Journal of Infection 90 (2025) 106376

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Infectious Disease Practice

Real-world multicentre study of cefiderocol treatment of immunocompromised patients with infections caused by multidrug-resistant Gram-negative bacteria: CEFI-ID

Sarah Soueges [a,*], Emmanuel Faure [b], Perrine Parize [c], Fanny Lanternier-Dessap [c], Hervé Lecuyer [d], Anne Huynh [e], Guillaume Martin-Blondel [f,g], Benjamin Gaborit [h], Mathieu Blot [i], Arnaud Magallon [j], Elodie Blanchard [k], Xavier Brousse [l], Marin Lahouati [m,n], Anne-Sophie Brunel [o], Eloise Le Banner [p], François Camelena [q], Romaric Larcher [r], Alix Pantel [s], Giovanna Melica [t], Keyvan Razazi [u], François Danion [v], Frederic Schramm [w], Oana Dumitrescu [x], Baptiste Hoellinger [v], Florence Ader [a,y], On behalf of the G2I (Groupe Immunodepression et Infections) network [1]

[a] *Département des Maladies Infectieuses et Tropicales, Hospices Civils de Lyon, F-69004 Lyon, France*
[b] *CHU Lille, Service Universitaire de Maladies Infectieuses, Lille, France*
[c] *Service de Maladies Infectieuses et Tropicales, Hôpital Necker-Enfants malades, Groupe hospitalier AP-HP Centre, Université Paris Cité, Paris, France*
[d] *Laboratoire de Microbiologie Clinique, Hôpital Necker Enfants Malades, Assistance Publique-Hôpitaux de Paris, Université de Paris, Paris, France*
[e] *CHU-Institut Universitaire du Cancer Toulouse, Oncopole, Toulouse, France*
[f] *Institut Toulousain des Maladies Infectieuses et Inflammatoires (Infinity), INSERM UMR1291-CNRS UMR5051, Université Toulouse III, Toulouse, France*
[g] *Service des Maladies Infectieuses et Tropicales, Centre Hospitalier Universitaire de Toulouse, Toulouse, France, Toulouse, France*
[h] *Service de Maladies Infectieuses et Tropicales, Hôpital du Confluent, Nantes, France*
[i] *Département de Maladies Infectieuses, Centre Hospitalo-Universitaire de Dijon-Bourgogne, Université de Bourgogne, France*
[j] *Département de Bactériologie, Centre Hospitalo-Universitaire de Dijon-Bourgogne, Université de Bourgogne, France*
[k] *CHU Bordeaux, Service de Pneumologie, Bordeaux, France*
[l] *Service des Maladies Infectieuses & Tropicales, Hôpital Pellegrin, CHU de Bordeaux, Bordeaux, France*
[m] *Université de Bordeaux, INSERM U1034, Biologie des Maladies Cardiovasculaires, Pessac, France*
[n] *CHU de Bordeaux, Service de Pharmacie Clinique, Bordeaux, France, INSERM U1034, Biologie des Maladies Cardiovasculaires, Pessac, France*
[o] *Maladies Infectieuses et Tropicales – Centre Hospitalier Régional Universitaire, 25030 Besançon, France*
[p] *Service de Maladies Infectieuses et Réanimation Médicale, Hôpital Pontchaillou, CHU Rennes, Rennes, France*
[q] *Département de Bactériologie, Assistance Publique-Hôpitaux de Paris (AP-HP), Groupe Hospitalier St Louis-Lariboisière, Paris, France*
[r] *Département de Maladies Infectieuses et Tropicales, CHU de Nîmes, 30000 Nimes, France*
[s] *Département de Microbiologie et d'hygiène Hospitalière, CHU Nîmes, Univ. Montpellier, Nîmes, France*
[t] *Département de Maladies Infectieuses et Immunologie, Hôpital Universitaire Henri Mondor, Assistance Publique Hôpitaux de Paris - University Paris Est Créteil, France*
[u] *Hôpitaux Universitaires Henri Mondor, DMU Médecine, Service de Médecine Intensive Réanimation, Assistance Publique-Hôpitaux de Paris (AP-HP), 94010 Créteil, France*
[v] *Département de Maladies Infectieuses et Tropicales, Hôpitaux Universitaires de Strasbourg, Strasbourg, France*
[w] *Laboratoire de Bactériologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France*
[x] *Laboratoire de Bactériologie, Hospices Civils de Lyon, F-69004 Lyon, France*
[y] *Centre International de Recherche en Infectiologie (CIRI), Inserm 1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, École Normale Supérieure de Lyon, Univ Lyon, F-69007, France*

* Correspondence to: Département des Maladies infectieuses et tropicales, Hôpital de la Croix-Rousse, Hospices Civils de Lyon, 104 Grande-Rue de la Croix-Rousse, 69317 Lyon Cedex 04, France.
E-mail address: sarah.soueges@chu-lyon.fr (S. Soueges),

[1] On behalf of the G2I (Groupe Immunodepression et Infections) network (members in alphabetical order): Florence Ader, Claire Aguilar, Serge Alfandari, Elodie Blanchard, Mathieu Blot, Anne-Sophie Brunel, Xavier Brousse, François Danion, Blandine Denis, Emmanuel Faure, Benjamin Gaborit, Anne Huynh, Hannah Kaminski, Fanny Lanternier-Dessap, Paul Loubet, Guillaume Martin-Blondel, Giovanna Melica, Keyvan Razazi, Alexis Redor, Christine Robin, Anne Scemla, Betoul Schvartz.

https://doi.org/10.1016/j.jinf.2024.106376

ARTICLE INFO

Article history:
Accepted 7 December 2024
Available online 15 December 2024

Keywords:
Cefiderocol
Immunocompromised patients
Stenotrophomonas maltophilia
Multi drug resistant gram-negative bacteria

SUMMARY

Introduction: The increase in the population of immunocompromised patients due to advances in management of end-stage diseases and transplants poses challenges in treating infections caused by multi-drug resistant (MDR) pathogens. Cefiderocol (FDC), a siderophore cephalosporin, has shown efficacy against carbapenem-resistant Gram-negative bacteria.

Methods: This retrospective multicentre study investigated the real-world use of FDC in 114 immunocompromised adults treated for MDR infections in 12 French hospitals (June 2020–November 2023). Clinical and microbiological outcomes, including infection cure, relapse, as well as mortality, and resistance acquisition, were assessed at days 28 and 90. Antibiotic prescription compliance with current guidelines was investigated.

Results: At day 28, clinical success was achieved in 53.3% of cases, and overall mortality was 37.7%, consistent with other studies (33–37%). Infection-related mortality accounted for 25.4%. Relapse occurred in 17.5% of patients by day 28, rising by an additional 9.8% among survivors by day 90. Resistance acquisition was observed in two cases at day 28 (*Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*) and in three additional cases by day 90. FDC was used as monotherapy in 49.1% of cases, with a median treatment duration of 10 days. Nearly 25% of strains collected in FDC-treated patients were susceptible to best-practice alternatives.

Conclusion: These findings highlight FDC's utility in difficult-to-treat infections, particularly *S. maltophilia*, but 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.

Introduction

The population of immunocompromised patients is constantly increasing as a result of advances in the management of end-stage diseases, auto-immune and inflammatory diseases, malignancies and solid organ or haematopoietic stem cell transplantations.[1] In these settings, infections with multi-drug resistance (MDR) bacteria are a major cause of morbi-mortality and antimicrobial stewardship plays a central role.[2,3] Cefiderocol (FDC) is a recent antibiotic, combining a cephalosporin and a catechol-type siderophore allowing bacterial internalization via multiple iron transporters. Thanks to two randomized trial, FDC received Food and Drug Administration authorization for use in urinary tract infections (UTI), hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) related to Gram-negative pathogens in 2019 and 2020, respectively, and European Medicines Agency approval for infections related to carbapenem-resistant Gram-negative pathogens (Enterobacterales and non-fermentative Gram-negative bacteria) with limited treatment options.[4,5] Recent guidelines have advised the use of FDC as an alternative for KPC- and OXA-48 producing enterobacterales after beta lactam + inhibitors, and as the recommended drug in alternative to ceftazidime/avibactam + aztreonam for NDM producers. For *Pseudomonas aeruginosa* (*P. aeruginosa*), FDC was proposed as an alternative after ceftolozane/tazobactam, ceftazidime/avibactam, and imipenem-cilastatin/relebactam in case of carbapenem resistance with exception for UTI.[6,7]

Most existing post-marketing real-world data have been acquired in complex UTI and in critically ill patients with HAP/VAP or based on pre-defined pathogens.[8–12] Yet, very few data are available in immunocompromised populations in whom most FDC prescriptions have primarily targeted multi-resistant *P. aeruginosa* and carbapenem resistant *Acinetobacter baumanii* (CRAB) infections. To date, 27 immunocompromised patients have been included in the pivotal study CREDIBLE-CR, but there has been no analysis of outcomes in this specific subset.[4] The three largest cohorts including real-life data on immunocompromised patients (adult and children) included nine, eight and seven patients respectively, with highly heterogeneous data regarding clinical success and mortality.[13–15] Updated data on clinical outcomes in these populations are therefore needed, with consideration also being given to the wider use of FDC in other difficult-to-treat non-fermentative Gram-negative bacteria infections, such as *Stenotrophomonas maltophilia* (*S. maltophilia*) infections.

We conducted a retrospective national multicenter study to investigate the real-world use of FDC in immunocompromised patient populations aiming at describing the settings in which it was used, the clinical and microbiological outcomes, as well as mortality.

Patients and methods

Study design and patient population

A retrospective, multicentre cohort study was conducted among immunocompromised adult patients (≥ 18-year-old) hospitalized in 12 French tertiary-care university hospitals (Lyon [Hospices civils de Lyon], Saint-Louis, Mondor and Necker hospitals [Assistance Publique-Hôpitaux de Paris], Nantes, Strasbourg, Nîmes, Bordeaux, Dijon, Toulouse, Besançon and Lille) treated with FDC for a documented infection between June 2020 and November 2023. Immunocompromised patients were defined as patients who had received solid organ transplantation (SOT) or hematologic stem cell transplantation (HSCT), patients with a history of hematological malignancy or solid cancer treated within the past 6 months or undergoing treatment, and patients receiving immunosuppressive treatment for interstitial lung disease.

The following patient characteristics were collected: demographics, underlying conditions, immunosuppressive regimen, site (s) of infection and clinical outcomes at days 28 and 90 (cure defined as complete symptom resolution or failure), overall mortality and attributable mortality defined as infection-related mortality at days 28 and 90. Clinical data were systematically collected by thoroughly reviewing the medical charts that were implemented in the centralized medical software of each hospital. The following microbiological characteristics were recorded: causal pathogen(s), presence or absence of associated bloodstream infection, antimicrobial susceptibility testing (AST) of each strain through broth microdilution and/or disk diffusion, and microbiological outcomes at days 28 and 90 (relapse, persistence, resistance acquisition). Relapse of infection was defined as a new infection after recovery from the infection for which the FDC had been primarily used, caused by a similar and/or different pathogen(s). Persistence of infection was

defined as the absence of sterilization of the infectious focus assessed by culture positivity of biological samples with causal bacterial agent(s) and/or the persistence of clinical signs of infection without evidence of another causal agent. Finally, FDC treatment characteristics were recorded: dose, duration of intravenous infusion and side effects. FDC activity on identified bacterial agent(s) was defined as susceptible or resistant using EUCAST breakpoints for either disk diffusion or broth microdilution depending on the method used. Moreover, multi-resistance mechanisms were explored through carbapenemase detection assays in enterobacterales and *P. aeruginosa*.

Because of the retrospective observational nature of the CEFI-ID study and the absence of modification of patients' management, all patients received written information, but the need for informed consent was waived. CEFI-ID was approved by the scientific and ethical committee of the principal investigating center (*Hospices Civils de Lyon, HCL 23–5369*) and of the French Infectious Diseases Society (*Comité d'Ethique de Recherche en Maladies Infectieuses et Tropicales, CER-MIT 2023–1107*).

Endpoints

The primary objective consisted of determining the clinical outcome at day 28 through three endpoints defined as infection cure, relapse and overall and attributable mortality. Attributable mortality was defined by the authors as the mortality related to the infection for which FDC was used. Secondary objectives were to determine the clinical outcome at day 90, microbiological outcome at days 28 and 90 through the recording of positive bacteriological cultures, and to assess antibiotic prescription compliance with current guidelines (limited treatment options) according to EUCAST breakpoints.

Statistical analysis

Descriptive data were used to estimate the frequencies of the study variables, expressed as count (percentage, %) for dichotomous variables and as medians (interquartile range [IQR]) for continuous variables. The number of missing values was excluded from the denominator for percentage calculation. Non-parametric tests were used to compare groups ($\chi 2$, Fisher exact test or Mann-Whitney U tests where appropriate). Factors associated with the main study endpoints were investigated using a univariate and multivariate logistic regression, expressed as odds ratios (OR) with 95% confidence intervals (95% CI). The variable in the univariate model with a value of $P < 0.2$ were included in the multivariate model. A value of $p < 0.05$ was considered significant. All analyses were performed using SPSS v19.0 (SPSS, Chicago, IL, USA).

Results

Patient's characteristics

A hundred and fourteen immunocompromised patients treated with FDC for an infection related to MDR bacteria were included. Median age [IQR] was 60 [50–67.7] years. Sex ratio M/F was 2.6. Median [IQR] Charlson comorbidity index was 4.5 [3–6]. Hematological malignancies accounted for 38.5% (n=44) of the immunocompromised population, among whom 52.3% (n=23/44) were acute myeloid leukemia. SOT accounted for 35% (n=40), among whom 17, 11, 10, 2 were lung, liver, kidney, and heart transplantations, respectively. HSCT accounted for 16.6% (n=19), among whom 13 and 6 were allogeneic and autologous HSCT, respectively. Active solid neoplasia represented 24.5% (n=28) of patients, including 15 digestive or biliary cancers. Finally, 3.5% (n=4) were treated for interstitial lung disease. When considering immunosuppressive treatments, 43.8% (n=50) of patients received a calcineurin inhibitor, 38.5% (n=44) received corticosteroids (≥10 mg equivalent to prednisone and ≥21 days), and 33.3% (n=38) received mycofenolate mofetil (MMF) (Table 1). At the onset of infection, neutropenia (< 0.5 G/L of polymorphonuclear neutrophils) was present in 13.1% (n=15) of cases.

Table 1
Characteristics of patients treated with cefiderocol for documented Gram-negative bacilli infection.

n=114		
Demographics		
Age (year)		60 [50–67.7]
Sex ratio (M/F)		2.6
Underlying conditions		
Charlson comorbidity index		4.5
SOT		40 (35%)
	Lung	17 (42.5%)
	Kidney	10 (25%)
	Liver	11 (27.5%)
	Heart	2 (5%)
Hematological malignancy		44 (38.5%)
	Myeloid	27 (61.3%)
	Lymphoid	17 (38.7%)
HSCT		19 (16.6%)
	Allo HSCT	13 (68.4%)
	Auto HSCT	6 (31.6%)
Active solid neoplasia		28 (24.5%)
	Digestive/biliary/pancreas	19 (67.8%)
	Lung	4 (14.2%)
	ENT	4 (14.2%)
	Urinary tract/kidney	1 (3.8%)
Interstitial lung disease		4 (3.5%)
Immunosuppressive drugs		
Calcineurin inhibitor		50 (43.8%)
Steroids (≥10 mg equivalent to prednisone and ≥21 days)		44 (38.5%)
Mycofenolate mofetil		38 (33.3%)
mTOR inhibitor		5 (4.3%)
Belatacept		3 (2.6%)
Azathioprine		1 (0.8%)

Data are presented as n (%) for dichotomous variables and median [IQR] for continuous variables. Abbreviations: ENT, ear, nose, throat; HSCT: hematologic stem cell transplantation; IQR, interquartile range; mTOR, mechanistic target of rapamycin; SOT, solid organ transplantation.

The most frequent sites of infection were respiratory (48.2%, n=55), urinary (14%, n=16), intra-abdominal (9.6%, n=11), venous catheter-related (8.7%, n=10), skin and soft tissue (7%, n=8), central nervous system (2.6%, n=3), or undetermined sites (4.3%, n=5). Bloodstream infections (BSI) were associated with infected sites in 38.8% (n=42) of the cases. Isolated BSI occurred in 5.2% (n=6) of the cases. Intensive care unit (ICU) admission was required for 58.7% (n=67) of patients, among whom 70% (n=47) and 64.1% (n=43) required mechanical ventilation and vasopressive support, respectively (Table 2). Invasive surgery or radiological drainage was performed in 24.5% (n=28) of the cases.

Patient's outcomes

At day 28, infection cure was achieved in 53.3% (n=61) of the cases. Overall mortality was 37.7% (n=43), among whom attributable mortality accounted for 25.4% (n=29). Overall mortality was significantly associated with bloodstream and respiratory tract infections in multivariable analysis adjusted on septic shock (aOR 4.12, 95% CI [1.48–11.5], *p=0.007* and OR 8.04, 95% CI [2.48–26.03], *p < 0.001*, respectively). Infection with *P. aeruginosa* was associated to a significantly lower risk of death (OR 0.30, 95% CI [0.17–0.8], *p=0.016*) (see Supplementary, Tables 1 and 2). No other clinical or biological factor was significantly associated with infection cure in univariate analysis (see Supplementary, Table 3).

Overall mortality at day 90 was 52.2% (n=58/111, 3 lost to follow-up), among whom attributable mortality accounted for 35.1% (n=39) (Table 2).

Table 2
Characteristics of infections and patient's outcome.

Site of infection	
Respiratory tract infection	55 (48.2%)
Urinary tract infection	16 (14%)
Intra-abdominal infection	11 (9.6%)
Venous catheter related infection	10 (8.7%)
Skin and soft tissue infection	8 (7%)
Central nervous system infection	3 (2.6%)
Associated bloodstream infection	42 (38.8%)
Complications of infections	
ICU admission	67 (58.7%)
Mechanical ventilation	47 (70%)
Vasopressive support	43 (64.1%)
Day 28 outcomes	
Infection cure	61 (53.3%)
Overall mortality	43 (37.7%)
Attributable mortality	29 (25.4%)
Day 90 outcomes	
Overall mortality	58 (52.2%)
Attributable mortality	39 (35.1%)
Lost to follow up	3 (2.6%)

Data are presented as n (%) for dichotomous variables and median [IQR] for continuous variables. Abbreviations: ICU, intensive care unit; IQR, interquartile range.

Table 3
Microbiological data.

Enterobacterales antibiotic susceptibility, (n=24)	
Ceftazidime/avibactam	26.6% (n=4/15)
Imipenem-cilastatin/relebactam	25% (n=2/8)
Meropenem/vaborbactam	71.4% (n=5/7)
Colistine	26.6% (n=4/15)
***P. aeruginosa* antibiotic susceptibility, (n=68)**	
Ceftolozane/tazobactam	21.6% (n=13/60)
Ceftazidime/avibactam	21.3% (n=13/61)
Imipenem-cilastatin/relebactam	23.8% (n=10/42)
Colistine	96.1% (n=50/52)
Relapses and resistance acquisition	
Day 28 relapses	20 (17.5%)
Day 28 resistance acquisition	2 (10%)
Day 90 relapses	7 (9.8% of alive patients at day 28)
Day 90 resistance acquisition	1 (14.2%)

Data are presented as n (%) for dichotomous variables and median [IQR] for continuous variables. Abbreviations: IQR, interquartile range; NFGNB, non-fermentative Gram-negative bacilli.

Microbiological data

Most infections treated with FDC were monomicrobial (79.8%, n=91). Non-fermentative Gram-negative bacteria (NFGNB) were the most frequent pathogens including, in decreasing order, *P. aeruginosa* (56%, n=51) of which 11.7% (n=8) were VIM producers, other NFGNB (31.8%, n=29), among which 44.8% (n=13) were *S. maltophilia*, 20.6% (n=6) were carbapenem-resistant OXA23 producing *Acinetobacter* and Enterobacterales (12%, n=11). Polymicrobial infections mostly included *P. aeruginosa* with another NFGNB (43.4%, n=10), *P. aeruginosa with an* Enterobacterales (26.1%, n=6), or NFGNB with an Enterobacterales (26.1%, n=6) and one case of infection with *P. aeruginosa*, Enterobacterales and NFGNB (4.3%, n=1) (Fig. 1).

Regarding minimum inhibitory concentration (MIC) determinations, among the 68 tested strains of *P. aeruginosa*, the median MIC for FDC was 1 [0.25–1] mg/L using microdilution on 40/68 strains. Using EUCAST breakpoint, susceptibility to ceftolozane/tazobactam, ceftazidime/avibactam and colistine were 21.6% (n=13/60), 21.3% (n=13/61), and 96.1% (n=50/52), respectively. Among the 24 strains of *S. maltophilia* tested, according to CLSI and EUCAST guidelines (MIC ≥ 32 mg/L), resistance to ceftazidime was found in 70.5% (n=12/17) of the cases.

In the Enterobacterales group (n=24), *Enterobacter cloacae* was the most frequent isolated strain (41.6%, n=10). Resistance mechanisms were distributed as follows: 45.8% (n=11) of extended spectrum beta lactamase (ESBL), 20.8% (n=5) of VIM, 12.5% (n=3) of NDM, and 4.1% (n=1) of Oxa-48. When tested, ceftazidime/avibactam and colistine were susceptible in 26.6% (n=4/15 tested strains) and 66.6% (n=6/9 tested strains), respectively (Table 3). At day 28, relapses occurred in 17.5% (n=20) of cases, especially with *P. aeruginosa* (70%, n=14, OR 2.32, 95% CI [0.77–6.91], *p=0.130*). There was no significant association between treatment regimen (single therapy or combination) nor the site and the pathogen involved in the infection, and relapse (see Supplementary, table 4). At relapse, FDC resistance acquisition was observed twice, in a *P. aeruginosa* and a *S. maltophilia* strain. Seven additional relapses occurred between days 28 and 90 (9.8% of alive patients at day 28). Four of the relapsed cases were *P. aeruginosa*, with no evidence of resistance to FDC for the 3 strains tested and 3 were *S. maltophilia*, one of which had developed resistance to FDC (Table 3).

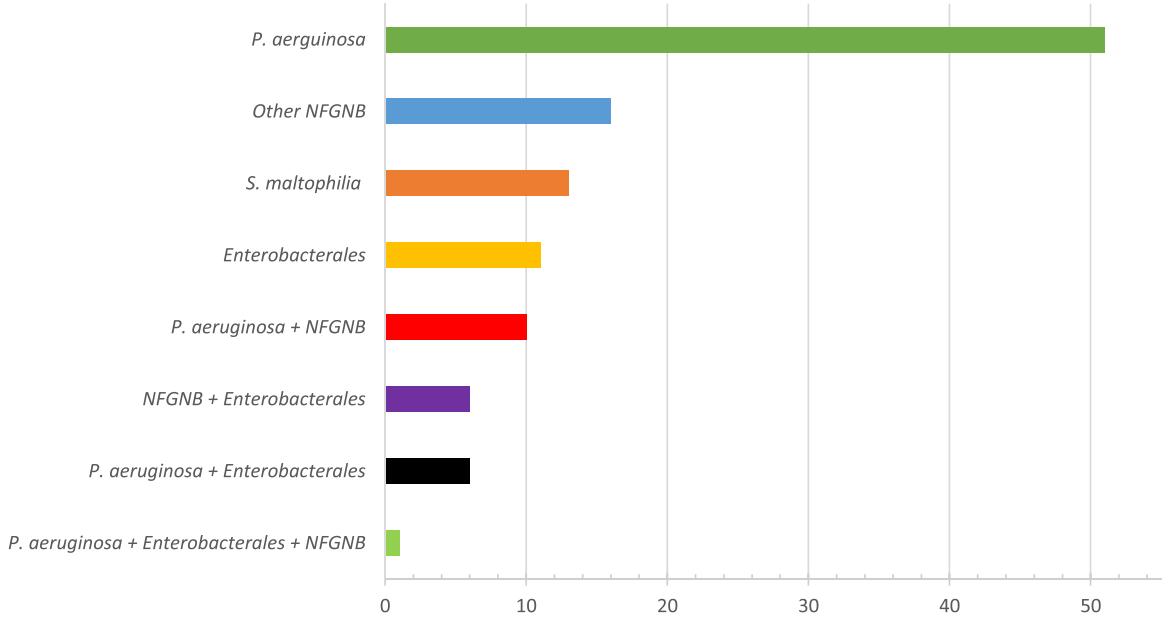

Fig. 1. Distribution of bacterial strains treated with cefiderocol. Abbreviations: NFGNB: non-fermentative Gram-negative bacilli.

Use of cefiderocol

FDC was used in monotherapy in 49.1% (n=56) of the cases. Median [IQR] duration of FDC was 10 [7–16] days. Median [IQR] dose of FDC was 81.5 [64.5–102] mg/kg/day. Intermittent prolonged infusion (3 to 4 h) was the most frequent infusion mode (75.5%, n=77/102 available data), whereas the rest (24.5%) was intermittent 30-min perfusion.

Discussion

The present study shows that clinical success rates in the immunocompromised setting are not different that of the rates previously reported in pivotal randomized control trials that included very few of this patient's subset. In addition, we found that in that specific setting, FDC was not always used as a last resort beta-lactam antibiotic. Lastly, it brings evidence of the efficacy of FDC for *S. maltophilia* infections.

At day 28, the clinical success rate of 53.3% was comparable to that observed in the pivotal phase 3 randomized trial and most retrospective observational studies. This indicates that immunosuppression is not a factor that impacts clinical success.[4,5,8,16] Regarding mortality, small retrospective cohort studies focusing on immunocompromised patients have found a higher mortality than in phase 3 studies, which has led us to conduct the present study.[13,14] At day 28, our results shows that mortality was very close to the one observed by Piccica et al. (37%) in a cohort of 142 patients, as well as Palermo et al. (36.6%) in a cohort of 41 patients and in the CREDIBLE-CR phase 3 study (33%) regardless of patients' immune statue.[4,8,16]

We also report that nearly 25% of strains collected in FDC-treated patients were susceptible to best-practice alternatives, mostly combinations of beta-lactam + inhibitors. We hypothesize that this relatively poor compliance to current guidelines[6,7] can be explained by prescriber caution in managing fragile patients' population, in which inadequate initial empirical antibiotic therapy is likely associated with impaired outcome.[17,18] It is also plausible that empiric antibiotic therapy may not be always revised in light of AST results upon availability.

The lower mortality observed in infections caused by *P. aeruginosa* may reflect this concern on the part of prescribing clinicians who have chosen to use FDC early.

We are witnessing an extension of the use of FDC to other NFGNB, particularly those with limited therapeutic alternatives. In our study, 24 strains of *S. maltophilia* were treated with FDC, which is the largest real-life series to date. The use of FDC for *S. maltophilia* infections was not associated with excess mortality, nor clinical failure in comparison to other NFGNB. This is consistent with a preclinical study carried out in persistent neutropenic rabbits with *S. maltophilia* pneumonia that found in the FDC treated group significant clinical success rate and bacterial eradication both superior to the trimethoprim sulfamethoxazole treated group.[19]

Finally, we are observing a high rate of infection relapses, and the concurrent emergence of resistance, which has already been described with certain bacterial species.[20] These findings therefore indicate that prescription review upon full AST result is advised to narrow the antibiotic spectrum whenever possible.[21]

The present study has limitations. Data should be interpreted with caution because of the retrospective nature of the study. In the present cohort, the criteria used to define the use of a preferred antibiotic and single-drug or a combined antibiotic regimen was left at the discretion of the referent physician, thus resulting in analyzing outcome parameters in a non-controlled manner. The FDC MIC measurement methods varied during the period covered by the study between disk diffusion and microdilution, depending on the center and the availability of the methods at that time; this may be a limiting factor, particularly with regard to resistance detection by the disk diffusion method, considered as less precise.[22] The lack of consistency regarding treatment duration likely reflects differences among management strategies in recruitment centers. The outcome criteria were not standardized, which prevented a more precise assessment of treatment efficacy.

In conclusion, immunocompromised status does not influence the clinical outcome. Caution is advised regarding the trend in first line use of FDC for *P. aeruginosa* and enterobacteria infections. The results confirm real-world efficacy of FDC in *S. matlophilia* infections, for which therapeutic armamentarium is limited.

Funding

No external funding was received for this study.

Author contributions

SS contributed to study conception and design, acquisition of the data, interpretation of the data, drafted the manuscript and approved the final version; FA is the project initiator, contributed to study conception and design, drafted the manuscript, and approved the final version. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: SS received travel grants from Shionogi.

Acknowledgments

The authors and the members of the G2I network gratefully acknowledge Christèle Cheneau, Nathalie Gastellier of the RENARCI and the Société de Pathologies Infectieuses de Langue Française Française (SPILF).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106376.

References

1. Harpaz R, Dahl RM, Dooling KL. *Prevalence of immunosuppression among US adults, 2013. JAMA* 2016 Dec 20;**316**(23):2547.
2. Curcio D. *Multidrug-resistant Gram-negative bacterial infections: are you ready for the challenge? Curr Clin Pharmacol* 2014 Feb 31;**9**(1):27–38.
3. Dumford DM, Skalweit M. *Antibiotic-resistant infections and treatment challenges in the immunocompromised host. Infect Dis Clin North Am* 2016 Jun;**30**(2):465–89.
4. Bassetti M, Echols R, Matsunaga Y, Ariyasu M, Doi Y, Ferrer R, et al. *Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. Lancet Infect Dis* 2021 Feb;**21**(2):226–40.
5. Wunderink RG, Matsunaga Y, Ariyasu M, Clevenbergh P, Echols R, Kaye KS, et al. *Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis* 2021 Feb;**21**(2):213–25.
6. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. *Infectious Diseases Society of America 2023 guidance on the treatment of antimicrobial resistant Gram-negative infections. Clin Infect Dis* 2023 Jul 18:ciad428.
7. Paul M, Carrara E, Retamar P, Tängdén T, Bitterman R, Bonomo RA, et al. *European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). Clin Microbiol Infect* 2022 Apr;**28**(4):521–47.
8. Piccica M, Spinicci M, Botta A, Bianco V, Lagi F, Graziani L, et al. *Cefiderocol use for the treatment of infections by carbapenem-resistant Gram-negative bacteria: an Italian multicentre real-life experience. J Antimicrob Chemother* 2023 Nov 6;**78**(11):2752–61.

9. Falcone M, Tiseo G, Leonildi A, Della Sala L, Vecchione A, Barnini S, et al. *Cefiderocol- compared to colistin-based regimens for the treatment of severe infections caused by carbapenem-resistant Acinetobacter baumannii. Antimicrob Agents Chemother* 2022 May 17;**66**(5):e02142-21.
10. Bavaro DF, Belati A, Diella L, Stufano M, Romanelli F, Scalone L, et al. *Cefiderocol-based combination therapy for "difficult-to-treat" Gram-negative severe infections: real-life case series and future perspectives. Antibiotics* 2021 May 29;**10**(6):652.
11. Hung KC, Tsai WW, Hsu CW, Lai CC, Tang HJ, Chen IW. *Clinical efficacy and safety of novel antibiotics for complicated urinary tract infection: a systematic review and meta-analysis of randomized controlled trials. Int J Antimicrob Agents* 2023 Jul;**62**(1):106830.
12. Viale P, Sandrock CE, Ramirez P, Rossolini GM, Lodise TP. *Treatment of critically ill patients with cefiderocol for infections caused by multidrug-resistant pathogens: review of the evidence. Ann Intensive Care* 2023 Jun 15;**13**(1):52.
13. Hoellinger B, Simand C, Jeannot K, Garijo C, Cristinar M, Reisz F, et al. *Real-world clinical outcome of cefiderocol for treatment of multidrug-resistant non-fermenting, gram negative bacilli infections: a case series. Clin Microbiol Infect* 2023 Mar;**29**(3):393–5.
14. Meschiari M, Volpi S, Faltoni M, Dolci G, Orlando G, Franceschini E, et al. *Real-life experience with compassionate use of cefiderocol for difficult-to-treat resistant Pseudomonas aeruginosa (DTR-P) infections. JAC Antimicrob Resist* 2021 Sep 30;**3**(4):dlab188.
15. Schmid H, Brown LAK, Indrakumar B, McGarrity O, Hatcher J, Bamford A. *Use of cefiderocol in the management of children with infection or colonization with multidrug resistant Gram-negative bacteria. Pediatr Infect Dis J* 2024;**43**:772–6.
16. Palermo G, Medaglia AA, Pipitò L, Rubino R, Costantini M, Accomando S, et al. *Cefiderocol efficacy in a real-life setting: single-centre retrospective study. Antibiotics* 2023 Apr 13;**12**(4):746.
17. Averbuch D, Tridello G, Hoek J, Mikulska M, Akan H, Yaňez San Segundo L, et al. *Antimicrobial resistance in gram-negative rods causing bacteremia in hematopoietic stem cell transplant recipients: intercontinental prospective study of the infectious diseases working party of the European Bone Marrow Transplantation Group. Clin Infect Dis* 2017 Nov 13;**65**(11):1819–28.
18. Martinez-Nadal G, Puerta-Alcalde P, Gudiol C, Cardozo C, Albasanz-Puig A, Marco F, et al. *Inappropriate empirical antibiotic treatment in high-risk neutropenic patients with bacteremia in the era of multidrug resistance. Clin Infect Dis* 2020 Apr 25;**70**:1068–74.
19. Petraitis V, Petraitiene R, Kavaliauskas P, Naing E, Garcia A, Georgiades BN, et al. *Efficacy of cefiderocol in experimental Stenotrophomonas maltophilia pneumonia in persistently neutropenic rabbits. Antimicrob Agents Chemother* 2022 Oct 18;**66**(10):e00618-22.
20. Karakonstantis S, Rousaki M, Kritsotakis EI. *Cefiderocol: systematic review of mechanisms of resistance, heteroresistance and in vivo emergence of resistance. Antibiotics* 2022 May 27;**11**(6):723.
21. Lehrnbecher T, Averbuch D, Castagnola E, Cesaro S, Ammann RA, Garcia-Vidal C, et al. *8th European Conference on Infections in Leukaemia: 2020 guidelines for the use of antibiotics in paediatric patients with cancer or post-haematopoietic cell transplantation. Lancet Oncol* 2021 Jun;**22**(6):e270–80.
22. Bonnin RA, Emeraud C, Jousset AB, Naas T, Dortet L. *Comparison of disk diffusion, MIC test strip and broth microdilution methods for cefiderocol susceptibility testing on carbapenem-resistant enterobacterales. Clin Microbiol Infect* 2022 Aug;**28**(8):1156.e1–5.