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Cefiderocol – insights into a novel cephalosporin

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ABSTRACT

Introduction: One of the most significant challenges in modern medicine is the increasing resistance of microorganisms. Very few new drugs are being registered, and those that are currently available are becoming less and less effective. Cefiderocol is one of the few novel antibiotics that were registered in the last decade.
Materials and methods: Two independent researchers searched PubMed for articles using the keyword "cefiderocol"; 700 results were found, and 13 articles fulfilled the inclusion and exclusion criteria.
Results: The non-inferiority of cefiderocol compared to carbapenems was demonstrated in several different studies. Comparative and descriptive statistics suggest that its safety might also be comparable. Antibiotic resistance to cefiderocol remains at a low level; however, some bacteria have developed an unknown mechanism of resistance to it. No interactions between cefiderocol and other drugs, no impact on the QT/QTc interval, and no influence of body iron levels on cefiderocol have been found so far.
Conclusion: Further studies are needed to assess its effectiveness and side effects in different clinical conditions; however, it appears to be a promising option for patients with limited treatment options.
Keywords: antibiotic; antibiotic resistance; carbapenems; healthcare-associated pneumonia; sepsis; urinary tract infections.

INTRODUCTION

The evolution of antibiotics, from the discovery of the first antibiotic (arsphenamine) in 1910, through the discovery of penicillin in 1928 and the golden age of antibiotics in the 1950s, has slowly led us to the current state, which can be described as a crisis of drug resistance in human pathogens [1]. More and more pathogens currently cultured from patients can be classified as multi- or extensively drug-resistant. One of the major challenges has become infections caused by carbapenem-resistant (CR) Gram-negative bacteria due to their high mortality and limited available therapeutic options. These pathogens have been found not only in inpatients and hospitals but also isolated from long-term care facilities and community settings [2].

Only a few new antimicrobial agents have been approved for treatment in humans over the last decade. One of them is cefiderocol, which was approved in November 2019 by the Food and Drug Administration (FDA) for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis caused by susceptible Gram-negative bacteria. It is believed to work as a "Trojan horse", as it uses bacterial siderophore molecules, which bind iron (Fe^{3+}) with high affinity, to deliver the antibiotic into the bacterial cell [3]. This research aims to summarize the current knowledge about this novel antibiotic.

MATERIALS AND METHODS

Two independent researchers searched PubMed for articles using the keyword "cefiderocol" on 25 February 2024. A total of 700 results were found. The inclusion criteria for further analysis were the presence of original data regarding cefiderocol and classification as a clinical trial, meta-analysis, or randomized controlled trial (RCT). All articles without an English translation or those primarily focused on pharmacokinetics were excluded. Thirteen articles fulfilled these criteria and were included in this research. The oldest article was from 2018, and the most recent was from 2024 (Fig. 1).

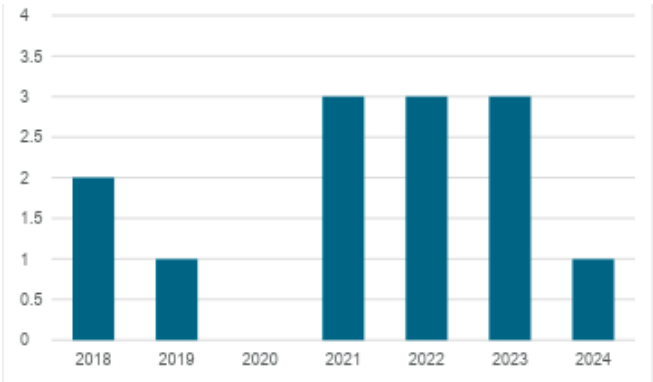

FIGURE 1. Included articles divided by publication year

RESULTS

Overall cefiderocol effectiveness and comparison with carbapenems in original research

Only a few original papers regarding cefiderocol effectiveness were found during this research. Portsmouth et al., in a multicenter, phase 2, randomized, double-blind, non-inferiority trial, compared it to imipenem-cilastatin in patients at risk of multidrug-resistant infection with a clinical diagnosis of cUTI or acute uncomplicated pyelonephritis. Only patients with Gram-negative pathogens susceptible to carbapenems, with no more than 2 pathogens in baseline urine culture and without fungal infection, were included. Assessment of clinical and microbiological response at 7 ±2 days after the end of treatment showed the non-inferiority of cefiderocol, with an adjusted treatment difference of 18.58% (95% confidence interval – CI 8.23–28.92; p = 0.0004). Further analysis showed non-inferiority regardless of the age, sex, and clinical diagnosis of patients; however, in patients with acute uncomplicated pyelonephritis, the treatment difference was statistically insignificant at 14.51% (95% CI –3.37–32.38). The safety of cefiderocol was also assessed in patients who received at least 1 dose of it. Adverse events occurred in 41% of patients who received this novel drug and in 51% of those receiving imipenem-cilastatin. However, no comparative analysis was conducted, so the statistical significance of this finding remains unknown [4].

Another proof of the non-inferiority of cefiderocol to carbapenems comes from a randomized, double-blind, parallel-group, phase 3, non-inferiority trial on Gram-negative: *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae* and *Stenotrophomonas maltophilia* in nosocomial pneumonia (APEKS-NP). In this study, cefiderocol was compared to a high-dose, extended-infusion of meropenem in adults with hospital-acquired, ventilator-associated, or healthcare-associated Gram-negative pneumonia. The primary endpoint was all-cause mortality at day 14 of treatment. For cefiderocol, it was 12.4% and for meropenem 11.6% – adjusted treatment difference 0.8% (95% CI 6.6–8.2). This outcome confirmed the non-inferiority hypothesis with p = 0.002. A descriptive analysis of adverse events during treatment was also performed and showed similar tolerability of both treatments, with reported adverse events in 88% of the cefiderocol group and 86% of the meropenem group [5].

One more phase 3 study assessed the effectiveness of cefiderocol. It was a randomized, open-label, multicenter, pathogen-focused, descriptive trial (CREDIBLE-CR). Its main goal was to compare cefiderocol to the best available therapy in CR, Gram-negative cUTI, nosocomial pneumonia (NP), bloodstream infections (BI), or sepsis. For cUTI, the primary endpoint was microbiological eradication at day 7 ±2 after the end of treatment, and for all the other diagnoses, it was clinical cure at that predefined moment. The results of this study showed a comparable efficiency of both treatments (Tab. 1).

Unfortunately, due to the significant diversification of patients in terms of clinical diagnoses, the subgroups in which these comparisons were made were rather small. This makes it considerably more difficult to draw definitive conclusions. However, the results suggest that cefiderocol might not be inferior to the best available therapy. In the same study, safety was assessed in all patients who received at least 1 dose of cefiderocol. Adverse events were reported in 91% of patients receiving cefiderocol and in 96% of those receiving other drugs. Unfortunately, mortality rates were numerically higher in the cefiderocol group (34%) compared to only 18% in the best available therapy group. Moreover, one of the deaths was considered to be related to cefiderocol [6].

TABLE 1. Comparison of the efficiency of cefiderocol to the best available therapy [6]

Infection	Cefiderocol	Best available therapy
Nosocomial pneumonia	50% (95% CI 33.8–66.2)	53% (95% CI 28.9–75.6)
Bloodstream infections or sepsis	43% (95% CI 23.2–65.5)	43% (95% CI 17.7–71.1)
Complicated urinary tract infection	53% (95% CI 27.8–77.0)	20% (95% CI 0.5–71.6)

CI – confidence interval

Timsit et al. conducted a post-hoc analysis of the last 2 cited studies (CREDIBLE-CR and APEKS-NP), focusing exclusively on patients with a pathogen producing metallo-β-lactamase (MBL). It showed that cefiderocol could be a potential treatment option for these patients, with a better microbiological eradication rate (58.3% vs. 30%), higher clinical cure rate (70.8% vs. 40%), and lower all-cause mortality at day 28 (12.5% vs. 50%) compared to its comparators. Unfortunately, only descriptive statistical analysis was performed [7].

Overall cefiderocol effectiveness and comparison with carbapenems in meta-analyses

In this research, we found 4 meta-analyses regarding the effectiveness of cefiderocol. Hung et al. summarized the clinical efficacy and safety of many novel antibiotics; however, only 1 of the papers included in that analysis referred to cefiderocol [8]. It was the previously cited study by Portsmouth et al. [4]. A statistical analysis showed the effectiveness of cefiderocol, with odds ratio – OR = 2.1 (95% CI 1.33–3.32; p = 0.001) for clinical cure rate when compared to imipenem-cilastatin [8].

Lin et al. also compared many non-polymyxin antibiotics [9]. Out of 26 included studies, 2 assessed the effectiveness of cefiderocol [4, 5]. As most trials concerning new antibiotics are designed to prove their non-inferiority to carbapenems, this meta-analysis demonstrated that no statistically significant differences between these drugs were found in terms of clinical response and mortality [9]. However, when P-score analysis considering adverse events and clinical response in subgroups was performed to assess the best treatment for different clinical states, cefiderocol was considered the best possible therapy for cUTI [9].

Another paper also referred to the cited studies [4, 5, 6] and presented a meta-analysis of their outcomes [10]. When the results of these 3 studies were considered collectively, the non-inferiority of cefiderocol was once again confirmed. For clinical response, OR = 1.04 (95% CI 0.73–1.48) and for microbiological eradication rate, OR = 1.44 (95% CI 0.84–2.47). Additionally, all-cause mortality was similar between cefiderocol and comparators, with 14-day mortality OR = 1.25 (95% CI 0.69–1.82) and 28-day mortality OR = 1.12 (95% CI 0.69–1.82). Furthermore, the differences in treatment-emergent adverse events, serious adverse events, drug-related adverse events, and discontinuation of study drug due to adverse events or drug-related adverse events were also statistically insignificant between the 2 groups [10].

The last meta-analysis we found focused specifically on CR *A. baumannii* infections. Six studies were included in this research. One of them was the previously cited RCT [6], and the other 5 were observational studies. The primary endpoint of this analysis was the mortality rate. Considering this, 5 studies were analyzed. By pooling OR, the authors showed that in-hospital mortality with cefiderocol-based regimens compared to alternative therapies (mainly based on colistin) was not significantly reduced, with OR = 0.64 (95% CI 0.40–1.04; p = 0.07; I^2 = 57.5%). However, the authors emphasized that the cited RCT had a high risk of bias due to the selection of reported results [11]. Some studies also evaluated other outcomes, such as clinical cure (n = 4), microbiological eradication (n = 5), and nephrotoxicity (n = 4). In none of these outcomes was a statistically significant superiority of cefiderocol proven: OR = 1.41 (95% CI 0.87–2.28; p = 0.17), OR = 1.26 (95% CI 0.67–2.36; p = 0.47), and OR = 0.50 (95% CI 0.20–1.24; p = 0.14), respectively. However, when only observational studies were taken into consideration, providing adjustment for confounders, a significant reduction in mortality rate was observed, with OR = 0.53 (95% CI 0.39–0.71; I^2 = 0.0%) [11].

Antibiotic resistance for cefiderocol

Clinical usage of antibiotics often leads to the development of antimicrobial resistance. It is crucial to understand its mechanisms and to slow down the global spread of resistant bacteria. For this purpose, Nordmann et al. further characterized isolates from APEKS-NP and CREDIBLE-CR with a ≥4 minimum inhibitory concentration (MIC) post-treatment increase. Fourteen isolates with reduced susceptibility were investigated; only 2 (*P. aeruginosa* and *A. baumannii*) were classified as resistant to cefiderocol according to all Clinical and Laboratory Standards Institute (CLSI), FDA, and European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines. Mutations in β-lactamase, specifically 4 amino acid deletion "TPMA" at position 316–319 (PDC-30) in *P. aeruginosa* and an amino acid substitution (A313P) in ACT-17 in *Enterobacter cloacae*, may contribute to the MIC increase. Despite investigations into genes previously associated with increased MIC of cefiderocol in other studies, the reasons for reduced susceptibility in most isolates remain unknown. No relationship between combination therapy and a reduced risk of resistance was observed [12].

Karakonstantis et al. conducted a systematic review and meta-analysis to estimate the global prevalence of cefiderocol non-susceptibility (NS) against major Gram-negative pathogens. Results depended on the breakpoints used, with CLSI breakpoints showing a notably lower prevalence of cefiderocol NS compared to EUCAST and FDA criteria [13].

Using the EUCAST breakpoint thresholds, results presenting antibiotic resistance in any phenotype, CR, and MBL in Enterobacterales, *P. aeruginosa*, and *A. baumannii* are shown in Table 2 [13].

Cefiderocol NS was extraordinarily high in New Delhi MBL and ceftazidime/avibactam-resistant species, but it maintains a good level of activity against most examined pathogens. However, empirical administration should be considered with caution, especially in pathogens with aggravated antimicrobial resistance or *A. baumannii*. Research showed a strong need to unify EUCAST, FDA, and CLSI breakpoints to estimate the global prevalence of cefiderocol NS and manage antimicrobials properly [13].

Impact of body iron on cefiderocol

Iron is one of the crucial mineral elements necessary to maintain homeostasis in the human body and is essential for bacteria to survive and develop properly. During infection, human iron homeostasis may be disturbed because of elevated hepcidin levels. Reduced availability of this element for pathogens during infection is assumed to decrease the virulence of bacteria and reduce their ability to reproduce. Some Gram-negative bacteria have developed the ability to secrete siderophore molecules, which can bind iron (Fe^{3+}) with high affinity. This system allows bacteria to import iron through the membrane. Cefiderocol is one of the drugs that uses this system to be delivered to the bacterial cell like a "Trojan horse". This mechanism of action raises the question of whether iron overload or deficiency has an impact on the efficiency of this drug. A post hoc analysis of APEKS-NP was carried out to answer this. Clinical data suggest that safety and efficacy are not disturbed by low total serum

TABLE 2. Global prevalence of cefiderocol non-susceptibility in chosen Gram-negative pathogens [13]

Gram-negative pathogens	Any phenotype	Carbapenem-resistant	MBL-producing
Enterobacterales	3.0% (95% CI 1.5–6.0)	12.4% (95% CI 7.3–20.0)	24.9% (95% CI 16.6–35.5)
Pseudomonas aeruginosa	1.4% (95% CI 0.5–4.0)	3.5% (95% CI 1.6–7.8)	1.8% (95% CI 0.3–10.4)
Acinetobacter baumannii	8.8% (95% CI 4.9–15.2)	13.2% (95% CI 7.8–21.5)	40.9% (95% CI 31.4–51.1)

MBL – metallo-β-lactamase; CI – confidence interval

iron levels in patients with critical NP, but also do not improve the effect of the drug. There was some dependence between a higher cure rate and normal iron levels; unfortunately, the number of patients without iron abnormalities was quite small in this investigation. All in all, according to this research, baseline iron level, blood transfusion, or iron supplementation should not affect the safety and efficacy of cefiderocol [3].

Effect on QT interval

According to a randomized, double-blind, active-controlled study on healthy adult males and females aged 18–50 years (body mass index – BMI = 18.5–30 kg/m^2), no clinically meaningful QT/QTc (corrected) interval prolongation (Fridericia formula) was observed after the administration of therapeutic (2 g) and supratherapeutic (4 g) doses. No other significant changes in electrocardiogram (ECG) parameters (heart rate, QRS intervals, and PR duration) were found [14].

Drug to drug interactions

A randomized, open-label, 2-sequence study involving 3 cohorts of healthy males and females (18–50 years old) with BMI 18.5–30 kg/m^2 examined potential interactions between cefiderocol and other drugs [15].

Co-administration of cefiderocol and furosemide, which is an organic anion transporter 1/3 (OAT1/3) substrate, had an impact on the concentration and absorption of furosemide. However, geometric least squares mean ratios (GMRs) for Cmax and AUC0-inf were close to 1, and recognized as clinically insignificant. Co-administration of metformin, an organic cation transporter 1/2 (OCT1/2) and multidrug and toxin extrusion (MATE2-K) substrate, showed a slightly higher Cmax, but the 90% CI of the GMRs included 1, which is considered not clinically meaningful. Co-administration of rosuvastatin, an organic anion transporting polypeptide (OATP1B3) substrate, meaningfully increased Cmax (GMRs 1.28; 90% CI 1.12–1.46) and AUC0-inf (GMRs 1.21; 90% CI 1.08–1.35), suggesting that cefiderocol is a weak inhibitor of OATP1B3, although this increase was considered not clinically meaningful [15].

All in all, there were no clinically significant interactions between the co-administration of cefiderocol (2 g every 8 h) and other drugs acting on the examined transporters [15].

DISCUSSION

During our research, we also found the viewpoint of some authors associated with the FDA; however, a disclaimer in that article clarifies that it does not represent the official view or policy of the entire FDA. The authors considered the increased mortality observed in the cefiderocol group in the CREDIBLE-CR study. They highlighted several limitations of that study, such as the small sample size, lack of formal statistical analysis, open-label assessment of clinical outcomes, continuous monitoring of unblinded results, and the inclusion of cUTI cases alongside much more severe infections. They also expressed concern that some data suggest cefiderocol might have reduced efficacy in NP, BI, and sepsis, particularly those caused by CR bacteria. They pointed out that, during the study period, cefiderocol was only registered for use in patients with limited or no alternative treatment options in cUTI [16]. Meanwhile, the European Medicines Agency (EMA) approved it for the treatment of infections caused by aerobic Gram-negative organisms in adults with limited treatment options [17].

The effectiveness and safety profile of cefiderocol is still under close monitoring. Since our research was conducted, some new papers have been published. An interim analysis of the ongoing PROVE retrospective chart review study included 774 hospitalized patients with Gram-negative infections treated with cefiderocol for ≥72 h. It showed that cefiderocol was used mostly in intensive care units (59.8%), with respiratory tract infections being the most common indication (54.1%). Overall, 71.6% of patients demonstrated a clinical response at the end of treatment, and 64% were considered clinically cured. Twenty-three serious adverse drug reactions were reported in 19 patients, leading to 11 treatment discontinuations [18].

Ramirez et al. conducted a retrospective, multicenter, observational study (2018–2022) on patients who received cefiderocol for respiratory tract infections, intra-abdominal infections, or UTI. The most frequently identified pathogens were *P. aeruginosa* and *K. pneumoniae*. Patients with *Acinetobacter* spp. infections were excluded. The overall clinical cure rate and 28-day mortality rate were 80.5% and 21.5%, respectively. Adverse effects were observed in 6 out of 261 patients (2.3%), with 1 fatal case due to toxic epidermal necrolysis [19].

Another meta-analysis focused on the effectiveness of cefiderocol against *P. aeruginosa* infections [20]. It showed that cefiderocol was not inferior to other conventional agents and was comparable to other novel β-lactams, such as ceftolozane-tazobactam and ceftazidime-avibactam, with no statistically significant differences observed. Onorato et al. conducted a meta-analysis focused solely on infections caused by CR *A. baumannii*. They included 1206 patients, of whom 733 received cefiderocol, and the remainder received the best available therapy. Their analysis showed a significantly lower mortality rate and a lower rate of adverse events among patients treated with cefiderocol [21].

All of these papers suggest that, although some serious adverse events may occur, cefiderocol might be the best option for even the most complicated cases.

It is also important to exercise particular caution when administering cefiderocol to patients who require a low-sodium diet. When reconstituted with the most commonly used solvent, 0.9% sodium chloride, a patient receiving 2 g of cefiderocol every 8 h will receive a total daily sodium dose of 2.1 g. This slightly exceeds the World Health Organization-recommended daily maximum for adults, which is 2 g. In cases where this amount is excessive, reconstituting cefiderocol in 5% dextrose should be considered to reduce the administered sodium dose by half [17].

CONCLUSIONS

The non-inferiority of cefiderocol compared to carbapenems was demonstrated in several studies involving patients with diverse diagnoses, including cUTI, acute uncomplicated pyelonephritis, NP, BI, and sepsis. Although there is no evidence of cefiderocol's superiority over other available drugs, some data suggest that it may be the best available therapy for cUTI. Only 1 comparative analysis regarding the safety of cefiderocol was found, indicating that it caused fewer adverse events than the best available therapy. Descriptive statistics also suggest that cefiderocol can be as safe as carbapenems, or even, in some cases, may cause fewer side effects. However, in 1 study, mortality was numerically higher in the cefiderocol group, and 1 death was considered related to cefiderocol.

Aside from some drug-resistant Gram-negative pathogens, cefiderocol maintained a good level of efficacy. The mechanism of antimicrobial resistance to cefiderocol remains unknown for most isolates. No significant impact of low body iron levels on the effectiveness of cefiderocol was observed. Furthermore, cefiderocol showed no meaningful negative effects on the QT/QTc interval and no clinically significant drug interactions have been reported so far.

Further studies on its effectiveness, antimicrobial resistance, and potential adverse events are needed, as cefiderocol remains under additional monitoring due to its recent registration. Unfortunately, cefiderocol is still not widely recognized, and many healthcare professionals are unaware that it could be an option in the most complicated cases. We hope that our research will not only summarize the current knowledge but also help draw attention to this novel antibiotic.

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