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REVIEW

From Clinical Trials to Real-World Experiences: Evidence About Cefiderocol Use and Potential Role in Empirical Therapy

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ABSTRACT

Cefiderocol is a novel siderophore cephalosporin that has gained attention for its potent activity against multidrug-resistant (MDR) Gram-negative pathogens, making it a valuable addition to the antimicrobial armamentarium. Its efficacy in treating complicated urinary tract infections (cUTIs) and nosocomial pneumonia has been well-established, although challenges remain regarding its role in *Acinetobacter baumannii* infections and the possible emergence of resistance. The decision to use cefiderocol as a monotherapy or in combination should be guided by pathogen susceptibility, clinical severity, and local epidemiology. Then, the potential to serve as an effective empirical therapy, careful stewardship, and further research are essential to maximize its therapeutic benefits and ensure its long-term efficacy. This review explores the efficacy of cefiderocol, resistance development, heteroresistance, its use as monotherapy or in combination therapy, and its role in empirical treatment regimens. We discuss data about clinical trials and real-world evidence to assess the future role of cefiderocol in antibiotic regimens.

Keywords: Cefiderocol; MDR pathogens; Heteroresistance; Monotherapy; Combination therapy; Empirical therapy

Key Summary Points

The efficacy of cefiderocol was widely assessed in clinical trials and real-world experiences.

Challenges remain regarding its role in *A. baumannii* infections and the possible emergence of resistance.

No definitive data are reported about its use in monotherapy or combination with other drugs.

The potential to serve as an effective empirical therapy should be evaluated.

Stewardship programs are essential to maximize its therapeutic benefits and ensure its long-term efficacy.

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INTRODUCTION

Cefiderocol is a novel siderophore cephalosporin that has gained attention for its potent activity against multidrug-resistant (MDR) Gram-negative pathogens. With increasing antimicrobial resistance worldwide, cefiderocol provides a promising option for the management of infections caused by carbapenem-resistant organisms, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and carbapenem-resistant Enterobacterales (CRE) [1–4]. This review explores the efficacy of cefiderocol, resistance development, heteroresistance, its use as monotherapy or in combination therapy, and its role in empirical treatment regimens. We discuss data about clinical trials and real-world evidence to assess the future role of cefiderocol in antibiotic regimens.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

DATA FROM CLINICAL TRIALS

Cefiderocol's unique mechanism of action involves its ability to exploit bacterial iron-uptake systems. As a siderophore cephalosporin, cefiderocol chelates iron, enabling it to penetrate bacterial outer membranes via iron transport channels. Once inside the periplasmic space, cefiderocol inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs), similar to other beta-lactam antibiotics. Its high affinity for PBP3, along with its ability to bypass efflux pumps and resist enzymatic degradation by most beta-lactamases (including metallo-beta-lactamases), contributes to its broad-spectrum activity [5].

Cefiderocol exhibits potent in vitro activity against carbapenem-resistant Gram-negative pathogens, including *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*. Importantly, cefiderocol maintains activity against bacteria that produce serine beta-lactamases (e.g., KPC, OXA-48) and metallo-beta-lactamases (e.g., NDM, VIM, IMP) [6–9].

Three different trials explored the role of cefiderocol for the treatment of severe infections caused by MDR pathogens [1–3], as reported in Table 1.

APEKS-cUTI was a phase III trial that compared cefiderocol with imipenem–cilastatin for the treatment of cUTIs. Cefiderocol achieved significantly higher microbiological eradication rates than imipenem-cilastatin (72.6% versus 54.6%), and clinical cure rates were also superior. Importantly, the trial highlighted cefiderocol's efficacy against multidrug-resistant *E. coli* and *K. pneumoniae*.

The CREDIBLE-CR trial evaluated cefiderocol's efficacy in patients with severe infections caused by carbapenem-resistant pathogens. It included patients with bloodstream infections (BSIs), hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and complicated urinary tract infections (cUTIs). Cefiderocol demonstrated noninferiority to the best available therapy (BAT) in terms of microbiological eradication rates and clinical outcomes for cUTIs and pneumonia.

However, the trial revealed a numerically higher all-cause mortality in the cefiderocol arm (34% versus 18% with BAT). Post hoc analyses identified a higher proportion of *A. baumannii* infections in the cefiderocol group, which may have contributed to these outcomes owing to the intrinsic virulence of this pathogen and its high resistance potential.

APEKS-NP evaluated cefiderocol's efficacy in patients with nosocomial pneumonia (HAP, VAP, or healthcare-associated pneumonia). Cefiderocol demonstrated noninferiority to meropenem with respect to 28-day all-cause mortality (21% versus 20%). Subgroup analyses showed robust activity against carbapenem-resistant Gram-negative pathogens, further supporting cefiderocol's role in treating life-threatening MDR infections.

In these studies, cefiderocol was generally well-tolerated, with a safety profile comparable to other beta-lactams. Common adverse events include diarrhea, infusion-site reactions, and elevations in liver enzymes. The higher mortality observed in the CREDIBLE-CR trial raises concerns about its efficacy in severe

Table 1 Efficacy data of cefiderocol

Clinical trial	Population studied	Comparison	Key results	Comments
APEKS-cUTI	Complicated and uncomplicated UTIs	Cefiderocol versus imipenem-cilastatin	Cefiderocol superior for microbiological eradication (72.6% versus 54.6%)	High efficacy against MDR *E. coli* and *K. pneumoniae*
CREDIBLE-CR	Infections caused by carbapenem-resistant pathogens	Cefiderocol versus BAT	Noninferiority for complicated urinary tract infections (cUTIs) and pneumonia. Higher mortality in the cefiderocol group (34% versus 18%)	Mortality mainly associated with *A. baumannii*
APEKS-NP	Nosocomial pneumonia (HAP, VAP)	Cefiderocol versus meropenem	Noninferiority for 28-day mortality (21% versus 20%)	Strong activity against carbapenem-resistant pathogens but limited for Gram-positives

infections caused by *A. baumannii*. Nevertheless, no definitive causal relationship has been established between cefiderocol and increased mortality [10, 11].

REAL-WORLD EXPERIENCE: EXPANDING THE EVIDENCE

Beyond clinical trials, real-world experiences have provided further insights into the effectiveness of cefiderocol. Case series and observational studies have reported successful outcomes in patients with various infections, including pneumonia, bloodstream infections, and intraabdominal infections, caused by highly resistant pathogens. These studies have highlighted the potential of cefiderocol to address unmet medical needs in patients with limited treatment options.

Real-world data have also shed light on the safety profile of cefiderocol. The drug has been generally well-tolerated, with a safety profile comparable to that observed in clinical trials. However, some studies have reported cases of increased mortality in patients treated with cefiderocol, particularly those with severe *Acinetobacter baumannii* infections. This finding has raised concerns about the optimal use of cefiderocol in this specific patient population and has prompted further research to clarify its role in the treatment of *Acinetobacter* infections.

On the basis of the available evidence, cefiderocol has demonstrated clinical efficacy in the treatment of severe infections caused by multidrug-resistant Gram-negative bacteria. Its unique mechanism of action allows it to overcome several resistance mechanisms, making it a valuable option for patients with limited treatment alternatives. However, the interpretation of clinical efficacy data requires careful consideration of several factors.

First, the clinical trials that supported the approval of cefiderocol were designed to demonstrate noninferiority to BAT. This means that cefiderocol was not necessarily superior to other available treatments, but rather equally effective. Second, the real-world evidence on cefiderocol is still limited, and further studies are needed to fully understand its effectiveness in various clinical settings.

Third, the emergence of resistance to cefiderocol is a potential concern. Although the drug has shown activity against many multidrug-resistant

pathogens, the development of resistance mechanisms could limit its long-term effectiveness. Therefore, the judicious use of cefiderocol and the implementation of antimicrobial stewardship programs are crucial to preserve its activity [12–15].

Despite its efficacy, resistance to cefiderocol has been reported in clinical and in vitro studies (see Table 2). Mechanisms of resistance include:

- Mutations in iron transport systems: Alterations in siderophore receptor proteins (e.g., *CirA*, *Fiu*) can reduce cefiderocol uptake into bacterial cells.
- Efflux pump overexpression: Increased activity of efflux pumps, such as MexAB-OprM in *P. aeruginosa*, may reduce intracellular drug concentrations.
- Beta-lactamase activity: Although cefiderocol resists degradation by most beta-lactamases, certain variants of metallo-beta-lactamases (e.g., NDM-5) and serine carbapenemases may partially hydrolyze cefiderocol.
- Porin loss: Downregulation of porins, such as OmpA in *A. baumannii*, can further impair cefiderocol uptake.

The emergence of resistance emphasizes the need for careful stewardship and surveillance when using cefiderocol, especially in settings with high MDR pathogen prevalence [16–18].

An important described phenomenon was related to heteroresistance. Of importance, heteroresistance, defined as the coexistence of susceptible and resistant subpopulations within the same bacterial isolate, has been documented with cefiderocol. This phenomenon has been reported in *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae*. Heteroresistance poses clinical challenges as it may not be detected by routine susceptibility testing, leading to therapeutic failure despite initial susceptibility results. The underlying mechanisms of heteroresistance to cefiderocol are not fully understood but are believed to involve dynamic changes in iron-uptake systems and efflux pumps. Strategies to address heteroresistance include optimizing cefiderocol dosing regimens and combining it with adjunctive antibiotics [19, 20].

The mechanisms underlying heteroresistance to cefiderocol are not yet fully understood. However, several potential mechanisms have been proposed.

- Mutations in iron transport genes: Cefiderocol utilizes bacterial iron transport systems to enter cells. Mutations in genes encoding these systems can reduce cefiderocol uptake and lead to resistance.
- Efflux pumps: Bacterial efflux pumps can actively expel cefiderocol from cells, reducing its intracellular concentration and leading to resistance.
- Target site modifications: Mutations in the target site of cefiderocol, such as penicillin-binding proteins (PBPs), can reduce its binding affinity and lead to resistance.

Table 2 Mechanisms of resistance to cefiderocol [15–18]

Mechanism	Description	Examples of involved pathogens
Mutations in iron transport systems	Alterations in siderophore receptors reduce drug uptake	*A. baumannii*, *K. pneumoniae*
Efflux pump overexpression	Efflux pumps (e.g., MexAB-OprM) expel cefiderocol from the bacterial cell	*P. aeruginosa*
Enzymatic degradation	Certain beta-lactamase variants, such as some NDM and KPC enzymes, can partially degrade cefiderocol	*K. pneumoniae*, *E. coli*
Porin loss	Downregulation of porins (e.g., OmpA) reduces drug entry into the cell	*A. baumannii*, *S. maltophilia*

- Phenotypic heterogeneity: Bacterial populations can exhibit phenotypic heterogeneity, with some cells expressing resistance mechanisms at a higher level than others. This can lead to heteroresistance.

Heteroresistance to cefiderocol has significant clinical implications. First, it can lead to treatment failure, even when the initial susceptibility testing indicates susceptibility. Second, it can contribute to the development of full resistance, which can limit future treatment options. Third, it can complicate the interpretation of susceptibility testing results, as standard methods may not detect heteroresistance.

The detection of heteroresistance to cefiderocol can be challenging. Standard susceptibility testing methods, such as broth microdilution and disk diffusion, may not detect low levels of resistance. More sensitive methods, such as population analysis profiling (PAP), may be required to detect heteroresistance.

Several factors can contribute to the development of heteroresistance to cefiderocol (see Table 3). These include:

- Antibiotic exposure: Exposure to cefiderocol can select for resistant subpopulations within bacterial populations.
- Bacterial species: Some bacterial species, such as *Acinetobacter baumannii*, may be more prone to heteroresistance than others.
- Infection site: The infection site can influence the development of heteroresistance. For example, heteroresistance may be more common in infections at sites with low antibiotic penetration (i.e., high inoculum infection as in a large abscess).
- Patient factors: Patient factors, such as immune status and comorbidities, can also influence the development of heteroresistance.

Several strategies can be employed to mitigate the risk of heteroresistance to cefiderocol. These include:

- Judicious use of cefiderocol: Cefiderocol should be used judiciously, only when necessary, to minimize the selective pressure for resistance development.
- Combination therapy: Combination therapy with other antibiotics may help to suppress the emergence of resistance.
- Optimal dosing and duration: Optimal dosing and duration of cefiderocol therapy can help to maximize bacterial killing and minimize the risk of resistance development.
- Infection control measures: Strict infection control measures can help to prevent the spread of cefiderocol-resistant bacteria.

Further research is needed to fully understand the mechanisms and clinical implications of heteroresistance to cefiderocol. Studies should investigate the prevalence of heteroresistance in various clinical settings, the factors that contribute to its development, and the best strategies to mitigate its impact [21–23].

Table 3 Heteroresistance to cefiderocol

Characteristic	Description	Clinical implications
Definition	Coexistence of susceptible and resistant bacterial subpopulations within the same isolate	May not be detected by standard susceptibility testing
Associated pathogens	*A. baumannii*, *K. pneumoniae*, *P. aeruginosa*	Risk of therapeutic failure despite initial susceptibility results
Underlying mechanisms	Dynamic changes in iron-uptake systems and efflux pump regulation	Monitoring with advanced tests and potential drug combinations recommended

MONOTHERAPY VERSUS COMBINATION THERAPY

The role of cefiderocol as monotherapy versus in combination therapy is an area of active investigation [24, 25], as reported in Table 4.

Clinical trials (e.g., APEKS-cUTI and APEKS-NP) have demonstrated the efficacy of cefiderocol as monotherapy for cUTIs and nosocomial pneumonia. Its robust in vitro activity against carbapenem-resistant pathogens supports its use as a standalone agent. However, monotherapy may be less effective against certain pathogens, such as *A. baumannii*.

Combination regimens may enhance efficacy by targeting multiple mechanisms of resistance. For example, combining cefiderocol with colistin or tigecycline has shown synergy against carbapenem-resistant *A. baumannii*. Additionally, dual therapy may reduce the risk of resistance emergence, particularly in settings with high bacterial inoculum. However, clinical evidence for combination therapy is limited, and its benefits must be weighed against the risk of increased toxicity and drug interactions [26–28].

Monotherapy with cefiderocol offers several potential advantages. First, it simplifies treatment regimens, reducing the risk of drug interactions and adverse events associated with multiple antibiotics. Second, it may help to minimize the selective pressure for resistance development, as combination therapy can sometimes lead to the emergence of strains resistant to multiple drugs.

However, monotherapy also has limitations. Cefiderocol, similar to other antibiotics, may not achieve adequate concentrations at all infection sites, particularly in patients with severe infections or compromised immune systems. In such cases, combination therapy may be necessary to enhance bacterial killing and improve clinical outcomes.

Combination therapy with cefiderocol and other antibiotics, such as fosfomycin, has been explored as a strategy to enhance its activity against MDR Gram-negative bacteria. The rationale for combination therapy is based on the potential for synergistic or additive effects, which could improve bacterial eradication and clinical response rates [29].

Of importance, combination therapy also has potential risks. It can increase the likelihood of drug interactions and adverse events, as well as the risk of resistance development. Additionally, the optimal combination of antibiotics and the duration of therapy are not always clear, and further research is needed to define the best approach [30].

The clinical evidence on monotherapy versus combination therapy with cefiderocol is mixed. Some studies have suggested that monotherapy with cefiderocol is effective for the treatment of severe infections caused by MDR Gram-negative bacteria, particularly in patients with less severe infections or those who are not critically ill [31, 32].

However, other studies have reported that combination therapy may be necessary for the treatment of severe infections caused by highly resistant pathogens, such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. In these cases, combination therapy may improve

Table 4 Monotherapy versus combination therapy

Strategy	Advantages	Disadvantages	Examples of clinical applications
Monotherapy	High activity against MDR pathogens; reduced risk of combination-related toxicity	Less effective against *A. baumannii* and pathogens with heteroresistance or high bacterial burden	cUTIs and pneumonia with known pathogens
Combination therapy	Synergy against *A. baumannii* and prevention of resistance	Increased risk of toxicity and cost	Severe infections caused by *A. baumannii*

clinical outcomes and reduce the risk of treatment failure.

The decision to use monotherapy or combination therapy with cefiderocol should be based on several factors, including the severity of the infection, the susceptibility of the pathogen, the patient's clinical status, and the availability of other treatment options.

In general, monotherapy may be appropriate for patients with less severe infections caused by susceptible pathogens. Combination therapy may be considered for patients with severe infections caused by highly resistant pathogens, particularly for those who are critically ill or have compromised immune systems.

Further research is needed to define the optimal use of cefiderocol, particularly regarding monotherapy versus combination therapy. Clinical trials should evaluate the efficacy and safety of different treatment strategies in various patient populations and infection types. Additionally, studies should investigate the potential for synergistic or additive effects of cefiderocol in combination with other antibiotics.

CEFIDEROCOL AS EMPIRICAL THERAPY

Given its broad-spectrum activity against MDR Gram-negative pathogens, cefiderocol is an attractive option for empirical therapy in critically ill patients at high risk for resistant infections.

- Advantages: Cefiderocol's potent activity against carbapenem-resistant pathogens and its stability against beta-lactamases make it a valuable empirical option for sepsis, HAP/VAP, and other life-threatening infections.
- Challenges: Its limited activity against Gram-positive pathogens and anaerobes necessitates the addition of agents such as vancomycin or metronidazole in empirical regimens. Furthermore, the high cost of cefiderocol may limit its use in certain healthcare settings.

Empirical use should be guided by local resistance patterns with antimicrobial stewardship programs for the appropriate use of cefiderocol in high-risk patients, and deescalation to narrower-spectrum agents should be performed once susceptibility data become available (see Table 5).

The escalating threat of multidrug-resistant (MDR) Gram-negative bacteria has prompted the exploration of novel antimicrobial agents, including cefiderocol, for empirical therapy. Empirical therapy, the administration of antibiotics before the identification of the causative pathogen, is crucial in the management of severe infections. However, the use of cefiderocol as empirical therapy raises several considerations and challenges.

Cefiderocol's unique mechanism of action, which allows it to overcome various resistance mechanisms, makes it an attractive option for empirical therapy against MDR Gram-negative bacteria. Its activity against difficult-to-treat pathogens, such as carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, could

Table 5 Cefiderocol as empirical therapy

Advantages	Disadvantages	Clinical considerations
Broad spectrum against MDR Gram-negative pathogens	Limited activity against Gram-positives and anaerobes	Requires combination with vancomycin or metronidazole for complete coverage
Efficacy against carbapenemase-producing pathogens	High cost compared with other agents	Indicated for critically ill patients with suspected MDR infections
Resistance to common beta-lactamases	Potential emergence of resistance with inappropriate use	Usage should be guided by local resistance patterns

potentially improve outcomes in patients with severe infections caused by these organisms.

Furthermore, the increasing prevalence of MDR Gram-negative bacteria in various clinical settings has led to a growing need for broad-spectrum antibiotics that can provide adequate coverage while awaiting culture results. Cefiderocol's activity against a wide range of MDR Gram-negative pathogens makes it a potential candidate for this role.

Despite its potential benefits, the use of cefiderocol as empirical therapy also presents several challenges and considerations. First, the broad-spectrum activity of cefiderocol could contribute to the development of resistance if used indiscriminately. Therefore, it is essential to implement antimicrobial stewardship programs to ensure its appropriate use and minimize the risk of resistance emergence.

Second, the cost of cefiderocol may limit its widespread use as an empirical therapy, particularly in resource-limited settings. The cost-effectiveness of cefiderocol as an empirical therapy needs to be carefully evaluated, considering both the potential benefits and the financial implications.

Third, the optimal dosing and duration of cefiderocol as an empirical therapy are not yet fully established. Further research is needed to determine the best approach for different patient populations and infection types.

Finally, the interpretation of clinical data on cefiderocol as empirical therapy can be challenging. Many studies have evaluated cefiderocol as salvage therapy in patients with known MDR Gram-negative infections. Previous infections or colonization by carbapenemase-producing Enterobacterales and/or difficult-to-treat resistant *P. aeruginosa* and *A. baumannii* should be carefully addressed. The extrapolation of these data to the empirical setting requires careful consideration (see Fig. 1).

The clinical evidence on cefiderocol as an empirical therapy is still evolving. Some studies have suggested that cefiderocol may be a valuable option for empirical therapy in patients with severe infections and risk factors for MDR Gram-negative bacteria.

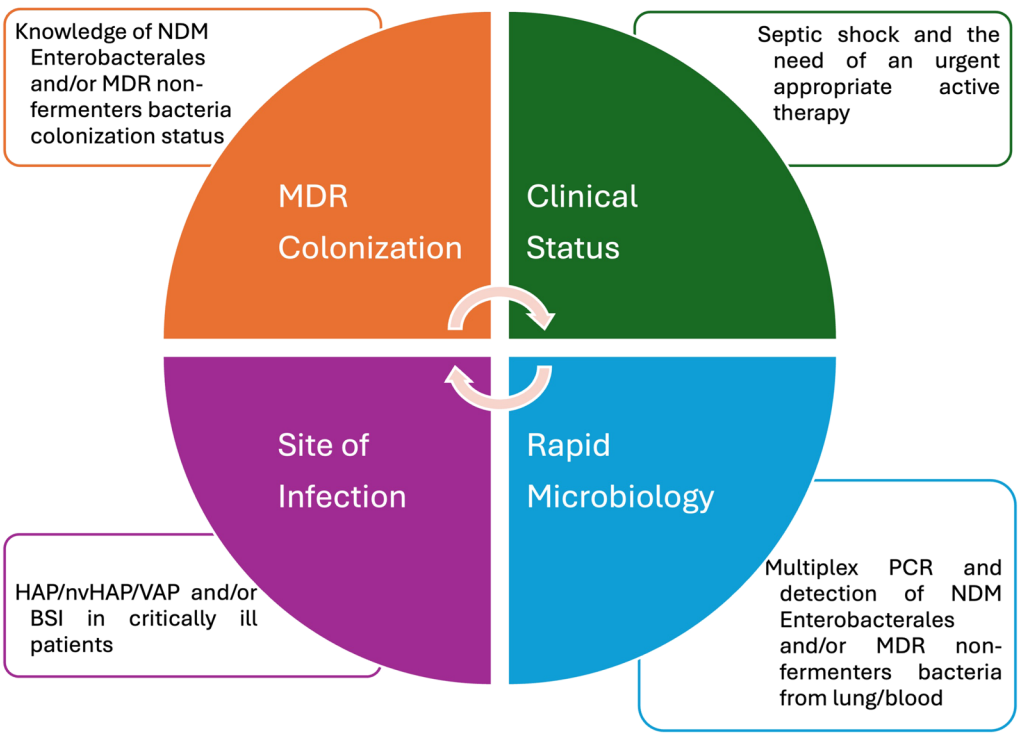

Fig. 1 Criteria for empirical use of cefiderocol

For example, a retrospective study by Bassetti et al. evaluated the use of cefiderocol as an empirical therapy in patients with ventilator-associated pneumonia (VAP) and risk factors for MDR Gram-negative bacteria [33]. The study found that cefiderocol was associated with favorable clinical outcomes and a low rate of resistance development.

However, other studies have reported mixed results. The randomized controlled trial by Wunderink et al. compared cefiderocol with high-dose meropenem as empirical therapy for hospital-acquired pneumonia (HAP) and VAP. The study found no significant difference in clinical cure rates between the two groups, with the limits of a noninferiority design and a low percentage of MDR pathogens [3].

Further research is needed to define the role of cefiderocol as an empirical therapy [34–36]. Clinical trials should evaluate the efficacy and safety of cefiderocol as an empirical therapy in various patient populations and infection types. Interestingly, Soueges et al. showed the utility of cefiderocol use in difficult-to-treat infections, particularly *S. maltophilia*, for the treatment of immunocompromised patients with infections caused by MDR Gram-negative bacteria. However, the high relapse rate and resistance acquisition underscore the need for careful monitoring, adherence to guidelines, and reconsideration of empirical use to prevent resistance and improve outcomes in fragile populations. [37].

Furthermore, the development of rapid diagnostic tests for the identification of MDR Gram-negative bacteria could help to guide the use of cefiderocol as empirical therapy. These tests could allow for the timely deescalation of therapy, reducing the risk of resistance development and minimizing the cost of treatment.

FUTURE PERSPECTIVES AND RESEARCH DIRECTIONS

Cefiderocol represents a significant advancement in the fight against antimicrobial resistance. However, several unanswered questions remain:

1. Optimal use in combination therapy: More clinical trials are needed to define the role of combination regimens in enhancing cefiderocol's efficacy and preventing resistance.
2. Surveillance of resistance: Ongoing monitoring of resistance patterns is essential to guide the clinical use of cefiderocol.
3. Biomarkers for therapy guidance: Identifying biomarkers to predict cefiderocol's efficacy (e.g., siderophore receptor expression) could improve patient selection and treatment outcomes.
4. Real-world data: Postmarketing studies are needed to assess cefiderocol's performance in diverse clinical settings, including resource-limited environments.

CONCLUSIONS

Cefiderocol is a promising antibiotic with potent activity against MDR Gram-negative pathogens, making it a valuable addition to the antimicrobial armamentarium. Its efficacy in treating cUTIs and nosocomial pneumonia has been well-established, although challenges remain regarding its role in *A. baumannii* infections and the emergence of resistance. The decision to use cefiderocol as monotherapy or in combination should be guided by pathogen susceptibility, inoculum of infection, clinical severity, and local epidemiology. While cefiderocol has the potential to serve as an effective empirical therapy, careful stewardship and further research are essential to maximize its therapeutic benefits and ensure its long-term efficacy.

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Declarations

Conflict of Interest. Alessandro Russo and Francesca Serapide declare no competing interests.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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