceftazidime-avibactam, ceftolozane-tazobactam and cefepime against of *Enterobacterales*, *P. aeruginosa* and *A. baumannii* isolates. Regarding *S. maltophilia* and *B. cepacia* complex, 99.4% and 94.4% respectively, showed cefiderocol MIC values ≤4 mg/L. It should be noted that there was no cross-resistance between cefiderocol and colistin. This study concludes that cefiderocol is a good therapeutic option in patients infected with multidrug-resistant Gram-negative bacilli due to its demonstrated activity against carbapenem-resistant Gram-negative isolates and MDR phenotypes, its stability to hydrolysis by different beta-lactamases and its activity against bacteria resistant to carbapenems by other resistance mechanisms.

At the international level, Hackel *et al.* [27] also demonstrated that cefiderocol is a more potent antimicrobial than cefepime, ceftazidime-avibactam and ceftolozane-tazobactam. The study included 1,022 meropenem-resistant *Enterobacterales* isolates collected between 2014 and 2016 by medical center laboratories in 52 countries (24 in Europe, 10 in Latin America, 2 in North America, 8 in Asia, 3 in the South Pacific, 2 in Africa and 3 in Middle East). The MIC_{90} value for cefiderocol was 4 mg/L with MIC ranges between 0.004 and 32 mg/L (97% of the isolates had MIC values ≤ 4 mg/L) [27]. Results of other studies are in agreement with those mentioned above, cefiderocol has excellent *in vitro* activity (MIC_{90} values ≤1 mg/L) against problematic isolates such as KPC- and MBL-producing *Enterobacterales* (including NDM-1 enzymes) and ESBL producers [30]. Regarding non-fermenting Gram-negative bacteria, Ito *et al.* obtained MIC_{90} values of 2 mg/L in *A. baumannii* isolates, 1 mg/L for *P. aeruginosa* and 0.5 mg/L for *S. maltophilia* isolates. These results also demonstrate the potent *in vitro* activity of cefiderocol against non-fermenters, with MIC_{90} values significantly lower than those obtained for ceftazidime, meropenem, levofloxacin, cefepime and piperacillin-tazobactam. Cefiderocol was also active against *A. baumannii*, including those isolates resistant to carbapenems [31].

At the national level, studies have also been published about the *in vitro* activity of cefiderocol in Spain, showing that it is a good therapeutic option for the treatment of infections caused by MDR bacteria. Thus, Cercenado *et al.* [32] recently published the subset of Spanish isolates from the SIDERO-WT-2014-2018 study, demonstrating that cefiderocol showed potent *in vitro* activity against Gram-negative bacilli isolated in different types of infection. Furthermore, a significant percentage of isolates ($p < 0.01$) were susceptible to cefiderocol. Susceptibility to cefiderocol in *Enterobacterales* was significantly better ($p < 0.01$) than ceftolozane-tazobactam and colistin but similar to meropenem and ceftazidime-avibactam, while susceptibility to cefiderocol in non-fermenting isolates was significantly better than all comparators ($p < 0.01$). It should be noted that cefiderocol activity was significantly better than all comparators against isolates from patients with nosocomial pneumonia.

In Greece, a country with high resistance rates, Falagas *et al.* [33] studied the *in vitro* activity of cefiderocol in carbapenem-resistant isolates and compared it with that of commercially available antibiotics. Cefiderocol demonstrated potent *in vitro* activity with MIC_{90} values ≤1 mg/L for all groups of microorganisms. However, MIC_{90} of cefiderocol was lower in non-fermenters than for *Enterobacterales*. In addition, they observed minor differences in MIC values according to specific resistance mechanisms.

Ballesté-Delpierre *et al.* [34] tested a diverse collection of *A. baumannii* clinical isolates, including Spanish one. The most active antimicrobials against this collection were colistin and cefiderocol, with 12.38% and 21.23% of non-susceptibility, respectively. Interestingly, a high proportion of multidrug-resistant (76.7%) and carbapenem-resistant (75.3%) *A. baumannii* isolates remained susceptible to cefiderocol, which was clearly superior to novel beta-lactam-beta-lactamase inhibitor combinations, including ceftazidime-avibactam, imipenem-relebactam and meropenem-vaborbactam. Cefiderocol-non susceptible isolates were more frequently observed among meropenem-resistant isolates, but could not be associated with any particular resistance mechanism or clonal lineage.

A recent publication including isolates collected from the United States and Europe collected as part of the SENTRY study in 2020, showed 99.8% *Enterobacterales* susceptibility to cefiderocol, with similar values (98.2%) in the subset of carbapenem resistant isolates [34]. In *P. aeruginosa* isolates, cefiderocol was the most active antimicrobial (99.6% susceptible). In XDR isolates cefiderocol susceptibility was very high

Table 2 Cefiderocol resistance mechanisms

Microorganisms	Cefiderocol MIC (MIC or range) (mg/L)	Resistance mechanism	Country (Year of publication)	Reference
K. pneumoniae	16 - >32	Mutation of two-component regulation system (BaeSR and OmpR/EnvZ). Mutation of *exbD* (accessory protein related to iron transport)	Japan (2020)	44
K. pneumoniae *E. coli* *E. cloacae*	4 - >32	KPC β-lactamase mutants	France (2021)	49
K. pneumoniae	8	KPC β-lactamase mutant (KPC-31)	Italy (2021)	50
E. cloacae	>16	AmpC R2 loop deletion	USA (2020)	10
E. cloacae	≥256	Mutations in *cir*A gene	Germany (2021)	13
P. aeruginosa	8	Mutations in *pir*A and deletion in piuA	USA (2021)	43
A. baumannii *B. multivorans* *P. aeruginosa* *S. maltophilia*	>4	PER and NDM β-lactamase Disruption of iron transport genes (*piu*A, *pir*A and *fiu*A)	Russia, Turkey and USA (2020)	45
A.baumannii	≥32	Loss of *pir*A and *piu*A	USA (2020)	46

(97.3%) compare with meropenem (only 7.4%). In this collection *Acinetobacter* spp and *S. maltophilia* susceptibility to cefiderocol was 97.7% and 97.9%, respectively [35].

CEFIDEROCOL RESISTANCE MECHANISMS

Mechanisms of resistance to cefiderocol are being described and different reviews include subheading of this emergence [4,36-40]. Nevertheless, and according with surveillance studies and clinical trials, prevalence of cefiderocol non susceptible or resistant isolates remains very low and their clinical implications remains to be clarified [41]. Table 2 summarized resistance mechanisms described to cefiderocol in different species. These mechanisms are complex and normally, they do not involve a single gene. Cefiderocol resistance has been described in *in vitro* mutants, in isolates recovered from surveillance studies and in clinical cases involving difficult to treat pathogens.

In carbapenemase producing microorganisms, it has been shown that the loss of Omp35 and Omp36 porins in *K. pneumoniae* isolates as well as the overproduction of MexA-MexB-OprM efflux pumps in *P. aeruginosa* isolates do not have a significant impact on cefiderocol activity [31]. On the contrary, mutants in TonB dependent iron transporter pathway might affect cefiderocol susceptibility [42]. This mechanism of resistance involves potential defects in the inner membrane proteins (TonB-ExbB-ExbD) and/or the corresponding two-component regulator systems that affect the necessary energy for the iron transportation and hence for cefiderocol [43].

The implication of iron transport pathway in cefiderocol resistance have been studied in *K. pneumoniae* isolates but also in *P. aeruginosa*, *A. baumannii* and other Gram-negative non-fermentative rods. In that sense, Yamano *et al.* [44] suggests the mutation of two-component regulation systems (BaeSR and OmpR/EnvZ) and iron transport-related proteins as a possible resistance mechanism involved *in vitro* cefiderocol resistant mutants of *K. pneumoniae* isolates. Moreover, in SIDERO-WT clinical studies, some isolates of different species (128 *A. baumannii*, 22 *Enterobacterales*, 7 *Burkholderia multivorans*, 2 *P. aeruginosa* and 2 *S. maltophilia*) with cefiderocol MICs >4 mg/L were found. Yamano *et al.* [45] performed molecular characterization of isolates with MICs >4 mg/L from these studies. They observed that PER and NDM enzymes (*bla*-PER were found in *A. baumannii* and *bla*NDM were found in *K. pneumonia*e and *A. baumannii*) could increase cefiderocol MIC values as well as disruption of iron transport genes (*piu*A, *pir*A and *fiu*A). Similarly, cefiderocol resistance (MIC ≥32 mg/L) have been described in *A. baumannii* isolates due to the loss of *pir*A and *piu*A genes which are two TonB-dependent receptors involved in the transport of siderophores or vitamin B12 in Gram-negative organisms, as well as carbohydrates, thiamine, and cations [46].

In *P. aeruginosa*, it has been also shown that certain mutations in the omega loop of the AmpC beta-lactamase can determine resistance to both ceftolozane-tazobactam and ceftazidime-avibactam but also reduced susceptibility to cefiderocol and increased susceptibility to imipenem-relebactam [47]. In *P. aeruginosa* PA01, *in vitro* inactivation of *piuA* (a gene encoding drug import channel) determined to a 16-fold increase

in cefiderocol MIC (0.5 to 8 mg/L). This increase was reverted with complementation experiments using a plasmid containing the *pirA* gene [48].

Within the clinical cases, in Germany, a 58-years-old male patient developed cefiderocol resistance within 3 weeks after therapy with cefiderocol in monotherapy. This MIC increase was observed in NDM- and OXA-48 producing *Enterobacter cloacae* and was caused by mutations of the *cir*A siderophore receptor during cefiderocol treatment [13]. Emergence of resistance can be also present in isolates recovered in patients with now previous treatment with cefiderocol. An elegant report published from USA by Streling *et al* [43] showed development of a cefiderocol non-susceptible *P. aeruginosa* isolate in a patient with previous treatment with different antimicrobials, including ceftazidime-avibactam. Resistance was due to mutations in major iron transport pathways previously associated with cefiderocol uptake.

In addition, cross-resistance, both to ceftazidime-avibactam and cefiderocol have been reported [49] using *in vitro* KPC beta-lactamase ceftazidime-avibactam-resistant mutants. This study evaluated the impact of these mutations on cefiderocol MICs, so that, in 76% of the KPC mutants studied, cefiderocol MIC increased compared to the wild isolate. This resistance mechanism was also observed in Pisa (Italy) in clinical isolates, where a KPC-31-producing *K. pneumoniae* was isolated from a 68-years-old male patient 7 days after ceftazidime-avibactam discontinuation [50]. Moreover, Poirel *et al* [51] recently confirmed that some KPC-3 mutants that confer resistance to ceftazidime-avibactam might also affect cefiderocol. This occurs with KPC-41 and to a lesser extend with KPC-50.

Apart from KPC carbapenemase variants affecting ceftazidime-avibactam susceptibility, some clavulanic acid inhibited extended spectrum beta-lactamases (ESBLs), such as PER, BEL and some SHV derivatives (i.e. SHV-12) might increase cefiderocol MIC values. This is also the case for some metallo-beta-lactamase (MBL) variants, including NDM and SPM. In both cases, ESBLs and MBL, the increase in MIC is more evident in *P. aeruginosa* than in *E. coli* or *K. pneumoniae* [52].

Other mechanism described that confers resistance to ceftazidime-avibactam and cefiderocol is AmpC R2 loop deletion in *E. cloacae*, which was isolated from a hospitalized patient with ventilator-associated pneumonia. The whole-genome sequencing of this isolate identified an alanine-proline deletion (A294_P295del) and a leucine-to-valine substitution (L296V) in the *amp*C gene. In the other hand, functional genome cloning of *E. cloacae* was performed obtaining several *E. coli* transformants; ceftazidime-avibactam and cefiderocol MICs of *E. coli* in which deletion was reverted by site-directed mutagenesis were both 0.5 mg/L suggesting the contribution of the R2 loop deletion to the ceftazidime-avibactam and cefiderocol MICs increase [10].

CONCLUSIONS

Cefiderocol is a new cephalosporin with a unique mechanism of action in which it also enters through the bacterial wall using the iron transport pathway. This fact determines that the *in vitro* study of cefiderocol by broth microdilution must be performed with the usual Mueller-Hinton medium, but depleted in iron so that MIC values are reproducible. Disk diffusion uses standard Mueller-Hinton agar. Surveillance studies indicate that it is one of the most active antimicrobials with a profile that includes *Enterobacterales*, including carbapenemase producers, *P. aeruginosa, Acinetobacter* spp, and other non-fermenters such as *S. maltophilia*. Isolates with impaired sensitivity or resistance to cefiderocol have been described in which the most common mechanism is disruption of the iron transport system, resulting in the loss of all or part of the advantage of cefiderocol entry via this route. Other situations in which higher MICs to cefiderocol may occur are in isolates expressing KPC variants that confer resistance to ceftazidime-avibactam or certain infrequent ESBL, or metallo-beta-lactamases, particularly in *P. aeruginosa*. However, in epidemiological surveillance studies and clinical trials such isolates are rare.

CONFLICT OF INTEREST

RC has participated in educational programs sponsored by Pfizer, MSD and Shionogi and has research grants from MSD, Shionogi and Vanarorx. PR has participated in educational programs sponsored by MSD and has research grants from MSD. Other authors declare no conflict.

REFERENCES

1. World Health Organization Global Action Plan on Antimicrobial Resistance. 2015. ISBN 978 92 4 150976 3 (https://www.who.int/publications/i/item/9789241509763, last access 04 May 2022)
2. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. WHO Pathogens Priority List Working Group. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018; 18:318-327. doi: 10.1016/S1473-3099(17)30753-3.
3. Talbot GH, Jezek A, Murray BE, Jones RN, Ebright RH, Nau GJ, Rodvold KA, Newland JG, Boucher HW; Infectious Diseases Society of America. The Infectious Diseases Society of America's 10 × '20 Initiative (10 New Systemic Antibacterial Agents US Food and Drug Administration Approved by 2020): Is 20 × '20 a Possibility? Clin Infect Dis. 2019 Jun 18;69(1):1-11. doi: 10.1093/cid/ciz089.
4. Simner PJ, Patel R. Cefiderocol antimicrobial susceptibility testing considerations: the Achilles' Heel of the Trojan Horse? J Clin Microbiol. 2020 Dec 17;59(1):e00951-20. doi: 10.1128/JCM.00951-20.
5. Bonomo RA. Cefiderocol: A Novel Siderophore cephalosporin defeating carbapenem-resistant pathogens. Clin Infect Dis. 2019; 69 (Suppl 7):S519-S520. doi: 10.1093/cid/ciz823.
6. Wu JY, Srinivas P, Pogue JM. Cefiderocol: A novel agent for the management of multidrug-Resistant Gram-Negative Organisms. Infect Dis Ther. 2020; 9(1):17-40. doi: 10.1007/s40121-020-00286-

6.

7. Sato T, Yamawaki K. Cefiderocol: discovery, chemistry, and *in vivo* profiles of a novel Siderophore Cephalosporin. Clin Infect Dis. 2019; 69 (Suppl 7):S538-S543. doi: 10.1093/cid/ciz826.
8. Yamano Y. *In Vitro* Activity of Cefiderocol against a broad range of clinically important Gram-negative bacteria. Clin Infect Dis. 2019; 69 (Suppl 7):S544-S551. doi: 10.1093/cid/ciz827.
9. Morris CP, Bergman Y, Tekle T, Fissel JA, Tamma PD, Simner PJ. Cefiderocol antimicrobial susceptibility testing against multidrug-resistant Gram-Negative bacilli: a comparison of disk diffusion to broth microdilution. J Clin Microbiol. 2020 Dec 17;59(1):e01649-20. doi: 10.1128/JCM.01649-20.
10. Kawai A, McElheny CL, Iovleva A, Kline EG, Sluis-Cremer N, Shields RK, et al. Structural basis of reduced susceptibility to ceftazidime-avibactam and cefiderocol in *Enterobacter cloacae* due to AmpC R2 loop deletion. Antimicrob Agents Chemother. 2020 Jun 23;64(7):e00198-20. doi: 10.1128/AAC.00198-20.
11. Shields RK, Iovleva A, Kline EG, Kawai A, McElheny CL, Doi Y. Clinical evolution of AmpC-mediated ceftazidime-avibactam and cefiderocol resistance in *Enterobacter cloacae* complex following exposure to cefepime. Clin Infect Dis. 2020; 71:2713-2716. doi: 10.1093/cid/ciaa355.
12. Tiseo G, Falcone M, Leonildi A, Giordano C, Barnini S, Arcari G, et al. Meropenem-vaborbactam as salvage therapy for ceftazidime-avibactam-, cefiderocol-resistant ST-512 *Klebsiella pneumoniae*-Producing KPC-31, a D179Y Variant of KPC-3. Open Forum Infect Dis. 2021 Mar 20;8(6):ofab141. doi: 10.1093/ofid/ofab141.
13. Klein S, Boutin S, Kocer K, Fiedler MO, Störzinger D, Weigand MA, et al. Rapid development of cefiderocol resistance in carbapenem-resistant *Enterobacter cloacae* during therapy is associated with heterogeneous mutations in the catecholate siderophore receptor cira. Clin Infect Dis. 2021 Jun 3:ciab511. doi: 10.1093/cid/ciab511.
14. Albano M, Karau MJ, Schuetz AN, Patel R. Comparison of agar dilution to broth microdilution for testing *In vitro* activity of cefiderocol against Gram-Negative bacilli. J Clin Microbiol. 2020 Dec 17;59(1):e00966-20. doi: 10.1128/JCM.00966-20.
15. Bonnin RA, Emeraud C, Jousset AB, Naas T, Dortet L. Comparison of disk diffusion, MIC test strip and broth microdilution methods for cefiderocol susceptibility testing on carbapenem-resistant enterobacterales. Clin Microbiol Infect. 2022 May 6:S1198-743X(22)00221-X. doi: 10.1016/j.cmi.2022.04.013.
16. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing. M100. 32st ed. Wayne, PA, USA: CLSI; 2022.
17. Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF. Reproducibility of broth microdilution MICs for the novel siderophore cephalosporin, cefiderocol, determined using iron-depleted cation-adjusted Mueller-Hinton broth. DiagnMicrobiol Infect Dis. 2019; 94:321-325. doi: 10.1016/j.diagmicrobio.2019.03.003.
18. Nakamura R, Ito-Horiyama T, Takemura M, Toba S, Matsumoto S, Ikehara T, et al. *In vivo* pharmacodynamic Study of cefiderocol, a novel parenteral siderophore cephalosporin, in murine thigh and lung infection models. Antimicrob Agents Chemother. 2019 Aug 23;63(9):e02031-18. doi: 10.1128/AAC.02031-18.
19. Guidance document on broth microdilution testing of cefiderocol. Eucast. 2020 Dec. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Guidance_documents/Cefiderocol_MIC_testing_EUCAST_guidance_document_201217.pdf (last access 04 May 2022).
20. Critchley IA, Basker MK. Conventional laboratory agar media provide an iron-limited environment for bacterial growth, FEMS Microbiology Letters, Volume 50, Issue 1, April 1988, Pages 35–39, https://doi.org/10.1111/j.1574-6968.1988.tb02907.x
21. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 12.0, 2022. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_12.0_Breakpoint_Tables.pdf, last Access 04 May 2022).
22. Cefiderocol. Summary of product characteristics. EMA. (https://www.ema.europa.eu/en/documents/product-information/fetcroja-epar-product-information_en.pdf, last Access 04 May 2022).
23. Food and Drug Administration. Cefiderocol injection. Antibacterial Susceptibility Test Interpretive Criteria. (https://www.fda.gov/drugs/development-resources/cefiderocol-injection, last access 04 May 2022)
24. The United States Committee on Antimicrobial Susceptibility Testing (USCAST). Breakpoint tables for interpretation of MIC and zone diameter results. Version 7.0, 2021. (https://app.box.com/s/zmpi2qeh2wcs905b1fp9sjn06bf3jj4a, last access 04 May 2022)
25. European Committee on Antimicrobial Susceptibility Testing. Cefiderocol Rationale Document, version 1.1, 2022. (https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/Cefiderocol_Rationale_Document_1.1_20220411.pdf, last access 04 May 2022).
26. Matuschek E, Longshaw C, Takemura M, Yamano Y, Kahlmeter G. Cefiderocol: EUCAST criteria for disc diffusion and broth microdilution for antimicrobial susceptibility testing. J AntimicrobChemother. 2022 Mar 15:dkac080. doi:10.1093/jac/dkac080.
27. Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF. *In vitro* Activity of the Siderophore Cephalosporin, Cefiderocol, against Carbapenem-Nonsusceptible and Multidrug-Resistant Isolates of Gram-Negative Bacilli Collected Worldwide in 2014 to 2016. Antimicrob Agents Chemother. 2018 25;62:e01968-17. doi: 10.1128/AAC.01968-17.
28. Kazmierczak KM, Tsuji M, Wise MG, Hackel M, Yamano Y, Echols R, Sahm DF. *In vitro* activity of cefiderocol, a siderophore cephalosporin, against a recent collection of clinically relevant carbapenem-non-susceptible Gram-negative bacilli, including serine carbapenemase- and metallo-β-lactamase-producing isolates (SIDERO-WT-2014 Study). Int J Antimicrob Agents. 2019; 53:177-184. doi: 10.1016/j.ijantimicag.2018.10.007.
29. Karlowsky JA, Hackel MA, Tsuji M, Yamano Y, Echols R, Sahm DF. *In vitro* Activity of Cefiderocol, a Siderophore Cephalosporin, Against Gram-Negative Bacilli Isolated by Clinical Laboratories in North America and Europe in 2015-2016: SIDERO-WT-2015. Int J Antimicrob Agents. 2019; 53:456-466. doi: 10.1016/j.ijantimicag.2018.11.007.

30. Kohira N, West J, Ito A, Ito-Horiyama T, Nakamura R, Sato T, et al. I*n vitro* antimicrobial activity of a siderophore cephalosporin, S-649266, against Enterobacteriaceae clinical isolates, including carbapenem-resistant strains. Antimicrob Agents Chemother. 2015: 16; 60:729-34. doi: 10.1128/AAC.01695-15.

31. Ito A, Kohira N, Bouchillon SK, West J, Rittenhouse S, Sader HS, et a. *In vitro* antimicrobial activity of S-649266, a catechol-substituted siderophore cephalosporin, when tested against non-fermenting Gram-negative bacteria. J AntimicrobChemother. 2016; 71:670-7. doi: 10.1093/jac/dkv402.

32. Cercenado E, Cardenoso L, Penin R, Longshaw C, Henriksen AS, Pascual A. *In vitro* activity of cefiderocol and comparators against isolates of Gram-negative pathogens from a range of infection sources: SIDEROWT2014-2018 studies in Spain. J Glob Antimicrob Resist. 2021;15:S2213-7165(21)00164-8. doi: 10.1016/j.jgar.2021.06.011.

33. Falagas ME, Skalidis T, Vardakas KZ, Legakis NJ; Hellenic Cefiderocol Study Group. Activity of cefiderocol (S-649266) against carbapenem-resistant Gram-negative bacteria collected from inpatients in Greek hospitals. J AntimicrobChemother. 2017: 1;72:1704-1708. doi: 10.1093/jac/dkx049.

34. Ballesté-Delpierre C, Ramírez Á, Muñoz L, Longshaw C, Roca I, Vila J. Assessment of *in vitro* cefiderocol susceptibility and comparators against an epidemiologically diverse collection of *Acinetobacter baumannii* clinicalIsolates. Antibiotics (Basel). 2022 Jan 31;11(2):187. doi:10.3390/antibiotics11020187.

35. Shortridge D, Streit JM, Mendes R, Castanheira M. *In vitro* activity of cefiderocol against U.S. and european gram-negative clinical isolates collected in 2020 as Part of the SENTRY Antimicrobial Surveillance Program. MicrobiolSpectr. 2022 Apr 27;10(2):e0271221. doi: 10.1128/spectrum.02712-21.

36. McCreary EK, Heil EL, Tamma PD. New Perspectives on antimicrobial Agents: cefiderocol. Antimicrob Agents Chemother. 2021 Jul 16;65(8):e0217120. doi: 10.1128/AAC.02171-20.

37. Yao J, Wang J, Chen M, Cai Y. Cefiderocol: An overview of its in-vitro and in-vivo activity and Underlying Resistant Mechanisms. Front Med. 2021 Dec 7;8:741940. doi: 10.3389/fmed.2021.741940.

38. Ong'uti S, Czech M, Robilotti E, Holubar M. Cefiderocol: A new cephalosporin stratagem against multidrug-resistant gram-negative bacteria. Clin Infect Dis. 2022; 74:1303-1312. doi: 10.1093/cid/ciab757.

39. Simner PJ, Beisken S, Bergman Y, Ante M, Posch AE, Tamma PD. Defining baseline mechanisms of cefiderocol resistance in the Enterobacterales. Microb Drug Resist. 2022 Feb;28(2):161-170. doi: 10.1089/mdr.2021.0095.

40. Cantón R, Doi Y, Simner PJ. Treatment of carbapenem-resistant *Pseudomonas aeruginosa* infections: a case for cefiderocol. Expert Rev Anti Infect Ther. 2022 May 10:1-18. doi: 10.1080/14787210.2022.2071701.

41. Nordmann P, Shields RK, Doi Y, Takemura M, Echols R, Matsunaga Y, et al. Mechanisms of reduced susceptibility to cefiderocol among isolates from the CREDIBLE-CR and APEKS-NP clinical trials. Microb Drug Resist. 2022; 28:398-407. doi: 10.1089/mdr.2021.0180.

42. Schalk IJ, Mislin GL, Brillet K. Structure, function and binding selectivity and stereoselectivity of siderophore-iron outer membrane transporters. Curr Top Membr. 2012;69:37-66. doi: 10.1016/B978-0-12-394390-3.00002-1.

43. Streling AP, Al Obaidi MM, Lainhart WD, Zangeneh T, Khan A, Dinh AQ, Hanson B, Arias CA, Miller WR. Evolution of cefiderocol non-susceptibility in *Pseudomonas aeruginosa* in a patient without previous exposure to the antibiotic. Clin Infect Dis. 2021; 73:e4472-e4474. doi: 10.1093/cid/ciaa1909.

44. Yamano Y, Nakamura R, Takemura M, Echols R. 1455. Potential Mechanisms of Cefiderocol MIC Increase in Enterobacterales in *in vitro* Resistance Acquisition Studies. Open Forum Infect Dis. 2020: 31;7(Suppl 1):S730. doi: 10.1093/ofid/ofaa439.1636.

45. Yamano Y, Takemura M, Kazmierczak K, Wise MGG, Hackel M, Sahm DF, Echols R. 1452. Molecular Profile of β-Lactamase Genes and Siderophore-Dependent Iron Transporter Genes of Cefiderocol High MIC Isolates from SIDERO-WT Studies. Open Forum Infect Dis. 2020: 31;7(Suppl 1):S728–9. doi: 10.1093/ofid/ofaa439.1633.

46. Malik S, Kaminski M, Landman D, Quale J. Cefiderocol resistance in*Acinetobacter baumannii*: roles of β-lactamases, siderophore receptors, andPenicillin Binding Protein 3. Antimicrob Agents Chemother. 2020;64:e01221-20. doi: 10.1128/AAC.01221-20.

47. Simner PJ, Beisken S, Bergman Y, Posch AE, Cosgrove SE, Tamma PD. Cefiderocol activity against clinical *Pseudomonas aeruginosa* isolates exhibiting ceftolozane-tazobactam resistance. Open Forum Infect Dis. 2021 Jun 12;8(7):ofab311. doi: 10.1093/ofid/ofab311.

48. Luscher A, Moynié L, Auguste PS, Bumann D, Mazza L, Pletzer D, et al. TonB-dependent receptor repertoire of *Pseudomonas aeruginosa* for uptake of siderophore-drug conjugates. Antimicrob Agents Chemother. 2018 May 25;62(6):e00097-18. doi: 10.1128/AAC.00097-18.

49. Hobson CA, Cointe A, Jacquier H, Choudhury A, Magnan M, Courroux C, Tenaillon O, Bonacorsi S, Birgy A. Cross-resistance to cefiderocol and ceftazidime-avibactam in KPC β-lactamase mutants and the inoculum effect. Clin Microbiol Infect. 2021;27:1172.e7-1172.e10. doi: 10.1016/j.cmi.2021.04.016.

50. Tiseo G, Falcone M, Leonildi A, Giordano C, Barnini S, Arcari G, et al. Meropenem-vaborbactam as salvage therapy for ceftazidime-avibactam-, cefiderocol-resistant ST-512 *Klebsiella pneumoniae* producing KPC-31, a D179Y Variant of KPC-3. Open Forum Infect Dis. 2021 Mar 20;8(6):ofab141. doi: 10.1093/ofid/ofab141.

51. Poirel L, Sadek M, Kusaksizoglu A, Nordmann P. Co-resistance to ceftazidime-avibactam and cefiderocol in clinical isolates producing KPC variants. Eur JClin Microbiol Infect Dis. 2022;41:677-680. doi:10.1007/s10096-021-04397-x.

52. Poirel L, Ortiz de la Rosa JM, Sadek M, Nordmann P. Impact of acquired broad-spectrum β-lactamases on susceptibility to cefiderocol and newly developed β-lactam/β-lactamase inhibitor combinations in *Escherichia coli* and *Pseudomonas aeruginosa*. Antimicrob Agents Chemother. 2022 Apr 19;66(4):e0003922. doi:10.1128/aac.00039-22.

Official journal of the Spanish Society of Chemotherapy

José Ramón Azanza Perea[1]
Belén Sádaba Díaz de Rada[2]

Pharmacokinetics/Pharmacodynamics and tolerability of cefiderocol in the clinical setting

[1]Departamento de Farmacología, Universidad de Navarra
[2]Servicio de Farmacología Clínica. Clínica Universidad de Navarra

Revista Española de Quimioterapia
doi:10.37201/req/s02.04.2022

ABSTRACT

Cefiderocol is a new cephalosporin with a catechol in its chemical structure faciliting its access to the interior of bacteria through iron channels. In addition, it is broadly stable to beta-lactamases. The pharmacokinetic profile is a beta-lactam one: no oral absorption, and with a wide distribution within the vascular space and the interstitial fluid of well vascularized tissues, reaching therapeutic concentrations in the alveolar lavage fluid and within the macrophage. The binding of cefiderocol to human plasma proteins, primarily albumin, is moderate (range 40-60%). The terminal elimination half-life in healthy adult subjects was 2 to 3 hours. Cefiderocol is mainly renally eliminated, so dose adjustments are recommended in subjects with moderate / severe renal impairment, in case of dialysis, and probably in patients with external clearance. Like other beta-lactams, the PK / PD parameter that has been shown to best correlate with efficacy is the efficacy time of unbound plasma concentrations (%fT>MIC), which must be close to 100% to achieve a bactericidal effect. This is possible with 2 g in a 3-hour infusion every 8 hours. In controlled trials appears to be well tolerated, similar to comparators: meropenem or imipenem-cilastatin. Cefiderocol has no apparent clinically significant effect on ECG parameters nor on plasma iron values.

Keywords: Cefiderocol; pharmacokinetic; pharmacodynamic, tolerability

INTRODUCTION

The availability of a new antibiotic is, a priori, good news, since it represents an opportunity to potentially confront the advance of bacterial resistance. If, as is the case, the antibiotic seems to be characterized by its activity profile against this type of bacteria, the news can become transcendental.

Cefiderocol, at least due to its mechanism of action and antibacterial spectrum, can be clearly included in this group of drugs, so having the opportunity to review its pharmacokinetic (PK), pharmacodynamic (PD) and tolerability properties seems a magnificent opportunity.

CHEMICAL STRUCTURE

Cefiderocol (S-649266) is a cephalosporin with a very original chemical structure since it has a chlorocatechol ring that gives it the capacity to penetrate bacteria through iron channels. It is an aminothiazole-cephalosporin with a methoxymine group, common among third and fourth generation cephalosporins [1,2]. It has a molecular weight of 752.2 g/mol and a logP of -2.26. Its chemical name corresponds to (6*R*,7*R*)-7-[[(2*Z*)-2-(2-amino-1,3-thiazol-4-yl)-2-(2-carboxypropan-2-yloxyimino)acetyl]amino]-3-[[1-[2-[(2-chloro-3,4-dihydroxybenzoyl)amino]ethyl]pyrrolidin-1-ium-1-yl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

PHARMACOKINETICS

Cefiderocol is not absorbed after oral administration and is only available for intravenous parenteral administration.

The behaviour of the drug has been evaluated in different single [3] or multiple [3-5] dose studies, obtaining the parameters summarized in Tables 1 and 2.

The conventional dose is 2000 mg every 8 hours administered in a 3-hour extended perfusion. With this regimen and after administration of single and multiple doses, there was no drug accumulation when administered to healthy subjects [3-5].

Distribution. The binding of cefiderocol to human plasma proteins, mainly albumin, ranges from 40-60 %. The geometric

Correspondence:
José Ramón Azanza
Departamento de Farmacología, Universidad de Navarra, Spain.
E-mail: jrazanza@unav.es

Table 1 **Pharmacokinetic parameters (geometric mean and coefficient of variation) obtained in healthy volunteers after administration of single doses of cefiderocol (Modified from 3).**

Pharmacokinetic parameters	100 mg (n=6)	250 mg (n=6)	500 mg (n=6)	1000 mg (n=6)	2000 mg (n=6)
Cmax (mg/l)	7.76 (7.8)	18.9 (4.9)	46.6 (10.7)	76.4 (4.6)	156 (7.9)
Tmax (h)	1	1	1	1	1
AUC_{0-inf} (mg*h/l)	17.49 (8.5)	41.94 (6.3)	108.6 (22.7)	168.1 (7.0)	389.7 (9.0)
t1/2 (h)	2.00 (1.4)	1.98 (5.5)	2.12 (15.5)	2.26 (5.8)	2.74 (10.2)
Cl (l/h)	5.72 (8.5)	5.96 (6.3)	4.60 (22.7)	5.95 (7.0)	5.13 (9.0)
Ae 0-48(%)	68.4 (3.2)	64 (5.4)	65.8 (16.2)	68.3 (6.0)	61.5 (10.6)

Cmax: maximum plasma concentration. T_{max}: time to maximum plasma concentration. AUC_{0-inf}: area under the plasma concentration curve. t1/2: elimination half-life. Cl: total clearance. Ae 0-48%: percentage of drug eliminated unchanged in urine.

Table 2 **Pharmacokinetic parameters (geometric mean and coefficient of variation) obtained in healthy volunteers after multiple dose administration of cefiderocol (Modified from 3 and 5).**

PK parameter	Single dose 2000 mg in 1-hour infusion	Multiple dose (day 10) 2000 mg in 1 – hour infusion	Single dose 2000 mg in 3-hour infusion
Number of subjects	6	8	43
C_{max} (mg/l)	156 (7.9)	153 (12.9)	89.7 (20.5)
AUC_{0-inf} (mg*h/l)	389.7 (9.0)	366.5 (14.0)	386.1 (17.2)
Cl (l/h)	-	5.46 (14.0)	5.05 (17.1)
T1/2 (h)	2.74 (10.2)	2.72 (21.6)	2.41 (14.0)

C_{max}: maximum plasma concentration. AUC_{0-inf}: area under the plasma concentration curve. Cl: total clearance. T1/2: elimination half-life.

mean of the volume of distribution during the terminal phase in healthy adult subjects after intravenous administration of a single 2000 mg dose of cefiderocol was 18.0 L (CV 18.1 %), similar to the volume of extracellular fluid [3,4,6]. In another study in healthy subjects and in patients with varying degrees of renal impairment, slightly lower volume of distribution values of around 13 litres were reported [7].

The intrapulmonary pharmacokinetics of cefiderocol after administration to healthy volunteers has been evaluated. For this purpose, a single dose of 2000 mg, administered as a one-hour intravenous infusion, was administered to a group of healthy subjects. Each subject underwent bronchoscopy with alveolar lavage (BAL) and collection of material for the determination of drug concentrations. Bronchoscopy was performed at different times; 1, 2, 4 and 6 hours after the start of drug administration. Each group was composed of 5 subjects. The geometric mean concentrations of cefiderocol in BAL fluid in samples drawn 1, 2, 4 and 6 hours after administration were 13.8, 6.69, 2.78 and 1.38 mg/L, respectively. The range of the total BAL concentration/plasma concentration ratio at 6 hours after administration was 0.0927-0.116 while the ratio of the concentration within the alveolar macrophage (AM) to plasma was 0.00496-0.104. The ratio of AUC in BAL and MA to plasma was 0.101 and 0.0177, respectively, when calculated with the total drug concentration, while that calculated using the free fraction, not bound to proteins, stood at 0.239 and 0.0419, respectively [8].

These data are consistent with those described systematically for any cephalosporin and, therefore, consistent with a typical distribution profile of beta-lactam antibiotics, which is found in the vascular space and in the interstitial fluid of well-vascularized tissues. Therefore, the higher molecular weight of cefiderocol does not significantly influence its distribution characteristics in the different tissue components.

Biotransformation. Cefiderocol undergoes virtually no metabolism since the unmodified drug accounted for 92.3% of the AUC in plasma after administration of a single dose of 1000 mg radiolabeled with [14C], perfused for 1 hour. The predominant metabolite, pyrrolidine chlorobenzamide (PCBA, a degradation product of cefiderocol), accounted for 4.7% of the plasma AUC of total radioactivity, while each of the remaining metabolites accounted for <2% of the plasma AUC of total radioactivity [9].

Table 3 Cefiderocol dose recommended for patients with CrCl <90 ml/min[a] [6]

Renal Function	Dose	Frequency
Mild renal impairment (CrCl ≥60 to <90 ml/min)	2 g	Every 8 hours
Moderate renal impairment (CrCl ≥30 to <60 ml/min)	1,5 g	Every 8 hours
Severe renal impairment (CrCl ≥15 to <30 ml/min)	1 g	Every 8 hours
End stage renal disease (CrCl <15 ml/min)	0,75 g	Every 12 hours
Patients with intermittent haemodialysis[b]	0,75 g	Every 12 hours

[a]Calculated with Cockcroft-Gault formula.

[b]Since cefiderocol is eliminated by haemodialysis, administer cefiderocol as soon as possible after the end of the haemodialysis session on haemodialysis days.

Elimination. The elimination of cefiderocol is almost entirely active in the urine, with 74.6, 98.5 and 98.7% of the administered dose being detected between 0-6 hours, 0-48 hours and 0-120 hours, respectively, after the administration of 1000 mg. Only 2.8% of the administered dose was excreted in the feces [9].

The geometric mean clearance of cefiderocol in healthy subjects was estimated to be 5.18 (cv 17.2%) l/h and the terminal elimination half-life in healthy adult subjects to be 2 to 3 hours. Cefiderocol exhibits linear pharmacokinetics in the dose range of 100 mg to 4000 mg [3 4,6].

PHARMACOKINETIC IN SPECIAL POPULATIONS

Several studies have been performed to evaluate the population pharmacokinetics of cefiderocol without demonstrating a significant relationship between the PK parameters of cefiderocol and the various covariates evaluated, which included, among others, age, sex, race, or the location of the infection. The exception was renal function, as should be expected for a drug that is almost entirely eliminated in active form in the urine and whose clearance is directly related to creatinine clearance [10,11].

Paediatric population. No pharmacokinetic studies have been published yet with cefiderocol in children or adolescents under 18 years of age, although the efficacy of 60 mg/kg administration every 8 hours in children with cystic fibrosis has been described. A posological recommendation on the safety of the drug in this age group cannot be established at this time [12].

Renal function alterations. The high renal elimination of cefiderocol implies that alterations in renal function, either by increase or reduction, have an important impact on its pharmacokinetics and require the corresponding dosage adjustment.

Renal impairment. The pharmacokinetics of cefiderocol after administration of a single 1000 mg dose has been evaluated in subjects with mild renal insufficiency, (glomerular filtration rate [creatinine clearance: ClCr] estimated from 60 to <90 ml/min/1.73 m^2), moderate renal insufficiency (ClCr of 30-<60 ml/min/1.73 m^2), severe renal insufficiency (ClCr < 30 ml/min/1.73 m^2) and end-stage renal disease (ESRD) requiring hemodialysis, compared with that present in healthy subjects and therefore with normal renal function (ClCr > 90 ml/min). The geometric mean ratios for cefiderocol AUC in subjects with mild, moderate, severe renal impairment or ESRD without hemodialysis/normal renal function, and their 90 % confidence intervals (CI) were 1.0 (0.8, 1.3), 1.5 (1.2, 1.9), 2.5 (2.0, 3.3) and 4.1 (3.3, 5.2), respectively. As would be expected, the increase in AUC was due to a reduction in drug clearance without a significant change in the volume of distribution. Approximately 60 % of cefiderocol was eliminated by a 3- to 4-hour hemodialysis session [7]. Table 3 describes the dosage adjustment given in the drug's SmPC.

Patients with augmented renal clearance. Simulations using the population pharmacokinetics model demonstrated that the recommended dose adjustment for augmented renal clearance, administering 2000 mg every 6 hours, provides exposures, and time above MIC (%fT>CMI), of cefiderocol comparable to those of subjects with normal renal function [6,10].

Patients with renal replacement techniques. The available information is limited, but data have been published on plasma concentrations in 2 patients receiving cefiderocol while being treated with these techniques, and in both cases the values of the minimum concentration after therapeutic doses (6000 mg) were lower than those described in other patients, being around 15 mg/l (12 and 18 mg/l) [13]. The administration of 1500 mg every 12 h or 1500 mg every 8 hours, respectively, has been recommended in patients submitted to continuous venovenous hemofiltration and continuous venovenous hemodialysis or continuous venovenous hemodiafiltration [14].

Hepatic impairment. Hepatic impairment is not expected to alter the elimination of cefiderocol since hepatic metabolism and excretion play little role in the elimination of the drug.

INTERACTION WITH OTHER DRUGS

The involvement of cefiderocol in interactions with the various CYP450 isoenzymes and with various transporter proteins has been evaluated. Thus, administration of 2000 mg cefiderocol every 8 hours did not affect the pharmacokinetics of furosemide (a substrate of OAT1 and OAT3) or metformin (a substrate of OCT1, OCT2 and MATE2-K). Coadministration of the same dose increased the AUC of rosuvastatin (a substrate of OATP1B3) by 21%, which was not considered clinically significant or relevant and therefore no dose adjustment was required in any of the cases evaluated [15].

Cefiderocol induces CYP3A4 *in vitro* [4,6], therefore, the metabolism of drugs that are CYP3A4 substrates when co-administered, may increase and lead to an increase in their clear-

ance with a corresponding reduction in systemic exposure. In relation to these facts when cefiderocol is co-administered with CYP3A4 substrates, patients should be monitored for a reduction in the efficacy of the drug whose metabolism may have been induced. Since CYP3A4 induction in vitro by cefiderocol is mediated by pregnane X receptor (PXR), other PXR-inducible proteins, e.g. CYP2C family and P-glycoprotein (Pgp), may also be induced, the clinical relevance of the induction is so far unknown. As a consequence, if cefiderocol is administered together with CYP2C family or Pgp substrates, patients should be monitored for reduced efficacy of the concomitant drug. Based on in vitro studies and a phase 1 clinical evaluation, no significant drug-drug interactions are anticipated between cefiderocol and substrates or inhibitors of cytochrome P450 (CYP) enzymes or intestinal, renal, or hepatic drug transporters [6].

STABILITY

Chemical, microbiological, and physical stability has been demonstrated after dilution, for 6 hours at 25°C and for 24 hours at temperatures of 2 and 8°C. If protected from light it can be stable for more than 6 hours at 25°C [6].

PHARMACODYNAMICS

Cefiderocol is a siderophore cephalosporin with in vitro activity against most Gram-negative bacteria resistant to other drugs, including carbapenemase-producing bacteria. The drug is able to passively diffuse through outer membrane porin channels, binding to extracellular free iron through its siderophore side chain, allowing active transport into the periplasmic space by siderophore uptake systems. Subsequently, cefiderocol will bind to penicillin-binding proteins (PBPs), inhibiting the synthesis of the bacterial peptidoglycan cell wall, resulting in lysis and cell death [16,17].

The activity of cefiderocol against Gram-positive or anaerobic bacteria is small or null due to intrinsic resistance.

In vitro studies have shown that there is no antagonism between cefiderocol and amikacin, ceftazidime/avibactam, ceftolozane/tazobactam, ciprofloxacin, clindamycin, colistin, daptomycin, linezolid, meropenem, metronidazole, tigecycline or vancomycin (6).

The critical values of the minimum inhibitory concentration established by the European Committee on Antibiograms (EUCAST) for cefiderocol are ≤2 g/ml for *Enterobacterales* and *Pseudomonas aeruginosa* [6].

PHARMACOKINETICS/PHARMACODYNAMICS RELATIONSHIP (PK/PD)

It has been demonstrated, in mouse infection models, that the parameter that best correlates with the efficacy of cefiderocol is the time during which plasma concentrations of non-protein-bound cefiderocol exceed the minimum inhibitory concentration (fT%>CMI) [18-21].

A study carried out in rats with respiratory infection produced by two strains of *P. aeruginosa*, one susceptible and the other resistant to cephalosporins; 2 strains of *Acinetobacter baumannii* resistant and two strains of *Klebsiella pneumoniae* resistant to carbapenems, showed that the administration of cefiderocol at doses that allowed reaching concentrations similar to those achieved in humans with 2000 mg every 8 h in a 3-hour perfusion for 4 days, produced a reduction of $3\log_{10}$ in the number of viable bacteria in the lung, even in the case of carbapenem-resistant strains. When the infusion time was 1 hour, bactericidal activity was observed in all models, although the $3\log_{10}$ reduction was only achieved in three of the five carbapenem-resistant strains, which was related to the need to achieve the highest possible %fT>MIC and therefore to extend the infusion to three hours [22].

Identical results were obtained in a PK/PD characterization study to which the efficacy of cefiderocol is adjusted, in which it was found, in the mouse model of infection produced by *P. aeruginosa* with resistance to carbapenems, that the best correlation was achieved with the highest values of the efficacy time of the free fraction (%fT>CMI) compared to the remaining PK/PD parameters; ratio of maximum plasma concentration to MIC (Cmax/MIC) or area under the curve of plasma levels to MIC (AUC/MIC) [23].

PK/PD behavior of cefiderocol has been evaluated in the treatment of the neutropenic mouse after administration of cyclophosphamide; 150 mg/kg for 4 days, and subsequent inoculation of *Pseudomonas aeruginosa* showing an MIC between 0.63 and 0.5 0.063-0.5 mg/L. Cefiderocol was administered subcutaneously, with dose escalation between 4.2-166.7 mg/kg every 8 h. Dose-response curves were performed on the eight isolates evaluated which showed a sigmoidal pattern with gradually increasing reduction in the number of choline-forming units with the highest doses. The percentage of time during which free drug concentrations exceeded MIC (%fT>MIC) for bacteriostatic effect and 1 log10 and 2 log10 reduction ranged from: 44.4-94.7, 50.2-97.5 and 62.1-100, respectively [24].

A PK/PD analysis involving a Monte-Carlo simulation verified the probabilities of reaching the target (PTA) of the percentage of the interval during which the plasma concentration was higher than the MIC (%fT>MIC) for a range of concentrations from 0.25 to 16 mg/L. Pharmacokinetic parameters previously determined in patients with varying degrees of impaired renal function were used to perform these simulations. The dose of 2000 mg every 8 hours administered as a 3-hour infusion provides a 75% probability of achieving a %fT>MIC for an MIC ≤4 mg/L for patients with normal renal function, whereas more frequent administration (every 6 hours) appears to be required when the patient has elevated renal function. The dose should be reduced or the interval increased in patients with varying degrees of impaired renal function. Finally, it seems necessary to administer a supplementary dose immediately after the end of the hemodialysis session [25].

Recently, the results of a population pharmacokinetic model using 3,427 samples of plasma levels of cefiderocol

Table 4 **Cefiderocol. Adverse reactions [6]**

- Infections and infestations: Candidiasis, including oral candidiasis, vulvovaginal candidiasis, candiduria and yeast infection, *Clostridioides difficile* colitis, including pseudomembranous colitis and *Clostridioides difficile* infection.
- Immune system disorders*: Hypersensitivity, including skin reactions and itching
- Respiratory, Thoracic and Mediastinal Disorders: Coughing
- Gastrointestinal disorders: Diarrhea, nausea, vomiting
- Skin and subcutaneous tissue disorders: Rash, including macular rash, maculopapular rash, erythematous rash and drug eruption
- General disorders and administration site changes Infusion site reaction, including pain at the infusion site, pain at the injection site, erythema at the infusion site and phlebitis at the injection site.
- Additional tests: elevated alanine aminotransferase, elevated gamma-glutamyltransferase, elevated aspartate aminotransferase, altered liver function, including increased levels on liver function tests, elevated liver enzymes, elevated transaminases, and liver function test abnormalities.

Frequent (≥1/100 to <1/10) *Rare (≥1/1,000 to <1/100).

obtained in 91 patients without infection and 425 patients presenting with pneumonia, BSI, sepsis or complicated urinary tract infection have been published. The estimate of the time during which plasma concentrations were above the MIC was 100% in most of the patients evaluated; the probability of reaching a value of 100% was > 90% for all patients except those with sepsis or BSI and normal renal function, where it was 85% [11].

TOLERABILITY

Cefiderocol is a cephalosporin and as such has the usual adverse effect profile of the group, as has been shown in the pivotal clinical trials in which it was compared with meropenem [26], imipenem [27], or with the best antibiotic in the investigator's judgment [28].

A meta-analysis including the results of the three controlled trials of cefiderocol demonstrated the absence of statistically significant differences in the incidence of adverse effects between cefiderocol and the comparators [29].

A review of the technical data sheet of cefiderocol clearly reflects its beta-lactam profile in terms of tolerability, since the typical adverse effects are described, a summary of which is shown in Table 4.

A consequence of this good tolerability of the drug is the absence of contraindications other than a history of hypersensitivity to beta-lactams and cephalosporins [6].

Warnings and precautions include the potential risk of *Clostridioides difficile* infection and seizures, again related to class effects typical of cephalosporins [6].

Reconstitution of cefiderocol with saline for intravenous administration involves the administration of 2 g of sodium chloride daily, which should be considered in patients at associated risk [6].

As with any new antibiotic, there is insufficient information regarding the use of cefiderocol in pregnant women. Although animal studies do not suggest direct or indirect harmful effects in terms of reproductive toxicity, it is preferable to avoid the use of this drug during pregnancy. It is also not known whether cefiderocol or its metabolites are excreted in milk, so it should be decided whether it is necessary to interrupt lactation or discontinue treatment after considering the benefit of lactation for the child and the benefit of treatment for the mother.

Since the antibacterial effect of cefiderocol involves its penetration of the bacteria using siderophores, specific iron channels, it was important to verify the overall effect of the drug on iron concentrations among the treated patients. The administration of a single dose slightly modified plasma iron concentrations, which were at the lower limit of the normal range (range, 80 to 199 µg/dl for men and 70 to 179 µg/dl for women) on day 5 of the 500 mg administration (71.2 µg/dl) and on day 8 (68.3 µg/dl), and with the 1000 mg dose, only on day 8 (76.8 µg/dl). Despite this, no changes were observed in the group of subjects receiving 2000 mg.

In the multiple dose study, administration of cefiderocol for 17 consecutive days in three groups of subjects; 2 groups received 1000 mg/ 8 h and the third 2000 mg with the same interval, the mean values of plasma iron were slightly below the lower range of the limit of normality on days 5, 11, and 17 and 5, 11, 13, 13, 14, and 17, respectively, in each of the groups treated with 1 g every 8 h. The higher dose (2 g) did not produce abnormalities in plasma iron [3].

The impact of cefiderocol on the electrocardiographic QT interval has been evaluated. In the first study, increasing single doses of drug were used in healthy volunteers [3]. In the other crossover study, healthy subjects received single doses of 2000 mg and 4000 mg of cefiderocol perfused over 3 hours, and moxifloxacin 400 mg in single oral doses. No electrocardiographic alterations were observed in any of the subjects receiving cefiderocol [3,5].

CONFLICT OF INTEREST

Authors declare no conflict of interest.

REFERENCES

1. El-Lababidi RM, Rizk JG. Cefiderocol: A Siderophore Cephalosporin. An Pharmacother 2020;54(12):1215-1231
2. SatoT, Yamawaki K. Cefiderocol: Discovery, Chemistry, and In Vivo Profiles of a Novel Siderophore Cephalosporin. Clin Inf Dis2019; (69 (suppl 7): S538-S543.
3. Saisho Y, Katsube T, White S, Fukase H, Shimada J. Pharmacokinetics, Safety, and Tolerability of Cefiderocol, a Novel Siderophore Cephalosporin for Gram-Negative Bacteria, in Healthy Subjects. Antimicrob Agents Chemother. 2018 Feb 23;62(3):e02163-17.
4. Fetcroja (Cefiderocol) European Medicines Agency Assessment report EMA/H/C/04829/0000. 27 de Febrero 2020.
5. Sanabria C, Migoya E, Mason JW, Stanworth SH, Katsube T, et al. Effect of Cefiderocol, a Siderophore Cephalosporin, on QT/QTc Interval in Healthy Adult Subjects. Clin Ther. 2019 Sep;41(9):1724-1736.e4.
6. Fetcroja (Cefiderocol) Ficha técnica AEMPS. Junio 2021.
7. Katsube T, Echols R, Arjona Ferreira JC, Krenz HK, Berg JK, Galloway C. Cefiderocol, a Siderophore Cephalosporin for Gram-Negative Bacterial Infections: Pharmacokinetics and Safety in Subjects With Renal Impairment J Clin Pharmacol. 2017 May;57(5):584-591.
8. Katsube T, Saisho Y, Shimada J, Furuie H. Intrapulmonary pharmacokinetics of cefiderocol, a novel siderophore cephalosporin, in healthy adult subjects. J Antimicrob Chemother 2019; 74: 1971–1974
9. Miyazaki S, Katsube T, Shen H, Tomek Ch, Narukawa Y. Metabolism, Excretion, and Pharmacokinetics of [14C]-Cefiderocolv(S-649266), a Siderophore Cephalosporin, in Healthy Subjects Following Intravenous Administration. J Clin Pharmacol 2019;59(7):958-967.
10. Kawaguchi N, Katsube T, Echols R, Wajima. Population Pharmacokinetic Analysis of Cefiderocol, a Parenteral Siderophore Cephalosporin, in Healthy Subjects, Subjects with Various Degrees of Renal Function, and Patients with Complicated Urinary Tract Infection or Acute Uncomplicated Pyelonephritis. T. Antimicrob Agents Chemother. 2018 Jan 25;62(2):e01391-17.
11. Kawaguchi N, Katsube T, Echols R, Wajima T. Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses of Cefiderocol, a Parenteral Siderophore Cephalosporin, in Patients with Pneumonia, Bloodstream Infection/Sepsis, or Complicated Urinary Tract Infection. Antimicrob Agents Chemother. 2021 Feb 17;65(3):e01437-20.
12. 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.
13. Zimmer J, Röhr AC, Kluge S, Faller J, Frey OR, Wichmann D, et al. Validation and Application of an HPLC-UV Method for Routine Therapeutic Drug Monitoring of Cefiderocol. Antibiotics (Basel). 2021 Feb 28;10(3):242.
14. 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.
15. Katsube T, Miyazaki S, Narukawa Y, Hernandez-Illas M, Wajima T. Drug-drug interaction of cefiderocol, a siderophore cephalosporin, via human drug transporters. Eur J Clin Pharmacol. 2018 Jul;74(7):931-938.
16. Page MGP. The Role of Iron and Siderophores in Infection, and the Development of Siderophore Antibiotics. Clin Infect Dis. 2019 Nov 13;69(Suppl 7):S529-S537.
17. Negash KH, Norris JKS, Hodgkinson JT. Siderophore-Antibiotic Conjugate Design: New Drugs for Bad Bugs?. Molecules 2019 Sep 11;24(18):3314.
18. Nakamura R, Toba S, Ito A, Tsuji M, Yamano Y, Shimada J. A novel siderophore cephalosporin: V. Pharmacodynamic assessment in murine thigh infection models. 54th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 5–9 September 2014. Poster F-1559.
19. Horiyama T, Toba S, Nakamura R, Tsuji M, Yamano Y, Shimada J. A novel siderophore cephalosporin: VII. Magnitude of PK/PD parameter required for efficacy in murine thigh infection model. 54th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 5–9 September 2014. Poster F-1561. 16.
20. Horiyama T, Toba S, Nakamura R, Tsuji M, Yamano Y, Shimada J. A novel siderophore cephalosporin: VI. Magnitude of PK/PD parameter required for efficacy in murine lung infection model. 54th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 5–9 September 2014. Poster F-1560.
21. Yamano Y, Nakamura R, Sato T, Tsuji M, Echols R. Correlation of cefiderocol between in vivo efficacy murine thigh/lung infection models and MIC determined in iron-depleted conditions. IDWeek, San Diego, CA, 4–8 October 2017. Poster 1524.
22. Matsumoto S, Singley CM, Hoover J, Nakamura R, Echols R, Rittenhouse S, et al. Efficacy of Cefiderocol against Carbapenem-Resistant Gram-Negative Bacilli in Immunocompetent-Rat Respiratory Tract Infection Models Recreating Human Plasma Pharmacokinetics. Antimicrob Agents Chemother 2017 Aug 24;61(9):e00700-17.
23. Nakamura R, Ito-Horiyama T, Takemura M, Toba S, Matsumoto S, Ikehara T, et al. In Vivo Pharmacodynamic Study of Cefiderocol, a Novel Parenteral Siderophore Cephalosporin, in Murine Thigh and Lung Infection Models. . 2019 Aug 23;63(9):e02031-18.
24. Ghazi IM, Monogue ML, Tsuji M, Nicolau DP. Pharmacodynamics of cefiderocol, a novel siderophore cephalosporin, in a Pseudomonas aeruginosa neutropenic murine thigh model. Int J Antimicrob Agents . 2018 Feb;51(2):206-212.
25. Katsube T, Wajima T, Ishibashi T, Arjona Ferreira JC, Echols R. Pharmacokinetic/Pharmacodynamic Modeling and Simulation of Cefiderocol, a Parenteral Siderophore Cephalosporin, for Dose Adjustment Based on Renal Function. Antimicrob Agents Chemother. 2016 Dec 27;61(1):e01381-16.
26. 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 pneu-

monia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis. 2021 Feb;21(2):213-225.

27. 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 Dec;18(12):1319-1328.
28. 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.
29. Hsueh SC, Chao CM, Wang CY, Lai CC, Chen CH. Clinical efficacy and safety of cefiderocol in the treatment of acute bacterial infections: A systematic review and meta-analysis of randomised controlled trials. J Glob Antimicrob Resist. 2021 Mar;24:376-382.

Official journal of the Spanish Society of Chemotherapy

Cefiderocol, the first catechol-cephalosporin

María Carmen Fariñas

Clinical experience of cefiderocol

Servicio de Enfermedades Infecciosas, Hospital Universitario Marqués de Valdecilla. Universidad de Cantabria. Santander. Cantabria, Spain

Revista Española de Quimioterapia
doi:10.37201/req/s02.05.2022

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.

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

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.

Correspondence:
María Carmen Fariñas
Servicio de Enfermedades Infecciosas, Hospital Universitario Marqués de Valdecilla. Universidad de Cantabria. Santander. Cantabria, Spain.
E-mail: mcarmen.farinas@scsalud.es

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.

Official journal
of the Spanish Society
of Chemotherapy

Emilio Maseda[1]
Alejandro Suárez de la Rica[2]

The role of cefiderocol in clinical practice

[1]Servicio de Anestesia y Reanimación, Hospital Universitario La Paz, Madrid, Spain
[2]Servicio de Anestesia y Reanimación, Hospital Universitario Marqués de Valdecilla, Santander, Spain

Revista Española de Quimioterapia
doi:10.37201/req/s02.06.2022

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*

Correspondence:
Emilio Maseda
Servicio de Anestesia y Reanimación. Hospital Valdecilla, Santander, Spain
E-mail: emilio.maseda@gmail.com

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].

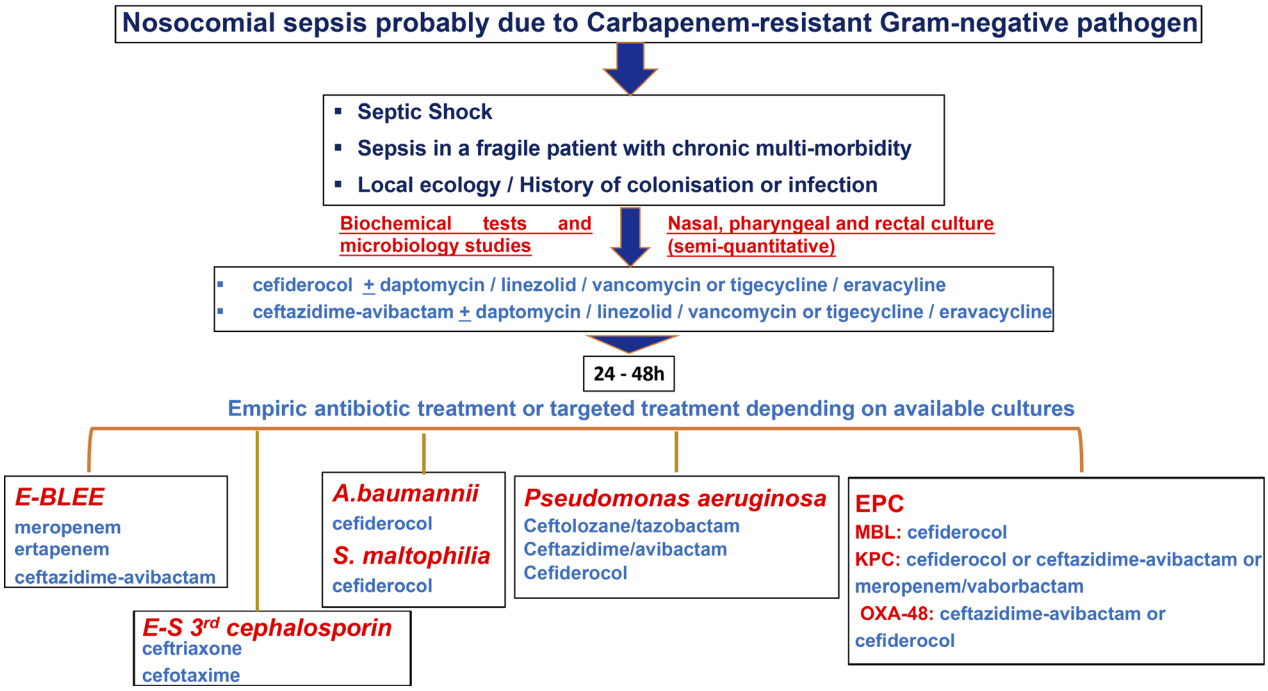


Figure 1 | **Clinical algorithm for using new antibiotics as an empirical treatment against carbapenem-resistant Gram-negative.**

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

REFERENCES

1. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. WHO Pathogens Priority List Working Group. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis 2018; 18: 318-27. doi: 10.1016/S1473-3099(17)30753-3.
2. 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 βlactamase producing *Enterobacterales* (ESBL-E), carbapenem-resistant *Enterobacterales* (CRE), and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*). Clin Infect Dis 2021; 72: e169-83. doi: 10.1093/cid/ciaa1478.
3. Portsmouth S, van Veenhuyzen D, Echols R, Machida M, Ferreira JCA, Ariyasu M, Tenke P, Nagata TD. 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.
4. 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..
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 Feb;21(2):226-240. doi: 10.1016/S1473-3099(20)30796-9.
6. 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 Nov 1;74(11):3399-3401. doi: 10.1093/jac/dkz318.
7. 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.
8. 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.

9. 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.
10. Canton R, Doi Y, Simner PJ. Treatment of carbapenem-resistant *Pseudomonas aeruginosa* infections: a case for cefiderocol. Expert Rev Anti Infect Ther. 2022 May 10:1-18. doi: 10.1080/14787210.2022.2071701.
11. Falcone M, Tiseo G, Leonildi A, Della Sala L, Vecchione A, Barnini S, et al. Cefiderocol- Compared to Colistin-Based Regimens for the Treatment of Severe Infections Caused by Carbapenem-Resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother. 2022 May 17;66(5):e0214221. doi:10.1128/aac.02142-21.
12. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest. 1999 Feb;115(2):462-74. doi: 10.1378/chest.115.2.462..
13. Lodise TP Jr, Patel N, Kwa A, Graves J, Furuno JP, Graffunder E, et al. Predictors of 30-day mortality among patients with *Pseudomonas aeruginosa* bloodstream infections: impact of delayed appropriate antibiotic selection. Antimicrob Agents Chemother. 2007 Oct;51(10):3510-5. doi:10.1128/AAC.00338-07.
14. Kollef M, Micek S, Hampton N, Doherty JA, Kumar A. Septic shock attributed to *Candida* infection: importance of empiric therapy and source control. Clin Infect Dis. 2012 Jun;54(12):1739-46. doi: 10.1093/cid/cis305.
15. Zasowski EJ, Claeys KC, Lagnf AM, Davis SL, Rybak MJ. Time is of the essence: the impact of delayed antibiotic therapy on patient outcomes in hospital-onset *enterococcal* bloodstream infections. Clin Infect Dis. 2016 May 15;62(10):1242-1250. doi: 10.1093/cid/ciw110.
16. Harris PNA, Tambyah PA, Lye DC, Mo Y, Lee TH, Yilmaz M, et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with *E coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance: a randomized clinical trial. JAMA. 2018 Sep 11;320(10):984-994. doi: 10.1001/jama.2018.12163
17. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006 Jun;34(6):1589-96. doi: 10.1097/01.CCM.0000217961.75225.E9.
18. Zilberberg MD, Shorr AF, Micek ST, Vazquez-Guillamet C, Kollef MH. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: a retrospective cohort study. Crit Care. 2014 Nov 21;18(6):596. doi: 10.1186/s13054-014-0596-8.
19. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801-10. doi: 10.1001/jama.2016.0287.
20. Huang CT, Tsai YJ, Tsai PR, Yu CJ, Ko WJ. Severe sepsis and septic shock: timing of septic shock onset matters. Shock. 2016 May;45(5):518-24. doi: 10.1097/SHK.0000000000000540.
21. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021 Nov;47(11):1181-1247. doi: 10.1007/s00134-021-06506-y.
22. Vazquez-Guillamet C, Scolari M, Zilberberg MD, Shorr AF, Micek ST, Kollef M. Using the number needed to treat to assess appropriate antimicrobial therapy as a determinant of outcome in severe sepsis and septic shock. Crit Care Med. 2014 Nov;42(11):2342-9. doi: 10.1097/CCM.0000000000000516.
23. Panidis D, Markantonis SL, Boutzouka E, Karatzas S, Baltopoulos G. Penetration of gentamicin into the alveolar lining fluid of critically ill patients with ventilator-associated pneumonia. Chest. 2005 Aug;128(2):545-52. doi: 10.1378/chest.128.2.545.
24. Tsuji BT, Pogue JM, Zavascki AP, et al. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy. 2019 Jan;39(1):10-39. doi: 10.1002/phar.2209.
25. Bassetti M, Peghin M. How to manage KPC infections. Ther Adv Infect Dis. 2020 May 14;7:2049936120912049. doi: 10.1177/2049936120912049.
26. Burillo A, Muñoz P, Bouza E. Risk stratification for multidrug-resistant Gram-negative infections in ICU patients. Curr Opin Infect Dis. 2019 Dec;32(6):626-637. doi: 10.1097/QCO.0000000000000599.
27. Cano A, Gutiérrez-Gutiérrez B, Machuca I, Gracia-Ahufinger I, Pérez-Nadales E, Causse M, et al. Risks of infection and mortality among patients colonized with *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*: validation of scores and proposal for management. Clin Infect Dis. 2018 Apr 3;66(8):1204-1210. doi: 10.1093/cid/cix991.
28. Giannella M, Pascale R, Gutiérrez-Gutiérrez B, Cano A, Viale P. The use of predictive scores in the management of patients with carbapenem-resistant *Klebsiella pneumoniae* infection. Expert Rev Anti Infect Ther. 2019 Apr;17(4):265-273. doi: 10.1080/14787210.2019.1595590.
29. Wilson GM, Suda KJ, Fitzpatrick MA, Bartle B, Pfeiffer CD, Jones M, et al. Risk factors associated with carbapenemase-producing carbapenem-resistant Enterobacteriaceae positive cultures in a cohort of US Veterans. Clin Infect Dis. 2021 Oct 20;73(8):1370-1378. doi: 10.1093/cid/ciab415.
30. Zhanel GG, Golden AR, Zelenitsky S, Wiebe K, Lawrence CK, Adam HJ, et al. Cefiderocol: a siderophore cephalosporin with activity against carbapenem-resistant and multidrug-resistant Gram-negative bacilli. Drugs. 2019 Feb;79(3):271-289. doi: 10.1007/s40265-019-1055-2.
31. 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. 2021 Jul 21:S1198-743X(21)00410-9. doi: 10.1016/j.cmi.2021.07.018.

32. Parsels KA, Mastro KA, Steele JM, Thomas SJ, Kufel WD. Cefiderocol: a novel siderophore cephalosporin for multidrug-resistant Gram-negative bacterial infections. J Antimicrob Chemother. 2021 May 12;76(6):1379-1391. doi: 10.1093/jac/dkab015.

33. Gatti M, Bartoletti M, Cojutti PG, Gaibani P, Conti M, Giannella M, et al. A descriptive case series of PK/PD target attainment and microbiological outcome in critically ill patients with documented severe XDR *Acinetobacter baumannii* BSI and/or VAP treated with cefiderocol. J Glob Antimicrob Resist. 2021 Oct 25:S2213-7165(21)00229-0. doi: 10.1016/j.jgar.2021.10.014.

34. Vissichelli NC, Sima AP, Wenzel RP. Severe sepsis: the fragile anatomy of crude mortality. Clin Infect Dis. 2021 Oct 20;73(8):1327-1329. doi: 10.1093/cid/ciab677..

35. Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF. In vitro activity of the siderophore cephalosporin, cefiderocol, against a recent collection of clinically relevant Gram-negative bacilli from North America and Europe, including carbapenem-nonsusceptible isolates (SIDERO-WT-2014 Study). Antimicrob Agents Chemother. 2017 Aug 24;61(9):e00093-17. doi: 10.1128/AAC.00093-17..

Official journal of the Spanish Society of Chemotherapy

José Mensa[1]
José Barberán[2]

Cefiderocol. Summary and conclusions

[1]Servicio de Enfermedades Infecciosas, Hospital Clínic de Barcelona, Universidad de Barcelona. IDIBAPS, Spain.
[2]Servicio de Medicina Interna - Enfermedades infecciosas Hospital Universitario HM Montepríncipe. Madrid, Spain.

Revista Española de Quimioterapia
doi:10.37201/req/s02.07.2022

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

Correspondence:
José Barberán
Servicio de Medicina Interna - Enfermedades infecciosas Hospital Universitario HM Montepríncipe. Universidad San Pablo CEU, Madrid, Spain.
E-mail: jbarberan@ceu.es.

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.

REFERENCES

1 Soriano A, Mensa J. Mechanism of action of cefiderocol. Rev Esp Quimioter 2022; 35 (Suppl. 2): 16-19

2 Garcia-Bustos V, Cabañero-Navalón M, Salavert M. Resistance to beta-lactams in Gram-negative bacilli: relevance and potential therapeutic alternatives. Rev Esp Quimioter 2022; 35 (Suppl. 2): 1-15

3 Gijón D, Castillo-Polo JA, Ruiz-Garbajosa P, Canton R. Antibacterial spectrum of cefiderocol. Rev Esp Quimioter 2022; 35 (Suppl. 2): 20-27

4 Azanza JR, Sádaba B. Pharmacokinetics/Pharmacodynamics and tolerability of cefiderocol in the clinical setting. Rev Esp Quimioter 2022; 35 (Suppl. 2): 28-34

5 Fariñas MC. Clinical experience of cefiderocol. Rev Esp Quimioter 2022; 35 (Suppl. 2): 35-38

6 Le C, Pimentel C, Pasteran F, et al. Human Serum Proteins and Susceptibility of Acinetobacter baumannii to Cefiderocol: Role of Iron Transport. Biomedicines 2022; 10: 600.

7 Nishimura B, Escalante J, Tuttobene MR, et al. Acinetobacter baumannii response to cefiderocol challenge in human urine. Sci Rep 2022; 12: 8763.

8 Maseda E. The role of cefiderocol in clinical practice. Rev Esp Quimioter 2022; 35 (Suppl. 2): 39-44