

Review

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Review

A New Hope Against Antimicrobial-Resistance Wars: Cefiderocol

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Abstract: The increasing diffusion of antimicrobial resistance represents one of the major public health problems worldwide. In the last years, novel antimicrobial molecules have been developed to contrast the emergence of antimicrobial resistance and to provide a valuable therapeutic options against multi drug-resistant (MDR) GNB microorganisms. A new siderophore cephalosporin, Cefiderocol, represents a novel valuable antimicrobial drug for the treatment of infections caused by MDR-GNB. The mechanism of cefiderocol to penetrate through the outer membrane of bacterial cell with a particular mechanism defined at “Trojan horse” render this molecule unique and immune against the different strategies adopted by GNB to counteract the activity of antimicrobial molecules. The broad spectrum of activity against different GNB species, the potent antibacterial activity, the pharmacokinetics properties, safety, and tolerability render cefiderocol a fundamental drug for the treatment of infections due MDR strains. Although this novel antimicrobial molecule has revolutionized the therapeutic antimicrobial armamentarium against MDR-GNB, the recent emergence of cefiderocol resistant strains have redefined its role in clinical practice and requested novel strategies to preserve its antibacterial activity. In this review, we discuss the mechanism of action of Cefiderocol, emerging resistance mechanisms, pharmacokinetic/pharmacodynamic (PK/PD) properties, efficacy data against the main Gram-negative bacteria, and future prospectives.

Keywords: antimicrobials; multidrug resistance; cephalosporins; PK/PD; emerging resistance

1. Introduction

Multi-drug resistant Gram-negative bacterial infections are among the most significant threats to human health, especially for critically ill and hospitalized patients [1]. In recent years, several therapeutic agents have been developed to enhance the anti-infective arsenal against difficult-to-treat Gram-negative bacteria [2,3]. However, effective therapies for metallo- β -lactamase (MBL)-producing *Enterobacterales* and glucose-nonfermenting Gram-negative organisms, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* complex, and *Stenotrophomonas maltophilia*, remain scarce [4,5].

Cefiderocol was approved in the USA in 2019 and in Europe in 2020 for the treatment of infections caused by Gram-negative microorganisms in adult patients. The indication for cefiderocol is specifically limited to patients who have limited or no alternative treatment options, such as those with infections caused by carbapenem-resistant *Enterobacterales*, *P. aeruginosa*, *A. baumannii*, and other difficult-to-treat pathogens. As a result, cefiderocol has become a key agent in the armamentarium against carbapenem-resistant Gram-negative infections [6]. Cefiderocol is a novel siderophore cephalosporin that employs a 'Trojan horse' strategy to enter the bacterial cell; it binds to extracellular free iron and utilizes bacterial active iron transport channels to hijack the cell and penetrate the outer cell membrane [7]. Cefiderocol primarily targets penicillin-binding protein 3 (PBP3), disrupting cell wall synthesis [8], however, modifications to PBP3 may confer resistance to cefiderocol [9].

Cefiderocol circumvents resistance mechanisms related to porin channel mutations and upregulated efflux pumps; it also possesses intrinsic stability against hydrolysis by carbapenemases [7]. In particular, its side-chain properties confer high stability against hydrolysis by a range of β -lactamases, including serine β -lactamases, such as ESBLs, and metallo- β -lactamases. This makes cefiderocol one of the few effective options against difficult-to-treat Gram-negative bacteria that produce metallo- β -lactamases, making it particularly useful in treating infections caused by pathogens resistant to almost all other β -lactams [10].

According to large cohort studies [11–13], cefiderocol demonstrates effectiveness against most strains of *Enterobacterales*, *P. aeruginosa*, *S. maltophilia* and *A. baumannii*, including those resistant to carbapenems, β -lactam/ β -lactamase inhibitor combinations and polymyxins. However, resistance to cefiderocol has been reported in certain cohorts [14–16], and increasing evidence highlights the emergence of resistance during treatment [9,17–20].

2. Cefiderocol: Mechanism of Action and In Vitro Activity

Cefiderocol (formerly S-649266, GSK2696266) is a new catechol-conjugated cephalosporin developed and marketed by Shionogi & Co., Ltd. as promising drug for treatment of multidrug resistant Gram-negative bacilli infections [21]. Its structure, which has similar features to those of cefepime and ceftazidime, is characterized by several constituent groups that are the basis of its multiple mechanisms of action (refer to Figure 1) [22].

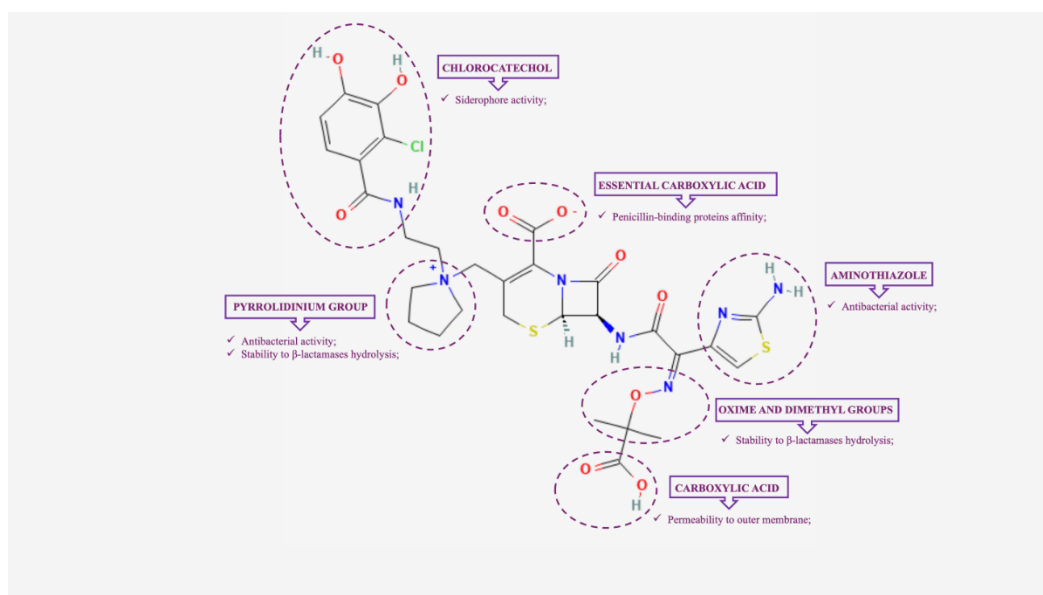


Figure 1. Two-dimensional representation of cefiderocol. Structure activity relationship on Gram-negative bacteria highlighted by the violet dotted circles.

On the C-7 side chain, aminothiazole, oxime and dimethyl groups, and carboxylic acid provide antibacterial activity, stability to β -lactamases hydrolysis, and permeability to outer membrane, respectively [22]. On the C-3 side chain, essential carboxylic acid, pyrrolidinium group, and chlorocatechol improve penicillin-binding proteins affinity, antibacterial activity and stability to β -lactamases hydrolysis, and confers the ability to bind free ferric ions, respectively [22]. It is precisely this latter siderophore activity in the extracellular environment that represents the unique and distinctive mechanism of action of cefiderocol. In fact, this property, which has been renamed the Trojan horse strategy, allows cefiderocol to enter the bacterial cell via the iron transport system, overcoming resistance mechanisms responsible for outer membrane impermeability (i.e. regulation efflux pump, loss of the porin channel) (refer to Figure 2).

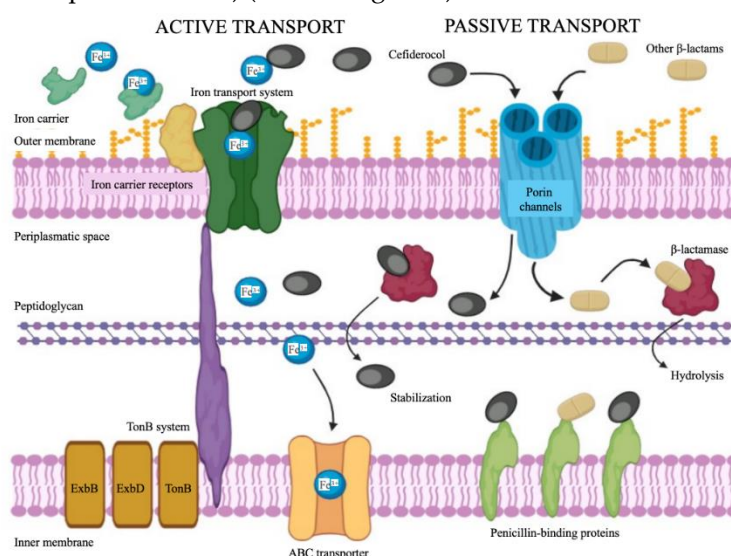
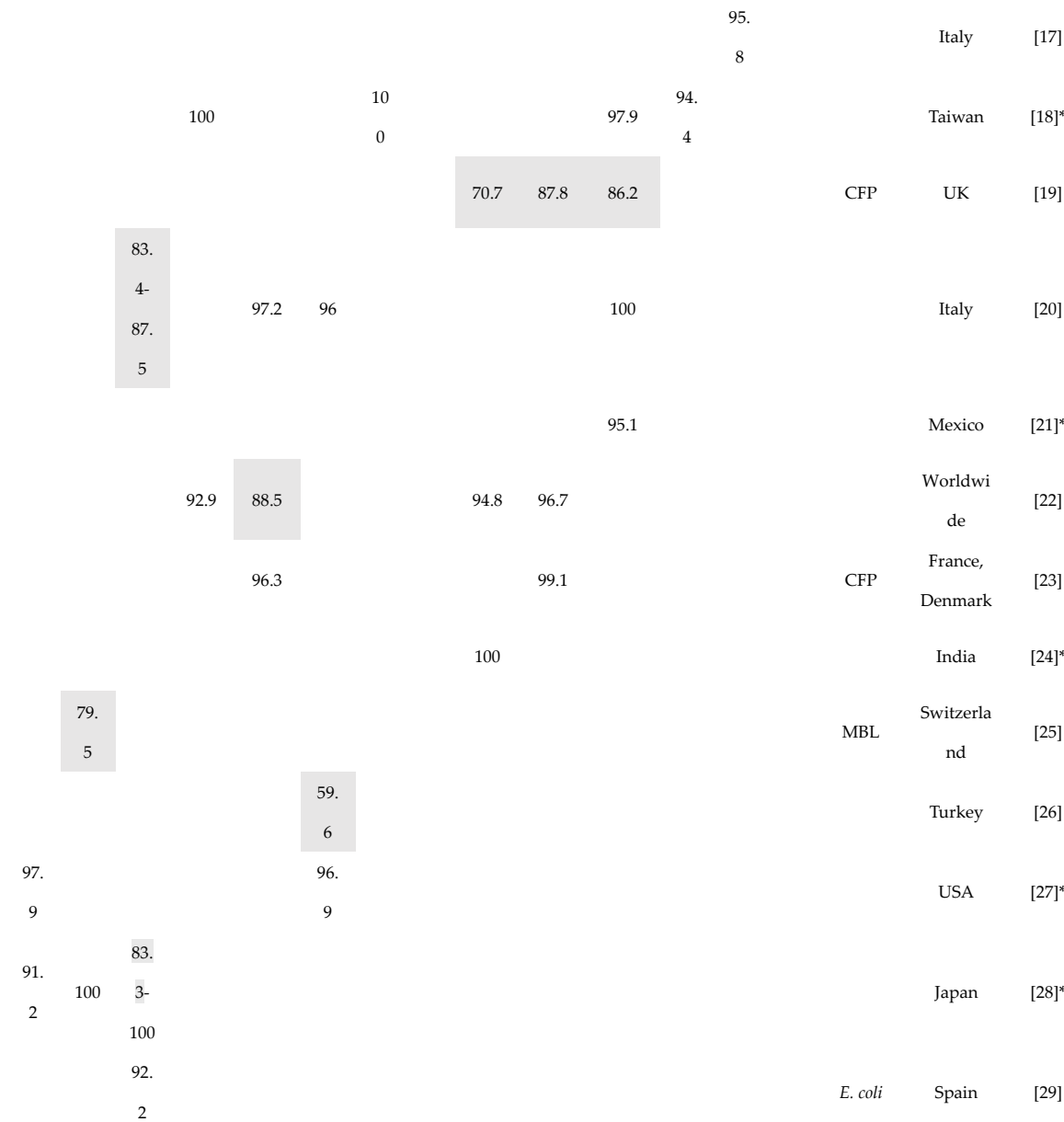


Figure 2. Mechanisms of action of cefiderocol on Gram-negative bacteria. Cefiderocol enters bacteria by both passive and active transport via the bacteria's own TonB iron transport system.

The high activity of cefiderocol has been reported in several in vitro studies (refer to Table 1) [23–49], the most robust reported in a recent systematic review and meta-analysis [23].

Table 1. *In vitro* activity of cefiderocol against major Gram-negative bacilli collections according to EUCAST breakpoints.

Cefiderocol susceptibility %															Study remarks	Country	Reference
Carbapenemase- producing strains			Carbapenem-non-susceptible strains						Overall								
AC B	PA	EB	BUR K	ACH R	AC B	PA	EB	BUR K	ACH R	STEM A	AC B	PA	EB				
55.3-59.1	77.1-98.2	61.2-75.1			86.8	96.5	87.6			99.6	91.2	98.6	97	Meta-analysis	Worldwide	[3]	
							80.6						82.3	K. pneumoniae	India	[4]*	
										100	98.4	100	99.5		Spain, Portugal	[5]*	
							93.3						97.9	K. pneumoniae	UAE	[6]*	
		86-90					90.3						95.6	K. pneumoniae	China	[7]*	
					84	82									Czech Republic	[8]	
					95.2	93.3									India	[9]*	
					93.4	100	97.2								India	[10]*	
												93.8			USA	[11]*	
					93.3							95.6			USA	[12]*	
					63							80.7		CFP	USA	[13]*	
69-100												95			Worldwide	[14]	
					85	97.8					92.4	98.9			Europe	[15]	
						70.6						91.5		CFP	Spain	[16]	



Grey shading indicates cefiderocol activity <90%. * According CLSI clinical breakpoints. Abbreviations: EB: Enterobacterales; PA: *Pseudomonas aeruginosa*; ACB: *Acinetobacter baumannii* complex; STEMA: *Stenotrophomonas maltophilia*; ACHR: *Achromobacter* species; BURK: *Burkholderia* species; MBL: metallo- β -lactamase; Cystic fibrosis patients, CFP.

Karakonstantis et al analysed 78 studies reporting more than 82000 worldwide clinical isolates. Prevalence of cefiderocol non-susceptibility was low overall but varied according to 1) species (*Enterobacterales* 3.0%, *P. aeruginosa* 1.4%, *A. baumannii* 8.8%, and *S. maltophilia* 0.4%), 2) phenotype (carbapenem-resistant *Enterobacterales* 12.4% and carbapenem-resistant *A. baumannii* 13.2%), and 3) genotype (New Delhi metallo- β -lactamase-producing *Enterobacterales* 38.8%, New Delhi metallo- β -lactamase-producing *P. aeruginosa* 22.9%, New Delhi metallo- β -lactamase-producing *A. baumannii* 44.7%, and ceftazidime/avibactam-resistant *Enterobacterales* 36.6%) [23]. Further evidence has been added to these data over the past year. Data from the main published series show that cefiderocol retains potent activity (>90%) against the main Gram-negative bacteria, with the exception of *Klebsiella pneumoniae* strains reported in an Indian study [24] and *P. aeruginosa* [33], *S. maltophilia*, *Achromobacter* and *Burkholderia* species isolates [39] detected from patients with cystic fibrosis. The data on susceptibility to cefiderocol tended to be reduced in sub-analyses that only considered collections of carbapenem non-susceptible strains, mainly involving *K. pneumoniae* (80.6%) [24], *P.*

aeruginosa (60.3% and 70.6%) [33,36], *A. baumannii* (85%) [35], and *Achromobacter* species (88.5%) [42]. Suboptimal activity of cefiderocol has been also reported in recent Czech [28] and Turkish [46] studies on carbapenem-non-susceptible *Enterobacterales* (82%), *P. aeruginosa* (84%), and *A. baumannii* (59.6%) isolates, respectively. Among studies characterising carbapenemase-producing strains, cefiderocol showed <90% activity against *Enterobacterales* (86-90%; 83.4-87.5%; 83.3%) [27,40,48] and *P. aeruginosa* (69%, 79.5%) strains collections [34,44]. In all cases, the most common concerned mechanism of resistance is metallo- β -lactamase production, especially New Delhi metallo- β -lactamase-type. On contrast, over 90% activity of cefiderocol against carbapenemase-producing *A. baumannii* (91.2% and 97.9%) has been shown in two reports of Japanese and American bacterial surveillance programmes [47,48].

3. Mechanisms of Cefiderocol Resistance

The key characteristics of cefiderocol are its active uptake mechanisms by Gram-negative bacteria under iron-depleted conditions and its improved stability to the hydrolytic activity of various types of β -lactamases. However, a variety of mechanisms may be involved in the acquisition of cefiderocol resistance, and they can be summarized into four groups: mutations in genes related to iron transfer systems, expression of β -lactamases, mutations in penicillin binding proteins, porin loss or efflux pump overexpression. Each of these mechanisms alone is generally not sufficient to increase cefiderocol MICs above PK/PD breakpoints. Therefore, resistance to cefiderocol is typically acquired as a consequence of various combinations of the above resistance mechanisms.

3.1. Mutations in Genes Related to Iron Transfer Systems

The role of siderophore receptor mutations in cefiderocol resistance has been shown by studies both on isogenic mutants and clinical isolates. Among the receptors recognized for cefiderocol uptake in *P. aeruginosa* and *A. baumannii* are two TonB-dependent receptors (TBDRs), PiuA and PirA [50]. Inactivation of *piuA* has been associated with a 16 to 32-fold increase of cefiderocol MIC in *P. aeruginosa* mutants [50,51]. Similarly, the deletion of *piuD* (an ortholog of *piuA*) increased cefiderocol MICs 32-fold in *P. aeruginosa* [51]. Moreover, deletion of *pirA* in *P. aeruginosa* was associated with low (two-fold increase) or no impact on cefiderocol MIC [50,51], but combining deletion of *piuA* or *piuD* with deletion of *pirA* the increase was of 32-fold and 64-fold, respectively [50,51]. In vivo emergence of cefiderocol resistance involving iron transport receptors has been reported in patients treated with ceftazidime/avibactam or ceftolozane/tazobactam [52,53]. Gomis-Font et al. reported the emergence of in vivo cefiderocol resistance development in *P. aeruginosa* caused by a large genomic deletion, including the *piuDC* region and the *ampC* regulator *AmpD*, in the absence of cefiderocol treatment. This deletion led to co-resistance to cefiderocol and ceftazidime/avibactam as result of *AmpC* overexpression and *PiuDC* loss [52]. Streling et al. reported a *P. aeruginosa* isolate that acquired resistance to cefiderocol after ceftolozane/tazobactam treatment and exhibited the substitution L147F in *AmpC* gene together with mutations in *piuA* and *pirR* genes compared to the ancestor isolate [53]. The relevant role of PiuA in cefiderocol resistance has also been demonstrated in *A. baumannii*. Genomic analysis of cefiderocol-resistant *A. baumannii* clinical isolates revealed deficiency of *piuA* alone or associated with reduced expression of *pirA* [54,55]. Recently, Findlay et al. reported the in vivo emergence of cefiderocol resistance following 10 days of cefiderocol treatment in a burn ICU patient with *A. baumannii* bloodstream infection. WGS analysis of cefiderocol-resistant and the ancestor cefiderocol-susceptible isolate revealed a three nucleotides deletion upstream of *piuA* causing the down expression of the gene [56]. Huang et al. identified *pirA* inactivation of by insertion of an ISAb36 element as key resistance mechanism following cefiderocol treatment in a patient with OXA-72-producing *A. baumannii* infection. [57].

In *Enterobacterales*, alterations in siderophore receptors CirA and/or Fiu have been associated with reduced susceptibility or resistance to cefiderocol. Various mutations in *cirA* resulted in increased cefiderocol MIC values in *K. pneumoniae* and *Enterobacter cloacae* complex strains, both on isogenic mutants and in vitro induced resistant strains [58,59]. Most of the cefiderocol-resistant *K. pneumoniae* or *Escherichia coli* clinical isolates presenting mutations in *cirA* were also producers of

NDM metallo- β -lactamases, highlighting the role of certain β -lactamases in contributing to resistance [60–64]. Experiments on isogenic mutants of *E. coli* showed that loss of *Fiu* resulted to two-fold increase of cefiderocol MIC, increasing up to 16-fold when combined with deletion of *cirA* [50]. Mutations in other iron uptake and transport related genes (e.g., *fhuA*, *fepA*, *iutA*, *cirA*, *sitC*, *apbC*, *fepG*, *fepC*, *fetB*, *yicI*, *yicJ*, and *yicL*) were identified in cefiderocol-resistant *K. pneumoniae* isolates [65]. Alterations in genes encoding three inner membrane proteins which transfer energy to the outer membrane for iron transport (TonB–ExbB–ExbD), other tonB-dependent receptors (*fecA*), ferric iron ABC transporter (*fbpA*), iron uptake system component (*efeo*) were also identified in in vitro derived cefiderocol-resistant *K. pneumoniae* mutants [66–68]. Moreover, mutations in *fhuA* (ferrichrome iron receptor) or *fepA* (ferric enterobactin receptor) were identified in two *K. pneumoniae* clinical isolates with cefiderocol MIC of 2 mg/L [69].

With regard to acquired resistance to cefiderocol in *S. maltophilia*, the data available in the literature are currently very limited. However, mutations affecting iron transport (*tonB*, *exbD*, *smlat1148*, *cirA*) were reported in in vitro derived cefiderocol-resistant *S. maltophilia* isolates [70,71].

Overall, given the multitude and diversity of genes involved in iron transfer systems suggest that further studies are needed to fully understand all possible pathways leading to cefiderocol resistance and their role in combinations including other types of resistance mechanisms.

3.2. Expression of β -Lactamases

Overall, although cefiderocol maintains relatively good activity against most carbapenem-resistant strains, its stability is incomplete especially against phenotypes including NDM-producing *Enterobacterales* and *A. baumannii* and ceftazidime/avibactam-resistant KPC-producing *Enterobacterales* [23]. In addition, this finding is further supported by the enhanced activity of cefiderocol when combined with clinically available β -lactamases inhibitors and dipicolinic acid in serine- β -lactamases- and metallo- β -lactamase-producing Gram-negative bacteria, respectively [72,73]. The contribution of the various types of β -lactamases is different as suggested by both cloning and mutagenesis experiments, and investigations on clinical isolates [9].

3.2.1. Metallo β -Lactamases

Contribution of NDM-type metallo- β -lactamase to cefiderocol hydrolysis was shown by cloning experiments in *E. coli*, *P. aeruginosa* and *A. baumannii* [75–78]. Four- to 64-fold increases in MIC values were observed, without significant difference among the different NDM variants (e.g. NDM-1, NDM-5, NDM-7, NDM-9) [73–76]. The combined effect of NDM expression and *cirA* deficiency in *K. pneumoniae* and *E. coli* was observed in several clinical isolates [60–64]. Moreover, increased copy number of *bla*NDM-5 together with increased expression of NDM-5 was associated with reduced susceptibility to cefiderocol in *E. coli* isolates [77,78]. In addition to the NDM type, other MBLs may be implicated although currently available evidence is limited. In vitro studies showed that introduction of SPM-1 gene caused significant decrease in cefiderocol activity in *E. coli* and *P. aeruginosa*, whereas VIM-2, AIM-1, and GIM-1 expression had low or no impact [75].

3.2.2. KPC Variants

One of the first pieces of evidence in favour of cross-resistance between ceftazidime/avibactam and cefiderocol in KPC-producing *K. pneumoniae* emerged by observing a significantly higher rate of cefiderocol resistance among ceftazidime/avibactam-resistant isolates than among susceptible ones (82.5% vs. 6.7%) [79]. To date, more than 200 variants of KPC have been reported worldwide and most of them were discovered in the last five years, following the introduction of ceftazidime/avibactam into clinical practice. Sequencing of *bla*KPC in clinical isolates with reduced susceptibility to cefiderocol and cloning experiments in isogenic strains confirmed that cross-resistance is due to expression of specific KPC variants, mostly with mutations in Ω loop of KPC (e.g. KPC-31, KPC-33, KPC-41, KPC-50, KPC-25, KPC-29, KPC-44, KPC-121, KPC-203, KPC-109, KPC-216) [80–85]. Given the structural similarity between ceftazidime and cefiderocol, mutations that increase

the hydrolytic activity of the β -lactamase towards ceftazidime lead to co-resistance or reduced susceptibility to cefiderocol. Indeed, in this regard, combination of cefiderocol with new β -lactamase inhibitors such as avibactam, vaborbactam or relebactam seems promising to enhance its activity [72].

3.2.3. OXA-Type β -Lactamases

The effect of OXA-type β -lactamases expression on cefiderocol resistance is limited. Cloning experiments showed that both narrow-spectrum (OXA-1) and most of carbapenem-hydrolyzing (OXA-23, OXA-48, OXA-58) class D β -lactamases do not affect cefiderocol susceptibility [73–76]. In contrast, the recently identified carbapenemase OXA-427 showed significant hydrolytic activity against cefiderocol [74–76], although a low effect on cefiderocol MIC (two-fold increase) was demonstrated in *E. coli* isogenic mutants [75]. In addition, resistance to cefiderocol was reported in a collection of OXA-427-producing *Enterobacterales* in Belgium [86].

3.2.4. AmpC β -Lactamases

The involvement of AmpC variants in cefiderocol resistance is demonstrated by clinical reports and cloning experiments. The A292_L293del AmpC variant was associated with cross-resistance to cefepime, ceftazidime/avibactam and cefiderocol in *E. cloacae* complex. Cloning of the encoding-gene into *E. coli* TOP10 led to resistance to cefepime and ceftazidime/avibactam, and >32-fold increase in the MIC of cefiderocol [87]. The role of four amino acid substitutions (A114E, Q120K, V211S, and N346Y) in CMY-2 AmpC (CMY-185) in development of cross resistance to ceftazidime/avibactam and cefiderocol was also shown in a *E. coli* clinical isolate [88]. Similarly, a new variant of CMY β -lactamase (CMY-186) characterized by a V159G amino acid substitution in the YXN loop of the enzyme was observed in a clinical isolate of *K. pneumoniae* [89].

Expression of AmpC variants carrying single amino acids substitutions (E247K and L147F) were also associated with the in vivo emergence of cross-resistance to ceftolozane/tazobactam and cefiderocol in *P. aeruginosa* [55,90].

3.2.5. Other β -Lactamases

Several in vitro studies have demonstrated high rates of cefiderocol resistance in *A. baumannii* and *P. aeruginosa* isolates expressing PER-type β -lactamases [15,73,91]. Cloning experiments of the various blaPER-like genes into *E. coli*, *P. aeruginosa* *A. baumannii* isogenic mutants showed a two- to 64-fold increase in the MIC of cefiderocol [73–75]. SHV-type EBSLs and BEL-type β -lactamases have been associated with increased cefiderocol MICs of cefiderocol following their introduction into isogenic mutants [73–75]. Amplification of blaSHV-12 has been associated with cefiderocol resistance in two hypervirulent *K. pneumoniae* clinical isolates in China [92]. In addition, the cephalosporinase PDC-30 was detected in two cases of in vivo cefiderocol-resistant *P. aeruginosa*, as the introduction of the respective gene in *E. coli* caused an eight-fold increase in the MIC of cefiderocol [17–93].

3.3. Mutations in Penicillin Binding Proteins

Since PBP-3 is the primary target of cefiderocol to exert its antibacterial effect, the presence of PBP-3 mutants represents the main mechanisms of resistance to cefiderocol at this level, although often in combination with other resistance markers (expression of β -lactamases and/or mutations in the in genes related to iron transfer systems). In detail, YRIN insertion in PBP-3 was observed in *E. coli* isolates with increased cefiderocol MIC values [60,68]. Barker et al. showed that PBP-3 mutant (insYRIN) alone was not sufficient to cause cefiderocol resistance, but its combination with NDM expression and/or cirA deletion was required [63]. This evidence is supported by cloning experiments of the gene encoding the mutated PBP-3 in *E. coli*, which showed only a two-fold increase in the MIC of cefiderocol [68]. Various mutations in PBP-3 among cefiderocol-resistant *A. baumannii* clinical isolates has been identified as potential resistance mechanisms to cefiderocol [54,57–93]. However, their effective contribution to cefiderocol resistance needs further investigations.

3.4. Porin Loss or Efflux Pump Overexpression

The mechanism of porin loss has been associated to cefiderocol resistance in *K. pneumoniae* (ompK35, ompK36, ompK37) [94,95], *E. cloacae* (ompC and ompF) [94], and *P. aeruginosa* clinical isolates (Opr-D) [17]. Furthermore, deletion of ompK35/ompK36 and oprD in *E. coli* and *P. aeruginosa* isogenic mutants showed a two-to four-fold increase of the MIC values of cefiderocol, respectively [50,96]. The role of efflux transport proteins overexpression in cefiderocol resistance emerged in carbapenem-resistant *K. pneumoniae* [95], *P. aeruginosa* (MexAB–OprM) [96], *S. maltophilia* (SmeDEF) [73], and *Achromobacter xylosoxidans* (AxyABM) isolates [97].

4. Pharmacokinetic/Pharmacodynamic Features

Similar to other beta-lactams, cefiderocol is a time-dependent cephalosporin characterized by linear pharmacokinetics, limited volume of distribution (approximatively 15 L), short half-life (2-3 hours), moderate protein binding (equal to 58%), and predominant renal clearance [98]. The fraction of dosing interval during which the free drug concentrations exceeds the minimum inhibitory concentration (%fT>MIC) represents the best pharmacokinetic/pharmacodynamic (PK/PD) predictor of cefiderocol efficacy in infections caused by *Enterobacterales*, *P. aeruginosa*, *A. baumannii*, and *S. maltophilia* strains [99]. Notably, several preclinical models [100–103] reported that a bacteriostatic effect was observed with the attainment of a cefiderocol PK/PD target equal to 40-70%fT>MIC, whereas a bactericidal effect corresponding to ≥ 1 -log kill reduction was reported with cefiderocol PK/PD target of 55-88%fT>MIC. Specifically, a *P. aeruginosa* neutropenic murine thigh model found that a fT>MIC of 76.3%, 81.9%, and 88.2% was required for stasis, 1-log kill, and 2-log kill reduction in bacterial burden, respectively [102]. Similarly, in murine thigh and lung infection models, the mean cefiderocol %fT>MIC needed for a 1-log kill reduction against 10 strains of *Enterobacteriaceae* and 3 strains of *P. aeruginosa* in the thigh infection models were 73.3% and 77.2%, respectively, whereas the mean %fT>MIC against *Enterobacteriaceae*, *P. aeruginosa*, *A. baumannii*, and *S. maltophilia* in the lung infection model were 64.4%, 70.3%, 88.1%, and 53.9%, respectively [104]. Overall, these preclinical data support the adoption of 2g every 8h administered over 3-h infusion for attaining the PK/PD target of 75%fT>MIC against Gram-negative pathogens showing MIC values of ≤ 4 mg/L [99].

However, recent preclinical and clinical studies suggested that the attainment of beta-lactam aggressive PK/PD targets (i.e., at least 100% fT>4 x MIC) may be recommended for maximizing not only clinical efficacy, but also for minimizing microbiological failure and suppressing resistance development [105; 106]. Notably, a recent meta-analysis including 21 observational studies with a total of 4,833 critically ill patients found that attaining aggressive PK/PD targets was significantly associated with higher clinical cure rate (OR=1.69; 95%CI 1.15–2.49) and lower risk of beta-lactam resistance development (OR=0.06; 95%CI 0.01–0.29). Conversely, failure in attaining aggressive PK/PD targets was significantly associated with higher risk of microbiological failure (OR=26.08; 95%CI 8.72–77.95) [106]. Although evidence concerning the adoption of aggressive PK/PD targets with novel beta-lactams are currently limited, this strategy should be pursued also in this setting, including patients receiving cefiderocol.

In this regard, although evidence investigating the relationship between cefiderocol PK/PD target attainment and clinical/microbiological outcome are limited, some interesting clues have been raised. Interestingly, a recent case series of 13 critically ill patients affected by severe COVID-19 pneumonia developing carbapenem-resistant *A. baumannii* bloodstream infections (BSIs) and/or ventilator-associated pneumonia treated with cefiderocol administered by extended infusion (EI) over 3-hours showed that only 38% attained aggressive PK/PD target (defined as a free trough concentration [fC_{min}]/MIC ratio > 4). Notably, patients attaining suboptimal PK/PD target attainment (i.e., a fC_{min}/MIC ratio < 1) had higher microbiological failure rate (80%) compared with those having quasi-optimal (i.e., a fC_{min}/MIC ratio 1–4) or optimal PK/PD targets (29%) [107]. Similarly, other two case series including respectively three patients affected by carbapenem-resistant *A. baumannii* infections and receiving cefiderocol administered by 3-hour EI during renal replacement therapy [108] and four cases of difficult-to-treat resistant (DTR) *P. aeruginosa* BSIs and/or nosocomial

pneumonia treated with 3-hour EI cefiderocol [109] reported the attainment of optimal PK/PD targets in 67% and 75% of cases, respectively.

These findings could support the rationale for implementing cefiderocol altered dosing strategies by continuous infusion (CI) (i.e. 2 g every 8 hours over 8 h infusion according to aqueous stability restriction) after proper loading (2 g over 2-3 h) for maximizing the attainment of aggressive PK/PD targets. Indeed, in a recent case series of five critically ill patients affected by severe carbapenem-resistant *A. baumannii* infections and receiving CI cefiderocol (i.e., 2 g q8h over 8-h infusion) during continuous veno-venous hemodiafiltration aggressive PK/PD targets were attained in all included patients, ensuring optimal coverage for MIC up to 4 mg/L included [110].

It is noteworthy that optimal penetration and consequent attainment of aggressive PK/PD targets in infection sites represent a mandatory goal in the treatment of deep-seated infections, as suggested by the “antimicrobial puzzle” concepts [111]. In this scenario, evidence concerning cefiderocol penetration and absolute tissue concentrations are available for lung, central nervous system (CNS), and abdominal fluid.

Specifically, a prospective observational study investigating epithelial lining fluid (ELF) penetration of cefiderocol administered at a dosage of 2 g every 8 hours by EI over in 7 critically ill patients affected by ventilator-associated pneumonia reported a mean ELF-to-plasma ratio of 0.34, being the attainment of aggressive PK/PD targets ensured only for MIC up to 0.5 mg/L included [112; 113].

Four case report assessed penetration rate and absolute concentrations of cefiderocol in cerebrospinal fluid (CSF) [114]. Specifically, cefiderocol CSF-to-plasma ratio ranged from 0.04 to 0.50, whereas absolute fC_{min} ranged from 0.65 mg/L to 10.46 mg/L with administration of 2g every 6-8 hours over 3 hours EI. Although retrieved concentrations allowed to attain optimal cefiderocol PK/PD target in three out of 4 cases according to the MIC values of isolated pathogens, only in one case observed concentrations ensured the attainment of optimal PK/PD target for MIC up to the clinical breakpoint of 2 mg/L [114].

In regard to abdominal fluid penetration, a case report of a critically ill patient affected by DTR *P. aeruginosa* infection and treated with CI cefiderocol during continuous venovenous hemofiltration reported absolute concentrations in abdominal drain fluid equal to 15.3 mg/L, ensuring the attainment of optimal PK/PD target for MIC values up to the clinical breakpoint of 2 mg/L [115].

Overall, these findings may strongly support the adoption of cefiderocol altered dosing strategies consisting in high dosage coupled with CI administration for maximizing the attainment of optimal PK/PD targets in case of deep-seated infections [116].

5. Clinical Usage

Multi-drug resistant (MDR) and extensively drug resistant (XDR) gram-negative bacteria (GNB) are an alarming clinical challenge, burdened by a mortality rate of 30-50%, and scarce therapeutic options. In this context, the advent of cefiderocol represented a crucial innovation for clinicians who are called to face this issue.

Between 2019 and 2020, commercialization of cefiderocol was approved by Food and Drug Administration (FDA) for treatment of complicated urinary tract infections (cUTIs) [117] and for hospital acquired pneumonia (HAP) and ventilator acquired pneumonia (VAP), based on the results of CREDIBLE-CR, APEKS cUTI and APEKS NP phase III clinical trials [18,118,119]. Subsequently, in 2020, European Medicines Agency (EMA) approved cefiderocol for treatment of infections caused by GNB with limited therapeutic options, including carbapenem resistant *P. aeruginosa* (CRPa), *S. maltophilia*, carbapenem resistant *Enterobacterales*, carbapenem resistant *A. baumannii* (CRAb) [120].

Despite the approval was limited to certain clinical syndromes, cefiderocol has immediately gained its place in therapy for the treatment of serious CR-GNB infections as salvage therapy, whereas treatment options are tight.

5.1. Carbapenem Resistant *Pseudomonas aeruginosa*

The introduction of cefiderocol between the therapeutic opportunities was a game changer for treatment of *P. aeruginosa* infection. Indeed, *P. aeruginosa* is provided with different mechanism of antibiotic resistance, and the prevalence of carbapenem resistant strains is between 10 and 25% in most European countries, and reaches 50% in Eastern regions [121]. Moreover, resistance to newer betalactams/beta lactamase inhibitors (BL/BLI) in CRPa is spreading; however, cefidercol seems to retain sensitivity against these strains [122]. By exploring real-world studies, de La Fuente et al. reported in a cohort of 13 patients mainly affected by CRPa pneumonia a 28-day crude mortality of 23%, with achievement of clinical and microbiological cure of 84.6% (assessed 7 days after the end of treatment) [123]. A larger real-world case series published by Gavaghan et al. including 24 subjects with CR-GNB infections (mainly CRAb-14,5% and CRPa-10,4%) treated with cefiderocol reported a clinical success of 46% and a 30-day mortality of 42% [124].

A paper including 27 ICU patients affected by difficult to treat non-fermenting gram-negative bacteria infection (*P. aeruginosa* in 81,5% of cases) treated with cefiderocol compared with 54 patients who received the best available therapy (BAT) showed a higher relapse rate in cefiderocol with a comparable result in clinical cure or mortality rates compared to BAT [125].

A recent retrospective, multicenter, observational chart review study named PERSEUS, found an overall clinical success rate, defined as the composite outcome of clinical cure and/or survival at day 28 of 84.3% and a 28-day all-cause mortality of 21.5% in patients treated with cefiderocol for GNB infection, mainly *P. aeruginosa* (66,7%) [133].

5.2. *Stenotrophomonas maltophilia*

Despite their poor frequency, treatment of infections caused by other fermenting gram negative bacteria, including *S. maltophilia*, result challenging due to the inherent antibiotic resistance of these pathogens. Mortality rates in *S. maltophilia* infection ranges to 21 and 69% [127]. Even in this scenario, cefiderocol seems to play a crucial role, as showed in a case series including 19 patients diagnosed with *S. maltophilia* infection treated with cefiderocol an in-hospital all-cause mortality at 14-day and 28-day of 36,8% and 21% respectively [128].

5.3. Carbapenem Resistant *Enterobacterales*

Cefiderocol, differently from the newer BL/BLI, retains efficacy against both serine- and metallo-beta lactamase. However, due to the lack of active drugs against metallo beta lactamase (MBL), cefiderocol could gain its place in therapy against *Enterobacterales* producing NDM, VIM, IMP. A subanalysis on results of CREDIBLE-CR and APEKS-NP trial including MBL infections (both *Enterobacterales* and on fermenting GNB) give us encouraging results, with higher rates of clinical cure, microbiological eradication and 28-day all-cause mortality, if compared to BAT or high dose meropenem respectively [129]. Nevertheless, some concerns should be investigated. In a real-world case series including 21 patients with infections caused by MBL-producing CR-*Enterobacterales*, the rate of cefiderocol resistance was 9,5% [130]. Indeed, according to microbiological data, cefiderocol resistance rates among NDM strains are of 81% and 12% using EUCAST and CLSI interpretive criteria, respectively [131].

According to these data, the empirical use of cefiderocol for treatment of MBL-*Enterobacterales* infections should be discouraged until result of microbiological susceptibility test.

5.4. Carbapenem Resistant *Acinetobacter baumannii*

Finally, during the last years, cefiderocol has been largely used for treatment of CRAb infections, primarily BSI and VAP, in context of intensive care units (ICU) wards.

Hence, several case series and comparative studies exploring the efficacy and safety of this new drug in "real-world" have been published. Bavaro et al. reported 13 cases of treated with cefiderocol-based combination therapy (10/13 CRAb), with a rate of microbiological eradication of 100% and a 30-day survival rate of 77% [132]. Similarly, another interesting case series including 10 critically ill

patients with bloodstream infection (BSI) or VAP mainly caused by CRAB, stated a clinical success of 70%, while 30-day mortality was of 10% [133]. Another study including 118 patients with CRAB monomicrobial bacteremia showed a significantly lower 30-day mortality in patients treated with cefiderocol if compared to patients treated with colistin (40% vs 59%, $p = 0.045$), and cefiderocol based treatment resulted protective. [134].

Dalfino et al. explored the difference in terms of clinical failure between patients affected by CRAB VAP treated with cefiderocol-based regimens and colistin-based regimen: a higher Charlson comorbidity index independently predicted the occurrence of clinical failure, while timely targeted antibiotic treatment and cefiderocol-based first-line regimens reduced the risk of treatment failure [135]. Further studies highlighted how the use of cefiderocol for treatment of VAP caused by CRAB was associated with a benefit on 28-day [136] and 30-day mortality [137]. An additional study including patients affected by CRAB BSI treated with cefiderocol or colistin showed a significantly higher clinical cure in cefiderocol group, lower rate of adverse events; particularly, in HAP/VAP group treatment with cefiderocol was associated with lower 30-day mortality and higher clinical cure [138].

An Italian multicentric retrospective study by Pascale et al, including 107 patients admitted in ICU for COVID19 who developed CRAB infection treated with cefiderocol as monotherapy in 45% of cases and colistin-based regimens in 55%, showed any difference in all-cause 28-day mortality rate between the two groups; however, in multivariable analysis, cefiderocol was associated with a non-significant lower mortality risk [139].

The ARES study, a multicentric retrospective cohort study including critically ill patients treated with cefiderocol for CRAB infection, resulted in a clinical success rate of 53 %, with better results in subjects who were not affected by septic shock and COVID19, and with a lower SOFA score [140].

Overall, the results of real-world studies are more encouraging if compared to CREDIBLE-CR, where cefiderocol was non-inferior if compared to best available therapy in terms of clinical and microbiological response but resulted in a higher mortality rate (49% vs 18%), with the majority of deaths in CRAB group. Notably, cefiderocol group included patients with higher SOFA and CCI score, who experienced previous failure to BAT.

On the basis of the current available data, the latest Infectious Diseases Society of America (IDSA) guidance for treatment of Antimicrobial Resistant Gram-Negative Infections recommends limiting the use of cefiderocol as salvage therapy for CRAB infections, only in case of resistance or intolerance to other regimens, as part of a combination therapy [141].

6. Prospectives and Open Questions

Accordingly, the above-mentioned document of guidance opens another important and still unresolved question: the use of the molecule as monotherapy or as part of combination regimens.

Regarding combination therapy, despite its usefulness in clinical trials is not demonstrated, this strategy could be successful in clinical practice for different reasons: i) the synergistic effect; ii) to avoid resistance development; iii) to extend spectrum of antimicrobial activity in the first phase of treatment, when the causative pathogen and its sensitivity profile are still unknown. In this sense, a good partner for cefiderocol could be intravenous fosfomycin, even for CRAB, which results intrinsically resistant to the epoxide molecule [142]: indeed, its mechanism of action lead to a stressful condition that make pathogens more sensitive to other antimicrobial agents and prevent the development of resistance [143].

Despite resistance to cefiderocol is not frequently detected, it should be taken into account, when susceptibility test is not available. Interestingly, multiple mechanisms contribute to this condition: increased expression of beta-lactamase (metallo beta lactamase), mutation of target protein or siderophore receptor and outer membrane porine, overexpression of efflux transport proteins [9,144].

Moreover, the rise of resistance in course of treatment has been described. In particular, among different reasons, the phenomenon of heteroresistance could be involved in this process: it occurs

when a small proportion of bacteria develop resistance under antibiotic pressure; as a consequence, the unsusceptible population grows in course of prolonged antibiotic exposure [86,91,145–147]

Combination therapy could play a role in reducing this phenomenon, along with the optimization of pharmacokinetics/pharmacodynamics parameters of cefiderocol [148].

Despite the innovativeness of this molecule, the encouraging results of real-world study in terms of safety and effectiveness, and the need of new antibiotic for treatment of XDR GNB, some open questions about its use in daily clinical practice remain. The prescription of cefiderocol in hospital settings where the rate of CR-GNB is high could be considered in case of severe infections and septic shock, in absence of other therapeutic chances, in order to provide promptly an effective therapy. Further clinical trial to optimize the use of cefiderocol are warranted.

7. Conclusions

The limited antimicrobial options for treatment of infections due to MDR microorganisms poses the urgent need of new antimicrobial drugs. To fight this plague and to contrast the increasing diffusion of the antimicrobial resistance in gram negative bacteria, in the last years, the development of novel antimicrobial molecules have been proposed. In this context, Cefiderocol, a new siderophore-conjugated cephalosporin, have revolutionated the therapeutic schemes of treatment for infections due to MDR pathogens. In contrast to other cephalosporin, cefiderocol is a siderophore compound with a the catechol residue acting as an iron chelator able to cross the outer membrane of Gram-negative bacteria through the siderophore iron uptake system. The unique mechanism of entry into the bacterial cells by taking advantage of the iron uptake system, have defined this strategy as a “Trojan horse”. This innovative strategy used by Cefiderocol render this molecules protect against the different bacteria mechanisms to counteract the bacteria cells import of different antimicrobial drugs such as mutations (i.e. efflux pumps’ overexpression and porins’ downregulation or truncation) by altering the outer membrane permeability.

The numerous advantages offered by cefiderocol including the high antibacterial activity, the excellent profile of safety and tolerability and the broad range of activity against various gram negative pathogens has earned the role of “*promising antibiotic*” for treatment against MDR bacteria posed the basis for novel antimicrobial weapons by defining new paradigms of treatment for the and infections especially in critical ill patients.

Despite the initial promising *in vitro* and *in vivo* results, the emergence of resistant to cefiderocol have been observed worldwide with an increasing number of clinical reports. Therefore, the adaptability to the different antimicrobial molecules is a common strategy observed in the bacterial’s world. In this context, the development of different mechanisms to counteract to the activity of cefiderocol is not immune. However, the broad range of activity against different MDR pathogens, the high penetrability in several anatomical sites and the evidence of the efficacy and safety render this molecule a fundamental tool in the clinical real-life especially for the treatment of Difficult-to-treat (DTR) infections due to MDR pathogens.

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