European Journal of Clinical Microbiology & Infectious Diseases (2025) 44:1367–1374
https://doi.org/10.1007/s10096-025-05109-5

RESEARCH

Cefiderocol treatment for patients infected by *Stenotrophomonas maltophilia*, *Burkholderia cepacia* complex and *Achromobacter* spp.: subgroup analysis from the PERSEUS study

Julian Torre-Cisneros[1,2,3,4] · Ricard Ferrer[5] · Carmen De La Fuente Martos[1,2,6] · Jessica Sarda[7] · A. Javier Gonzalez Calvo[7] · Stefano Verardi[8] · Andreas Karas[8] · Alex Soriano[2,9,10]

Received: 5 November 2024 / Accepted: 14 March 2025 / Published online: 24 March 2025

Abstract

Purpose This subgroup analysis of the PERSEUS study aimed to describe the effectiveness of cefiderocol treatment in the early access programme in Spain in patients infected by *Stenotrophomonas maltophilia*, *Burkholderia cepacia* complex (Bcc) or *Achromobacter* species.

Methods In the retrospective, observational, multicentre PERSEUS study in Spain, the effectiveness and safety of cefiderocol treatment administered for at least 72 h up to 28 days in patients infected by Gram-negative bacteria, except *Acinetobacter* spp., in the early access programme was investigated. Patient demographics and baseline clinical characteristics, cefiderocol use, clinical cure at end of treatment, all-cause mortality at Day 28 were the main outcomes.

Results A total of 20 patients had *S. maltophilia* infections, and 14 patients had other rare glucose non-fermenters (Bcc 8, *Achromobacter* spp. 5, *Ralstonia mannitolilytica* 1). The median (interquartile range [IQR]) age was 60.5 (48.0–65.5) years and 49.5 (33.0–59.0) years for patients with *S. maltophilia* and other rare non-fermenters, respectively. The majority of patients had respiratory tract infections (*S. maltophilia* 55%; other rare non-fermenters 71.4%), and median (IQR) duration of cefiderocol treatment was 10.0 (6.5–13.5) days and 8.0 (6–14) days, respectively. Clinical cure rates were 70%, 62.5% and 80.0% for patients with *S. maltophilia*, Bcc and *Achromobacter* spp., respectively. Corresponding 28-day all-cause mortality rates were 30.0%, 37.5% and 40.0%, respectively. One patient with *R. mannitolilytica* had clinical cure and survived to Day 28.

Conclusions Cefiderocol is an important addition to the limited treatment options for patients infected by these rare glucose non-fermenting Gram-negative bacteria.

Trial registration ClinicalTrials.gov: NCT05789199 (Registration date: 16 February 2023).

Keywords Cefiderocol · *Stenotrophomonas maltophilia* · *Burkholderia cepacia* complex · *Achromobacter* spp · Non-fermenting Gram-negative bacteria

✉ Jessica Sarda
jessica.sarda@shionogi.eu

[1] Maimonides Institute for Biomedical Research, Córdoba, Spain

[2] Centro de Investigación Biomédica en Red de Enfermedades Infecciosas, Instituto de Salud Carlos III, Madrid, Spain

[3] Infectious Diseases Service, Hospital Universitario Reina Sofía, Córdoba, Spain

[4] Department of Medical and Surgical Sciences, University of Córdoba, Córdoba, Spain

[5] Intensive Care Department, Hospital Universitari Vall d'Hebrón, SODIR Research Group, Vall d'Hebron Institut de Recerca, Universitat Autònoma de Barcelona, Barcelona, Spain

[6] Critical Care Service, Hospital Universitario Reina Sofía, Córdoba, Spain

[7] Shionogi S.L.U, Calle de Serrano 45, Madrid 28001, Spain

[8] Shionogi BV, London, UK

[9] Department of Infectious Diseases, University of Barcelona, Hospital Clinic of Barcelona, Barcelona, Spain

[10] IDIBAPS, Institut d'Investigacions Biomèdiques Agustí-Pi Sunyer, Barcelona, Spain

Introduction

Stenotrophomonas maltophilia, *Burkholderia cepacia* complex (Bcc) and *Achromobacter* spp. are rare, opportunistic, glucose non-fermenting Gram-negative pathogens that can colonise the mucosa of in-patients who, typically, are under high antibiotic pressure, resulting in the potential for severe infections linked to increased risk of mortality and morbidity in vulnerable patients [1–12]. These species are frequently resistant to beta-lactam antibiotics, including penicillins, cephalosporins, carbapenems and beta-lactam–beta-lactamase inhibitor combinations, as well as agents in other antibiotic classes [3–5, 7, 13–16]. Thus, treatment of infections caused by *S. maltophilia*, Bcc or *Achromobacter* spp. is challenging [5, 7, 17–19].

Cefiderocol, a siderophore cephalosporin, has demonstrated excellent in vitro activity against *S. maltophilia*, Bcc and *Achromobacter* spp. isolates with low MIC values in multinational surveillance studies [14, 20–23]. The observational PERSEUS study investigated the effectiveness of cefiderocol treatment in the cefiderocol early access programme (EAP) in Spain and enrolled patients with infections caused by Gram-negative bacteria, excluding *Acinetobacter* spp [24]. In the PERSEUS study, clinical cure was achieved in 80.5% of patients and all-cause mortality at Day 28 was 21.5% overall [24].

In this subgroup analysis, we describe the clinical and microbiological characteristics of *S. maltophilia* and other rare, non-fermenting Gram-negative bacterial infections, including resistance and treatment patterns, in patients enrolled in the PERSEUS study, and report on the clinical outcomes and use of cefiderocol in this subset of patients.

Methods

Ethics and regulations

In Spain, access to locally unapproved medications can be granted in special circumstances following a Royal Decree (1015/2009), with each case considered on its own merits for approval by the Spanish Agency of Medicines. Prior to study start, the PERSEUS study was approved centrally by the Institutional Review Board of Hospital La Princesa, Madrid, under Royal Decree 957/2020 (3 November 2020). The study was conducted according to all legal and regulatory requirements, the International Conference on Harmonisation Good Clinical Practice E6 guidelines and the Declaration of Helsinki. Medical record data were collected and anonymised to protect patients' personal information. In accordance with Spanish regulations, patient consent was waived due to the retrospective design of the study as patients completed their treatment prior to study initiation; therefore, the study represented no harm for the participants.

The design of the PERSEUS study, eligibility criteria, populations, outcomes, variables, and definitions, and statistical analysis have been described in detail by Torre-Cisneros J, et al. [24].

Results

Patient disposition

Of the 261 patients included in the primary analysis population of the PERSEUS study, 34 were included in this subgroup analysis, of whom 20 patients had *S. maltophilia* infections and 14 had other glucose non-fermenting Gram-negative spp. infections, including 8 with Bcc infections, 5 with *Achromobacter* spp. infections and 1 with *Ralstonia mannitolilytica* infection.

Patient demographics and baseline characteristics

Across the different pathogen groups, most patients were male (except for those with *Achromobacter* spp. infections). Patients were generally young, particularly patients with Bcc, who had a median age of 41.0 years. The median CCI ranged between 1.0 and 3.0, and around three-quarters of patients had an underlying illness (Table 1, Table S1). Cancer and moderate or severe renal disease were more common in patients with *S. maltophilia* than in patients with infections caused by the other non-fermenting groups (Table S1). Structural lung disease was the most common condition in patients with other non-fermenting Gram-negative bacterial infections (i.e. those with Bcc infections). Other comorbidities included diabetes mellitus, cerebrovascular disease, and peripheral vascular disease (Table S1).

Between 60.0% and 87.5% of patients required admission to an ICU (Table 1). Across the pathogen groups, the median durations of hospital and ICU stays were 75.0–97.5 days and 25.0–89.0 days, respectively (Table S2). Over half of patients in each pathogen group (≥55%) were mechanically ventilated at baseline and/or were immunosuppressed. Additionally, 50% of patients (17/34) were solid organ or haematopoietic transplant recipients. Septic shock was reported in 12.5–30.0% of patients, and 25–42.9% of patients were receiving renal replacement therapy (Table 1). The median SOFA score was 9.0 in patients with *S. maltophilia* and 6.0 for other rare non-fermenters (Table 1).

In most patients, the primary infection site was respiratory (40.0–87.5% of patients across all pathogen groups) and infections were mainly monomicrobial (Table 1). Unlike patients with other pathogens, those with Bcc infections did

Table 1 Patients' baseline demographics and clinical characteristics by non-fermenting Gram-negative bacterial species

	S. maltophilia	Other non-fermenting Gram-negative bacteria		
	N = 20	Total *N* = 14[a]	Bcc *N* = 8	*Achromobacter* spp. *N* = 5
Age (years), median (IQR)	60.5 (48.0–65.5)	49.5 (33.0–59.0)	41.0 (28.5–54.0)	59.0 (56.0–61.0)
Sex (male), *n* (%)	14 (70.0)	9 (64.3)	7 (87.5)	2 (40.0)
CCI, median (IQR)	3.0 (2.0–5.0)	2.0 (1.0–3.0)	1.0 (1.0–3.0)	3.0 (2.0–3.0)
SOFA, median (IQR)	9.0 (8.0–11.0)	6.0 (4.0–11.0)	5.5 (3.0–11.0)	5.0 (4.0–10.0)
APACHE II, median (IQR)	15 (6.0–24.0)	15 (9.0–22.0)	14.0 (9.0–19.0)	16.0 (8.0–34.0)
ICU, *n* (%)	15 (75.0)	11 (78.6)	7 (87.5)	3 (60.0)
Mechanical ventilation at baseline, *n* (%)	11 (55.0)	10 (71.4)	6 (75.0)	3 (60.0)
Symptomatic COVID-19 during hospitalisation, *n* (%)	4 (20.0)	1 (7.1)	0 (0)	1 (20.0)
Ventilation for COVID-19-related symptoms, *n/N* (%)	4/4 (100)	1/1 (100)	0 (0)	1/1 (100)
Septic shock, *n* (%)	6 (30.0)	3 (21.4)	1 (12.5)	1 (20.0)
ECMO, *n* (%)	1 (5.0)	2 (14.3)	1 (12.5)	1 (20.0)
RRT, *n* (%)	5 (25.0)	6 (42.9)	3 (37.5)	2 (40.0)
Creatinine clearance < 60 mL/min, *n/N* (%)[b]	3/15 (20.0)	4/8 (50.0)	4/5 (80.0)	0/3 (0)
Immunosuppressed, *n* (%)[c]	11 (55.0)	9 (64.3)	5 (62.5)	3 (60.0)
Transplant recipient, *n* (%)	9 (45.0)	8 (57.1)	5 (62.5)	2 (40.0)
Solid	3/9 (33.3)	7/8 (87.5)	5/5 (100)	1/2 (50.0)
Haematopoietic	6/9 (66.7)	1/8 (12.5)	0/5 (0)	1/2 (50.0)
Primary infection site, *n* (%)				
Respiratory	11 (55.0)	10 (71.4)	7 (87.5)	2 (40.0)
Bloodstream (catheter related)	4 (20.0)	1 (7.1)	0 (0)	1 (20.0)
Bloodstream (unknown source)	1 (5.0)	0 (0)	0 (0)	0 (0)
Urinary	1 (5.0)	2 (14.3)	0 (0)	2 (40.0)
Intra-abdominal	2 (10.0)	1 (7.1)	1 (12.5)	0 (0)
Skin and soft tissue	0 (0)	0 (0)	0 (0)	0 (0)
Bone and joint	0 (0)	0 (0)	0 (0)	0 (0)
Other	1 (5.0)[d]	0 (0)	0 (0)	0 (0)
Secondary bacteraemia, *n* (%)	4 (20.0)	3 (21.4)	0 (0)	2 (40.0)
Polymicrobial infection, *n* (%)[e]	3 (15.0)	1 (7.1)	1 (12.5)	0 (0)
Previous colonisation, *n* (%)	9/19[f] (47.4)	7/13[f] (53.8)	5 (62.5)	2 (40.0)

Bcc, *Burkholderia cepacia* complex; CCI, Charlson Comorbidity Index; COVID-19, coronavirus disease-2019; ECMO, extracorporeal membrane oxygenation; NF-GN, non-fermenting Gram-negative; RRT, renal replacement therapy

[a]One patient had *Ralstonia mannitolilytica* infection (further details not shown), 8 patients had Bcc, 5 patients had *Achromobacter* spp

[b]Excludes RRT; denominator excludes the missing data

[c]Transplant recipient, immunosuppressive treatment (e.g. high-dose corticosteroids, calcineurin inhibitors, anti-CD20, IL-1 inhibitors and IL-6 inhibitors)

[d]Includes mediastinitis (*n* = 1)

[e]Primary pathogen in polymicrobial infections, for which cefiderocol was requested, was confirmed by the treating physician

[f]Information on previous colonisation was available for 19 *S. maltophilia* isolates and 13 other NF-GN isolates

not have secondary bacteraemia. There was a high rate of previous colonisation with the same pathogen (Table 1).

The reported susceptibility data showed that most isolates across these species were resistant to standard antibiotic treatments. Among *S. maltophilia* and other non-fermenting Gram-negative pathogens, susceptibility rates (combined susceptible + intermediate [susceptible, increased exposure by EUCAST]) to trimethoprim-sulfamethoxazole were 62.5% and 25.0%, respectively, 50.0% and 25.0%, respectively, to colistin, and 44.4% of *S. maltophilia* were susceptible to levofloxacin. Minocycline susceptibility rates of 80.0% and 66.7% were reported for *S. maltophilia* and other non-fermenting Gram-negative pathogens, respectively, while respective rates of susceptibility to ceftazidime-avibactam and ceftazidime were 0% and 14.2% for *S. maltophilia* and 20.0% and 0% for other non-fermenting Gram-negative pathogens (Table S3). All isolates tested were resistant to meropenem, ciprofloxacin and ceftolozane-tazobactam (Table S3).

Treatment patterns

Over 60% of patients in each pathogen group had received prior antibiotics (Table 2). The median number of courses

Table 2 Pattern of cefiderocol use, prior and concomitant antibiotic use by Gram-negative bacterial species

	S. maltophilia	Other non-fermenting Gram-negative bacteria		
	N = 20	Total *N* = 14[a]	Bcc *N* = 8	*Achromobacter* spp. *N* = 5
Prior antibiotics, *n* (%)[b]	16 (80.0)	10 (71.4)	7 (87.5)	3 (60.0)
Number of prior courses of antibiotic treatments, median (IQR)	2.5 (2.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–4.0)	2.0 (1.0–3.0)
1, *n* (%)	1/16 (6.3)	3/10 (30.0)	2/7 (28.6)	1/3 (33.3)
2, *n* (%)	7/16 (43.7)	3/10 (30.0)	2/7 (28.6)	1/3 (33.3)
≥3, *n* (%)	8/16 (50.0)	4/10 (40.0)	3/7 (42.9)	1/3 (33.3)
None, *n* (%)	3 (15.0)	3 (21.4)	1 (12.5)	1 (20.0)
Unknown, *n*	1	1	0	1
Duration of prior antibiotic treatment (days), median (IQR)	9.3 (5.6–15.9)	11.8 (6.0–23.0)	12.5 (6.0–23.0)	6.3 (3.0–49.5)
≤3, *n* (%)	1/16 (6.3)	2/10 (20.0)	1/7 (14.3)	1/3 (33.3)
4–7, *n* (%)	5/16 (31.3)	2/10 (20.0)	1/7 (14.3)	1/3 (33.3)
>7, *n* (%)	10/16 (62.3)	6/10 (60.0)	5/7 (71.4)	1/3 (33.3)
Rationale for administration of cefiderocol, *n* (%)[c]				
Resistance to all tested antibiotics	10 (50.0)	11 (78.6)	6 (75.0)	4 (50.0)
Treatment failure of prior antibiotics	12 (60.0)	5 (35.7)	5 (62.5)	0 (0)
Adverse events to other susceptible antibiotics	4 (20.0)	0 (0)	0 (0)	0 (0)
Other	5 (25.0)	1 (7.1)	0 (0)	1 (20.0)
Cefiderocol as first-line therapy, *n* (%)	3 (15.0)	3 (21.4)	1 (12.5)	1 (20.0)
Duration of cefiderocol treatment (days), median (IQR)	10.0 (6.5–13.5)	8.0 (6.0–14.0)	9.0 (6.5–14.0)	8.0 (4.0–8.0)
Combination therapy given with cefiderocol, *n* (%)[d]	9 (45.0)	9 (64.3)	7 (87.5)	2 (40.0)
Number of antibiotics concomitantly with cefiderocol, *n* (%)				
1	5/9 (55.6)	4/9 (44.4)	3/7 (42.9)	1/2 (50.0)
2	1/9 (11.1)	2/9 (22.2)	1/7 (14.3)	1/2 (50.0)
≥3	3/9 (33.3)	3/9 (33.3)	3/7 (42.9)	0 (0)
Cefiderocol dosing, *n* (%)				
Every 4 h	0 (0)	0 (0)	0 (0)	0 (0)
Every 6 h	2 (10.0)	1 (7.1)	1 (12.5)	0 (0)
Every 8 h	15 (75.0)	13 (92.9)	7 (87.5)	5 (100)
Every 12 h	3 (15.0)	0 (0)	0 (0.0)	0 (0)
Other	0 (0)	0 (0)	0 (0)	0 (0)

Bcc, *Burkholderia cepacia* complex; GN, Gram-negative; NF-GN, non-fermenting Gram-negative

[a]One patient had *Ralstonia mannitolilytica* infection (further details not shown), 8 patients had Bcc, 5 patients had *Achromobacter* spp

[b]Data are shown for patients with a full data set

[c]Not mutually exclusive; physicians could select ≥ 1 option

[d]Includes antibiotics with Gram-negative coverage that have been started before, concomitantly or during the same treatment period

and median duration of prior antibiotics were 2.0–2.5 and 6.3–12.5 days, respectively (Table 2). The most common (50.0%) prior antibiotic used for patients with *S. maltophilia* was trimethoprim-sulfamethoxazole. For patients with Bcc, meropenem and colistin, and for patients with *Achromobacter* spp., meropenem, ceftazidime-avibactam, and colistin were administered most commonly (Table S4).

Cefiderocol was infrequently administered as first-line therapy, and it was used mainly following reported resistance and treatment failure with all other tested antibiotics (Table 2). Cefiderocol combination treatment was given to between 40.0% and 87.5% of patients (the latter for Bcc) (Table 2). Concomitant antibiotics included mainly trimethoprim-sulfamethoxazole, colistin, tigecycline and ceftazidime-avibactam (Table S5). The median duration of cefiderocol treatment across pathogen types was 8.0–10.0 days (Table 2).

Outcomes

The clinical cure rate was 70.0% for *S. maltophilia* infections and 71.4% for infections caused by other non-fermenting Gram-negative bacteria, including rates of 62.5% for patients with Bcc and 80.0% for patients with *Achromobacter* spp. infections (Table 3). For 11 patients specifically with respiratory tract infections caused by *S. maltophilia*, the clinical cure rate was 63.6% (7/11). The mortality rate for patients with infections caused by *S. maltophilia* was 30.0% (Table 3), and 36.4% (4/11) in the 11 patients with *S. maltophilia* respiratory tract infections.

Table 3 Clinical cure at end of treatment, all-cause mortality and clinical success rates by Gram-negative bacterial species

	Overall	*S. maltophilia*	Other non-fermenting Gram-negative bacteria		
	N=261[a]	*N*=20	Total *N*=14[b]	Bcc *N*=8	*Achromobacter* spp. *N*=5
Clinical cure, *n* (%)	210 (80.5)	14 (70.0)	10 (71.4)	5 (62.5)	4 (80.0)
Patients with prior trimethoprim-sulfamethoxazole treatment	N/A	7/10 (70.0)	N/A	N/A	N/A
Patients without prior trimethoprim-sulfamethoxazole treatment	N/A	7/10 (70.0)	N/A	N/A	N/A
28-day mortality, *n* (%)	56 (21.5)	6 (30.0)	5 (35.7)	3 (37.5)	2 (40.0)
Patients with prior trimethoprim-sulfamethoxazole treatment	N/A	3/10 (30.0)	N/A	N/A	N/A
Patients without prior trimethoprim-sulfamethoxazole treatment	N/A	3/10 (30.0)	N/A	N/A	N/A
Clinical success, *n* (%)	220 (84.3)	14 (70.0)	10 (71.4)	5 (62.5)	4 (80.0)
Patients with prior trimethoprim-sulfamethoxazole treatment	N/A	7/10 (70.0)	N/A	N/A	N/A
Patients without prior trimethoprim-sulfamethoxazole treatment	N/A	7/10 (70.0)	N/A	N/A	N/A

Bcc, *Burkholderia cepacia* complex; N/A, not applicable; NF-GN, non-fermenting Gram-negative

[a]Published previously in reference 24

[b]One patient had *Ralstonia mannitolilytica* infection, and achieved clinical cure, clinical success and survived to Day 28; 8 patients had Bcc, 5 patients had *Achromobacter* spp

Among patients with *S. maltophilia* infections, prior trimethoprim-sulfamethoxazole treatment did not influence rates of clinical cure and mortality (Table 3).

One patient with *R. mannitolilytica* infection achieved clinical cure and survived to Day 28.

Discussion

The current data provide valuable information on the effectiveness of cefiderocol treatment for infections caused by rare non-fermenting Gram-negative species in patients with immunosuppression, pulmonary conditions, or malignancies.

In this analysis, the overall clinical cure rate ranged between 62.5% and 80% and the mortality rate between 30% and 40% among the small number of patients with the various species. By comparison, in the overall population of the PERSEUS study, cefiderocol treatment administered for a median of 10 days was highly effective, with a clinical cure rate of 80.5% and overall mortality rate of 21.5% [24]. It is worth noting that this subset of patients had clinical characteristics suggestive of more serious illness relative to the overall study population, which was confirmed by the very long hospitalisation periods and high rates of ICU admission and mechanical ventilation.

As expected in the early access programme, cefiderocol was initiated either because of resistance or treatment failure with other available antibiotics [24]. Cefiderocol treatment duration in these patients with rare non-fermenting Gram-negative infections was similar to that reported in the overall population and in patients with *Pseudomonas* spp. infections in the PERSEUS study, and followed lengthy prior treatment (median 6.3–12.5 days), with the majority of patients receiving prior antibiotics for >7 days. The relatively greater frequency of cefiderocol use in combination with other agents in this subgroup of patients, compared with the overall population, was expected given the challenging nature of these non-fermenting bacteria (particularly Bcc) and it is highlighted in the current treatment guidelines for *S. maltophilia* [5, 7, 17–19].

There are limited treatment options for *S. maltophilia* as it is intrinsically resistant to carbapenems and other beta-lactam antibiotics [2, 3]. The relatively low in vitro susceptibility (≤62.5%) to trimethoprim-sulfamethoxazole among tested *S. maltophilia* isolates in the present study, compared with previous findings from Spain [25], may have been due in part to the highly select nature of the patients, having prolonged hospitalisation and failure of several previous antibiotic regimens. Data from multinational surveillance studies showed that a significant proportion of Bcc isolates were resistant to ciprofloxacin, meropenem and tigecycline, while susceptibility rates ranged between 75.6% for minocycline and 98.5% for meropenem-vaborbactam [14]. Across 267 *Achromobacter* spp. isolates from patients with cystic fibrosis, of which nearly 50% were resistant to meropenem, antibiotic susceptibility rates ranged between 0% and 70% by EUCAST breakpoints [18] and only ceftazidime-avibactam (62%) and piperacillin-tazobactam (70%) showed susceptibility rates >50% [13].

There is limited data on the clinical efficacy of other antibiotics, with evidence largely confined to retrospective analyses and case reports. In these studies, in-hospital or 30-day mortality rates were reported as 5–56% with minocycline, 7–15% with fluoroquinolones, and 15–87% with trimethoprim-sulfamethoxazole [26–30]. In comparison with these reports, 28-day mortality rates were found to be within this range in patients in this subgroup analysis.

In the current cohort, most isolates with available reported susceptibility information were resistant to meropenem and other beta-lactam antibiotics, although a few *S. maltophilia* isolates were reported to be susceptible to minocycline, trimethoprim-sulfamethoxazole, and levofloxacin; these proportions were similar to those observed in global studies [14, 15]. It was demonstrated previously that cefiderocol had potent in vitro activity against Bcc and *Achromobacter* spp., including carbapenem-resistant strains, with the lowest MIC_{90} values across a range of antibiotic agents tested [14, 22]. Previous case reports and case series with cefiderocol involving nosocomial pneumonia, haemorrhagic pneumonia and/or bloodstream infections, and peri-prosthetic joint infections caused by *S. maltophilia*, including multidrug-resistant strains, included paediatric and adult patients with haematological malignancies, neutropenia and end-stage renal disease in whom prior antibiotic therapy had often failed [31–36]. Switching to cefiderocol monotherapy or adding cefiderocol in combination with trimethoprim-sulfamethoxazole and/or levofloxacin led to clinical improvement and microbiological eradication in most patients [31–36]. Cefiderocol-based treatment has demonstrated clinical activity against infections caused by Bcc or *Achromobacter xylosoxidans* in patients with CF and haematological malignancies, including recurrent pulmonary exacerbations, persistent bacteraemia and endocarditis, with reassuring clinical outcomes, including improved pulmonary function and high survival rates at 6 months [37–41].

In the above-mentioned real-world cases, patients infected with *S. maltophilia*, Bcc and *Achromobacter* spp. had similar clinical characteristics, risk factors, infection diagnoses and prior treatment failure to those described in the current cohort, supporting the effectiveness and activity of cefiderocol against these rare non-fermenters and the relatively high clinical cure rates in the PERSEUS study.

Based on global susceptibility results, in vivo preclinical findings and PK/PD standards, cefiderocol is currently recommended in the IDSA treatment guidance for the treatment of patients with infections caused by *S. maltophilia* in combination with other antibiotic agents to which this pathogen is susceptible [18]. Currently, there are no standard-of-care recommendations for infections caused by *Burkholderia* spp. or *Achromobacter* spp., and treatments are limited to those antibiotics that show in vitro activity in hospital laboratory testing.

Conclusions

This small cohort of patients treated with cefiderocol comprised a complicated, critically ill population who were frequently chronically colonised by the same pathogen, and had underlying complex conditions, often linked with immunosuppressed status. In this scenario, our results support the current guidelines suggesting that cefiderocol is an appropriate alternative agent for infections caused by *S. maltophilia*, Bcc and *Achromobacter* spp., particularly when options are limited.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10096-025-05109-5.

Acknowledgements Editorial and medical writing support was provided by Adrienn Kis and Rhian Harper Owen, Highfield, Oxford, United Kingdom, and this support was sponsored by Shionogi & Co., Ltd., Osaka, Japan.

Author contributions J.S., A.J.G.C., S.V., A.K. contributed to study design, data collection, and data analyses. J.T.C., R.F., C.D.L.F.M., A.S. contributed to the data collection. All authors have contributed to the interpretation of the data, drafting, reviewing of the manuscript and approved the final version for submission.

Funding The study was funded by Shionogi & Co., Ltd., Osaka, Japan.

Data availability Data analysed in the current analysis are not publicly available. At reasonable requests, data can be shared with investigators and researchers according to Shionogi's clinical trial data sharing policy. This policy can be found at: https://www.shionogi.com/global/en/company/policies/shionogi-group-clinical-trial-data-transparency-policy.html.

Declarations

Ethics approval The study was approved by the institutional review board of Hospital La Princesa, Madrid, on 3 November 2020 (Royal Decree 957/2020), which served as central reference ethics committee. The study was compliant with all legal and regulatory requirements, the International Conference on Harmonisation Good Clinical Practice E6 guidelines and the Declaration of Helsinki.

Consent to participate In accordance with Spanish regulations, patient consent was waived due to the retrospective design of the study as patients completed their treatment prior to study initiation; therefore, the study represented no harm for the participants.

Consent to publish Not applicable.

Competing interests Julian Torre-Cisneros has received educational grants and fee for advisory activities from Shionogi, Pfizer, MSD, Menarini; and unrestricted research grants from Pfizer and MSD. Alex Soriano has received honoraria for lectures and advisory boards from Shionogi, Pfizer, Menarini, Angelini, Advance Pharma and Gilead, and grants from Pfizer and Gilead. Ricard Ferrer has received honoraria for lectures from Gilead, Menarini, MSD, Shionogi, and ThermoFisher; consulting fees from Cytosorbent, Inoterm, and Pfizer; and holds stocks or stock options from Grifols. Carmen De La Fuente Martos received honoraria from Shionogi & Co., Ltd., Osaka, Japan, for participation in this study. Jessica Sarda, A. Javier Gonzalez Calvo, Stefano Verardi, Andreas Karas are employees of Shionogi.

References

1. Koulenti D, Vandana KE, Rello J (2023) Current viewpoint on the epidemiology of nonfermenting Gram-negative bacterial strains. Curr Opin Infect Dis 36(6):545–554. https://doi.org/10.1097/QCO.0000000000000977
2. Mojica MF, Bonomo RA, van Duin D (2023) Treatment approaches for severe *Stenotrophomonas maltophilia* infections. Curr Opin Infect Dis 36(6):572–584. https://doi.org/10.1097/QCO.0000000000000975
3. Brooke JS (2021) Advances in the microbiology of *Stenotrophomonas maltophilia*. Clin Microbiol Rev 34(3):e0003019. https://doi.org/10.1128/CMR.00030-19
4. Rhodes KA, Schweizer HP (2016) Antibiotic resistance in *Burkholderia* species. Drug Resist Updat 28:82–90. https://doi.org/10.1016/j.drup.2016.07.003
5. Guerci P, Bellut H, Mokhtari M, AZUREA research network et al (2019) Outcomes of *Stenotrophomonas maltophilia* hospital-acquired pneumonia in intensive care unit: a nationwide retrospective study. Crit Care 23(1):371. https://doi.org/10.1186/s13054-019-2649-5
6. Murray S, Charbeneau J, Marshall BC, LiPuma JJ (2008) Impact of *Burkholderia* infection on lung transplantation in cystic fibrosis. Am J Respir Crit Care Med 178(4):363–371. https://doi.org/10.1164/rccm.200712-1834OC
7. van den Bogaart L, Manuel O (2022) Antibiotic therapy for difficult-to-treat infections in lung transplant recipients: a practical approach. Antibiotics (Basel) 11(5):612. https://doi.org/10.3390/antibiotics11050612
8. Billiot CE, Novak L, McDaniel MS, Lindgren NR, Swords WE (2023) Pathogenesis of *Achromobacter xylosoxidans* respiratory infections: colonization, persistence, and transcriptome profiling in synthetic cystic fibrosis sputum medium. Infect Immun 91(12):e0041623. https://doi.org/10.1128/iai.00416-23
9. Daccò V, Alicandro G, Consales A et al (2023) Cepacia syndrome in cystic fibrosis: a systematic review of the literature and possible new perspectives in treatment. Pediatr Pulmonol 58(5):1337–1343. https://doi.org/10.1002/ppul.26359
10. Garrigos T, Dollat M, Magallon A et al (2022) Distribution of *Achromobacter* species in 12 French cystic fibrosis centers in 2020 by a retrospective MALDI-TOF MS spectrum analysis. J Clin Microbiol 60(6):e0242221. https://doi.org/10.1128/jcm.02422-21
11. Özer S, Akin M, Yasti AC (2023) A rare bacteremia in a burn patient: a case report of *Achromobacter xylosoxidans* and *denitrificans*. Cureus 15(9):e45909. https://doi.org/10.7759/cureus.45909
12. Shen BJ, Wang JT, Chang HT, Chang SC, Liao CH (2023) Single-center experience of control of ventilator-circuit-transmitted *Burkholderia cepacia* outbreak in an intensive care unit. Trop Med Infect Dis 8(7):335. https://doi.org/10.3390/tropicalmed8070335
13. Olbrecht M, Echahidi F, Piérard D et al (2023) In vitro susceptibility of *Achromobacter* species isolated from cystic fibrosis patients: a 6-year survey. Antimicrob Agents Chemother 67(7):e0037923. https://doi.org/10.1128/aac.00379-23
14. Takemura M, Nakamura R, Ota M et al (2023) In vitro and in vivo activity of cefiderocol against *Achromobacter* spp. and *Burkholderia cepacia* complex, including carbapenem-non-susceptible isolates. Antimicrob Agents Chemother 67(12):e0034623. https://doi.org/10.1128/aac.00346-23
15. Pfaller MA, Shortridge D, Carvalhaes CG, Castanheira M (2023) Trends in the susceptibility of U.S. *Acinetobacter baumannii-calcoaceticus* species complex and *Stenotrophomonas maltophilia* isolates to minocycline, 2014–2021. Microbiol Spectr 11(6):e0198123. https://doi.org/10.1128/spectrum.01981-23
16. Gijón D, García-Castillo J, Fernández-López MC et al (2024) In vitro activity of cefiderocol and other newly approved antimicrobials against multi-drug resistant Gram-negative pathogens recovered in intensive care units in Spain and Portugal. Rev Esp Quimioter 37(1):69–77. https://doi.org/10.37201/req/098.2023
17. Gibb J, Wong DW (2021) Antimicrobial treatment strategies for *Stenotrophomonas maltophilia*: a focus on novel therapies. Antibiotics (Basel) 10(10):1226. https://doi.org/10.3390/antibiotics10101226
18. Tamma PD, Heil EL, Justo JA, Mathers AJ, Satlin MJ, Bonomo RA (2024) Infectious diseases society of America 2024 guidance on the treatment of antimicrobial-resistant Gram-negative infections. Clin Infect Dis ciae403. https://doi.org/10.1093/cid/ciae403
19. Cantón R, Ruiz-Garbajosa P (2023) Treatment guidelines for multidrug-resistant Gram-negative microorganisms. Rev Esp Quimioter 36(Suppl 1):46–51. https://doi.org/10.37201/req/s01.11.2023
20. Shortridge D, Streit JM, Mendes R, Castanheira M (2022) In vitro activity of cefiderocol against U.S. and European Gram-negative clinical isolates collected in 2020 as part of the SENTRY antimicrobial surveillance program. Microbiol Spectr 10(2):e0271221. https://doi.org/10.1128/spectrum.02712-21
21. Karlowsky JA, Hackel MA, Takemura M, Yamano Y, Echols R, Sahm DF (2022) In vitro susceptibility of Gram-negative pathogens to cefiderocol in five consecutive annual multinational SIDERO-WT surveillance studies, 2014 to 2019. Antimicrob Agents Chemother 66(2):e0199021 https://doi.org/10.1128/aac.01990-21. Erratum in: (2023) Antimicrob Agents Chemother 67(6):e0042723 https://doi.org/10.1128/aac.00427-23
22. Jean-Pierre V, Sorlin P, Pantel A, Collaborative study group on antimicrobial resistance of *Achromobacter* spp. et al (2024) Cefiderocol susceptibility of *Achromobacter* spp.: study of an accurately identified collection of 230 strains. Ann Clin Microbiol Antimicrob 23(1):54 https://doi.org/10.1186/s12941-024-00709-z
23. Tunney MM, Elborn JS, McLaughlin CS, Longshaw CM (2024) In vitro activity of cefiderocol against Gram-negative pathogens isolated from people with cystic fibrosis and bronchiectasis. J Glob Antimicrob Resist 36:407–410. https://doi.org/10.1016/j.jgar.2024.01.023
24. Torre-Cisneros J, Almirante B, de la Fuente MartosC et al (2025) Real-world effectiveness and safety of Cefiderocol treatment in patients with Gram-negative bacterial infections in Spain in the early access programme: results of the PERSEUS study. Eur J Clin Microbiol & Infect Dis. https://doi.org/10.1007/s10096-025-05108-6
25. Delgado-Valverde M, Conejo MDC, Serrano L, Fernández-Cuenca F, Pascual Á (2020) Activity of cefiderocol against

high-risk clones of multidrug-resistant Enterobacterales, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*. J Antimicrob Chemother 75(7):1840–1849. https://doi.org/10.1093/jac/dkaa117
26. Sarzynski SH, Warner S, Sun J et al (2022) Trimethoprim-sulfamethoxazole versus levofloxacin for *Stenotrophomonas maltophilia* infections: a retrospective comparative effectiveness study of electronic health records from 154 US hospitals. Open Forum Infect Dis 9(2):ofab644 https://doi.org/10.1093/ofid/ofab644. Erratum in: (2023) Open Forum Infect Dis 10(4):ofad198 https://doi.org/10.1093/ofid/ofad198
27. Boonmee P, Nasomsong W, Lorchirachoonkul N et al (2023) The activities of antimicrobials against *Stenotrophomonas maltophilia* isolates and evaluation of clinical outcomes among treatment regimens in patients with *Stenotrophomonas maltophilia* infections: A retrospective multicenter cohort study. Infect Drug Resist 16:5173–5184. https://doi.org/10.2147/IDR.S416678
28. Hevia EC, Wooten L, Carr AL (2024) Trimethoprim/sulfamethoxazole vs minocycline for the treatment of nonurinary monomicrobial *Stenotrophomonas maltophilia* infections in hospitalized patients. Ann Pharmacother 58(7):698–704. https://doi.org/10.1177/10600280231201850
29. Junco SJ, Bowman MC, Turner RB (2021) Clinical outcomes of *Stenotrophomonas maltophilia* infection treated with trimethoprim/sulfamethoxazole, minocycline, or fluoroquinolone monotherapy. Int J Antimicrob Agents 58(2):106367. https://doi.org/10.1016/j.ijantimicag.2021.106367
30. Kim EJ, Kim YC, Ahn JY et al (2019) Risk factors for mortality in patients with *Stenotrophomonas maltophilia* bacteremia and clinical impact of quinolone-resistant strains. BMC Infect Dis 19(1):754. https://doi.org/10.1186/s12879-019-4394-4
31. Chambers MM, Gutowski CJ, Doktor K (2023) Cefiderocol for *Stenotrophomonas maltophilia* prosthetic joint infection: a case report. Ther Adv Infect Dis 10:20499361231174292. https://doi.org/10.1177/20499361231174292
32. Hsu AJ, Simner PJ, Bergman Y, Mathers AJ, Tamma PD (2023) Successful treatment of persistent *Stenotrophomonas maltophilia* bacteremia with cefiderocol in an infant. Open Forum Infect Dis 10(4):ofad174. https://doi.org/10.1093/ofid/ofad174
33. Lupia T, Carnevale-Schianca F, Vita D et al (2024) *Stenotrophomonas maltophilia* infections in haematological malignancies and hematopoietic stem cell transplantation: a case series including cefiderocol-based regimens. Med (Kaunas) 60(1):88. https://doi.org/10.3390/medicina60010088
34. Medioli F, Casali E, Viscido A, Pistolesi V, Venditti M, Oliva A (2023) First case of persistent *Stenotrophomonas maltophilia* bacteraemia due to septic thrombosis successfully treated with a cefiderocol-containing regimen. J Glob Antimicrob Resist 34:5–8. https://doi.org/10.1016/j.jgar.2023.05.013
35. Rashid MH, Bukhari SNY, Mousa A, Aziz AA, Hakobyan K (2023) Cefiderocol as a treatment option for *Stenotrophomonas maltophilia* causing hospital-acquired/ventilator-associated pneumonia. Cureus 15(5):e38613. https://doi.org/10.7759/cureus.38613
36. Zappulo E, Grimaldi F, Paolillo R, et al (2022) Successful treatment of MDR *Stenotrophomonas maltophilia*-associated pneumonia with cefiderocol-based regimen in a patient with hematological malignancy. Ann Hematol 101(12):2805–2806. https://doi.org/10.1007/s00277-022-05006-3
37. Bodro M, Hernández-Meneses M, Ambrosioni J et al (2021) Salvage treatment with cefiderocol regimens in two intravascular foreign body infections by MDR Gram-negative pathogens, involving non-removable devices. Infect Dis Ther 10(1):575–581. https://doi.org/10.1007/s40121-020-00385-4
38. Gainey AB, Burch AK, Brownstein MJ, et al (2020) Combining bacteriophages with cefiderocol and meropenem/vaborbactam to treat a pan-drug resistant *Achromobacter* species infection in a pediatric cystic fibrosis patient. Pediatr Pulmonol 55(11):2990–2994. https://doi.org/10.1002/ppul.24945
39. La Bella G, Salvato F, Minafra GA et al (2022) Successful treatment of aortic endocarditis by *Achromobacter xylosoxidans* with cefiderocol combination therapy in a non-Hodgkin lymphoma patient: case report and literature review. Antibiotics(Basel) 11(12):1686. https://doi.org/10.3390/antibiotics11121686
40. Nye C, Duckers J, Dhillon R (2022) Cefiderocol to manage chronic, multi-drug-resistant *Burkholderia cepacia* complex infection in a patient with cystic fibrosis: a case report. Access Microbiol 4(10):acmi000413. https://doi.org/10.1099/acmi.0.000413
41. Warner NC, Bartelt LA, Lachiewicz AM, et al (2021) Cefiderocol for the treatment of adult and pediatric patients with cystic fibrosis and *Achromobacter xylosoxidans* infections. Clin Infect Dis 73(7):e1754–e1757. https://doi.org/10.1093/cid/ciaa1847