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

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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 health-care-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-

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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].

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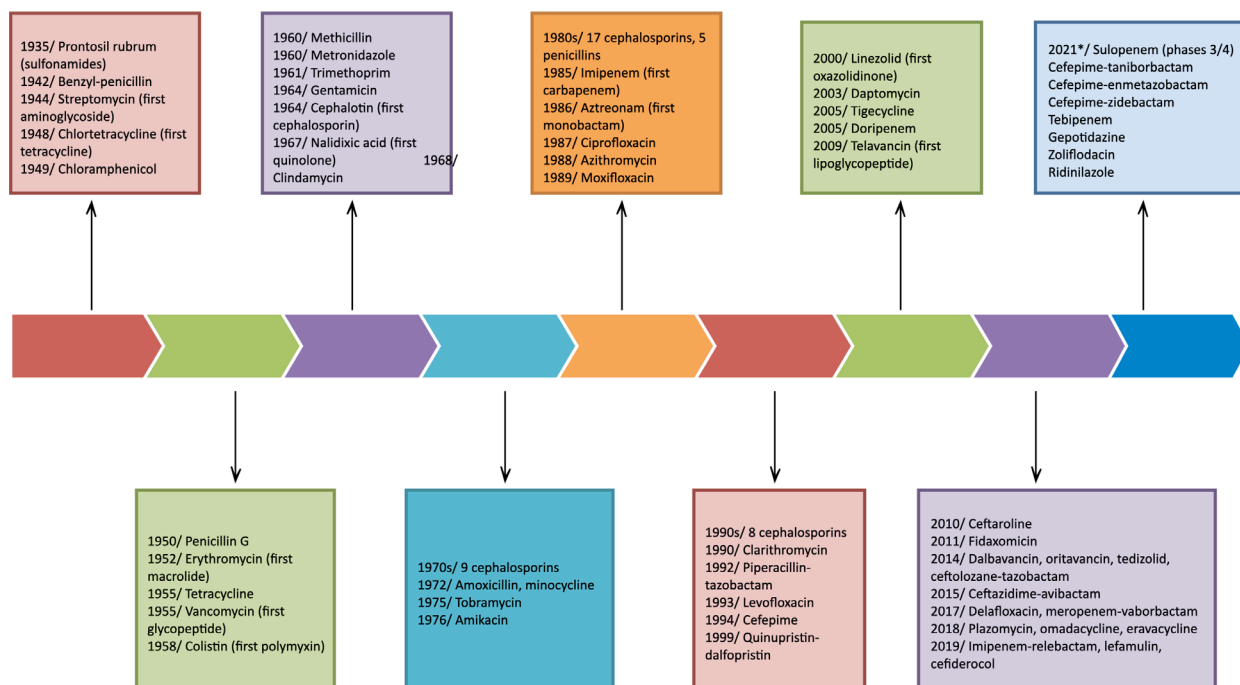
Figure 1 | **Chronological evolution of the investigation and development of antibiotics through time (antibiotic pipeline)**

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)

Antibiotics	ESBL and AmpC producer	KPC producer (class A)	NDM producer (class B)	OXA-48-like producer (class D)	Carbapenem-resistant *P. aeruginosa*	Carbapenem-resistant *A. baumannii*	*S. maltophilia*
Aztreonam-avibactam	green	green	green	yellow	yellow	red	green
Cefepime-taniborbactam	green	yellow	yellow	green	red	red	green
Cefepime-enmetazobactam	green	gray	green	green	red	gray	gray
Cefepime-zidebactam	green	yellow	green	green	yellow	green	green
Cefiderocol	green	green	green	green	green	green	green
Ceftazidime-avibactam	green	green	red	green	yellow	red	red
Ceftolozane-tazobactam	green	red	red	red	yellow	red	yellow
Colistin and polymyxin B	green	yellow	yellow	yellow	green	green	red
Eravacycline	green	green	green	green	red	green	green
Fosfomycin	green	yellow	yellow	yellow	green	red	red
Imipenem-relebactam	green	red	yellow	green	green	red	red
Meropenem-vaborbactam	green	green	red	green	green	red	red
Murepavadine[a]	gray	gray	gray	gray	green	gray	gray
Plazomicin	green	yellow	green	yellow	yellow	red	green
Temocillin	green	red	red	red	red	red	green
Tigecycline	green	green	green	green	red	green	green

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 imipe-

nem-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
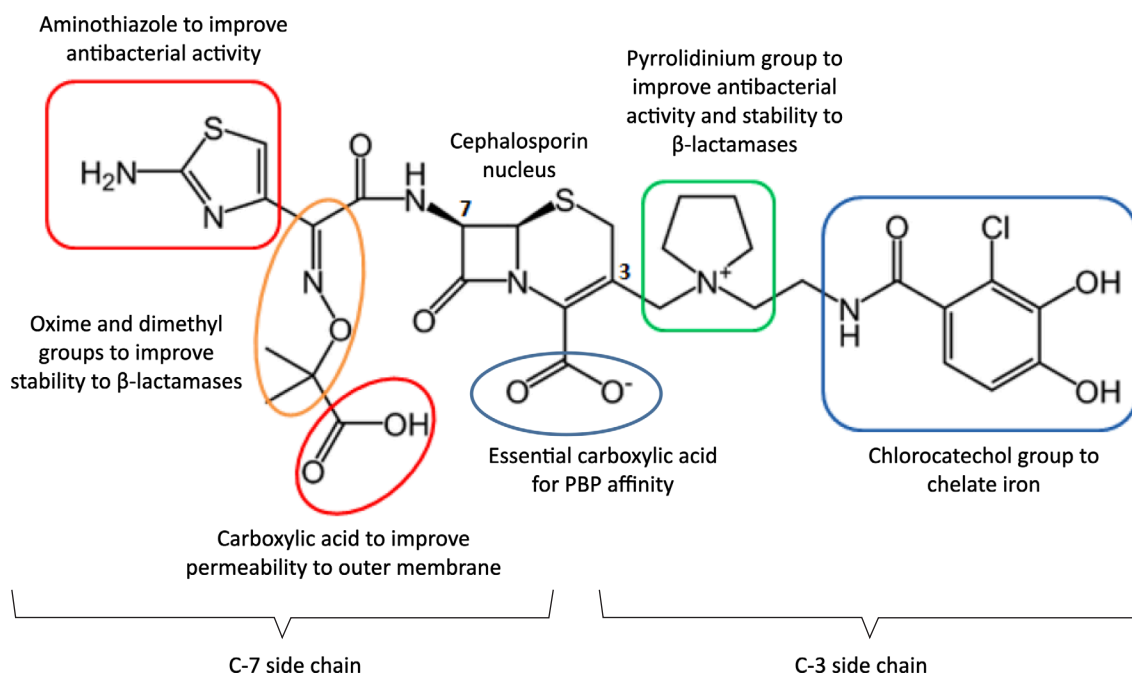
Figure 2   Relationship between structure and activity of cefiderocol

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.

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