Infect Dis Ther (2025) 14:657–669
https://doi.org/10.1007/s40121-025-01117-2

CASE SERIES

Cefiderocol for the Treatment of Nosocomial Bloodstream Infections Caused by *Stenotrophomonas maltophilia*: A Case Series and Literature Review

Antonio Vena · Laura Mezzogori · Nadia Castaldo · Silvia Corcione · Renato Pascale · Maddalena Giannella · Simone Mornese Pinna · Daniele Roberto Giacobbe · Davide Fiore Bavaro · Vincenzo Scaglione · Benedetta Fumarola · Gabriele Pagani · Francesco Giuseppe De Rosa · Michele Bartoletti · Matteo Bassetti · SITA GIOVANI (Young Investigators Group of the Società Italiana Terapia Antinfettiva)

Received: December 23, 2024 / Accepted: February 10, 2025 / Published online: March 4, 2025

ABSTRACT

***Introduction*:** The treatment of *Stenotrophomonas maltophilia* bloodstream infections (BSI) remains challenging due to the organism's intrinsic multidrug resistance and the potential side effects of commonly used first-line antibiotics.

***Methods*:** Here, we describe four cases of *S. maltophilia* BSI treated with cefiderocol (≥ 72 h) in different Italian hospitals. Additionally, we conducted a PubMed search to identify other studies reporting cases of *S. maltophilia* BSI managed with cefiderocol.

***Results*:** We reviewed a total of 8 cases of *S. maltophilia* BSI [median age 52.5 years (Q1–Q3 27.5–61.0), 50% males] treated with cefiderocol, including ours. BSI sources were mainly central venous catheters (62.5%) and the lower respiratory tract (25.0%). Cefiderocol was used as first-line therapy in 87.5% of patients (7/8), with a median treatment duration of 14 days

Laura Mezzogori and Nadia Castaldo are equal contributors.

Members of the OPERA SITA GIOVANI study group are listed in the Acknowledgements section.

A. Vena (✉) · L. Mezzogori · D. R. Giacobbe · M. Bassetti
Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy
e-mail: anton.vena@gmail.com

A. Vena · L. Mezzogori · D. R. Giacobbe · M. Bassetti
Infectious Disease Unit, IRCCS San Martino Polyclinic Hospital, Genoa, Italy

N. Castaldo
Department of Pulmonology, University of Udine and Azienda Sanitaria Universitaria Integrata di Udine, Udine, Italy

S. Corcione · S. M. Pinna · F. G. De Rosa
Department of Medical Sciences, Infectious Diseases, University of Turin, Turin, Italy

S. Corcione
Department of Infectious Diseases, Tufts University School of Medicine, Boston, MA, USA

R. Pascale · M. Giannella
Infectious Diseases Unit, IRCCS-Sant'Orsola Polyclinic, Bologna, Italy

R. Pascale · M. Giannella
Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

D. F. Bavaro
Clinic of Infectious Diseases, Department of Precision and Regenerative Medicine and Ionian Area, University of Bari "Aldo Moro", Bari, Italy

D. F. Bavaro · M. Bartoletti
Infectious Disease Unit, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

D. F. Bavaro · M. Bartoletti
Department of Biomedical Sciences, Humanitas University, Milan, Italy

(IQR 6.2–16.0). Combination therapy was administered in 62.5% of cases. Infection source control was required in 75.0% and achieved in 40.0%. Clinical success was observed in 62.5% of patients, with microbiological eradication in 87.5%. In-hospital mortality occurred in 37.5% of cases, with one death directly attributable to *S. maltophilia*. No significant differences were observed in terms of outcomes between cefiderocol monotherapy and combination therapy. ***Conclusions***: Based on our findings and a review of the literature, cefiderocol-based regimens show promise as an effective treatment option for *S. maltophilia* BSI, warranting further investigation in larger studies.

Keywords: *Stenotrophomonas maltophilia*; Bloodstream infections; Multidrug resistance; Cefiderocol

Key Summary Points

We reviewed 8 cases of *S. maltophilia* bloodstream infections, including 4 new cases treated with cefiderocol.

Central venous catheters (62.5%) and lower respiratory tract (25.0%) were primary infection sources; source control was achieved in 40.0%.

Cefiderocol was used as first-line therapy in 87.5%, achieving clinical success in 62.5% and microbiological eradication in 87.5%.

In-hospital mortality was 37.5%, with no outcome differences between monotherapy and combination therapy.

Cefiderocol shows promise as an effective treatment option for *S. maltophilia* BSI.

V. Scaglione
Infectious and Tropical Diseases Unit, Padua University Hospital, Padua, Italy

B. Fumarola
Unit of Infectious and Tropical Diseases, Department of Clinical and Experimental Sciences, University of Brescia and ASST Spedali Civili Di Brescia, Brescia, Italy

G. Pagani
Infectious Diseases Unit, Ospedale Nuovo di Legnano, ASST Ovest Milanese, Legnano, Italy

INTRODUCTION

Stenotrophomonas maltophilia is an opportunistic pathogen that predominantly causes nosocomial bloodstream infections (BSI) and pneumonia [1, 2] in critically ill and immunocompromised patients [3–5]. Over the last decade, it has been reported as a leading cause of carbapenem-resistant Gram-negative BSI in the USA [6], with a mortality rate of around 20%, reaching as high as 69% in some studies [3, 7].

Due to the presence of both intrinsic and acquired antibiotic resistance mechanisms [8–13], therapeutic options for *S. maltophilia* BSI are mainly limited to trimethoprim–sulfamethoxazole (TMP-SMX) [14], fluoroquinolones, tetracyclines, and glycylcyclines. However, these agents are not without drawbacks, including high rates of allergy [15], resistance [16, 17], side effects [18–20], and challenges in achieving pharmacodynamic targets [21]. Recently, cefiderocol, a novel siderophore cephalosporin, was approved by the Food and Drug Administration (FDA) for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria, including *S. maltophilia* [22]. However, this approval was based on randomized clinical trials that included only six patients with *S. maltophilia* infections [23, 24], none of whom had BSI.

To date, very few published observational case reports have provided data on the efficacy of cefiderocol in treating *S. maltophilia* BSI with promising results [25–27]. Nevertheless, experience in using cefiderocol for these infections remains limited. Therefore, clinical data to guide and support the use of this novel antibiotic in *S. maltophilia* BSI are urgently needed. The purpose of this study is to present a series of four consecutive patients treated with cefiderocol for

S. maltophilia BSI and to review published studies involving patients with *S. maltophilia* BSI.

METHODS

In the present report, we focus on four patients who had BSI caused by *S. maltophilia* and were treated (≥ 72 h) with cefiderocol. These patients are a part of a retrospective cohort study conducted from 1 January 2021 to 31 December 2022 across 14 hospitals in Italy. The study aimed to assess the impact of current Infectious Disease Society of America (IDSA) guidelines recommendations on the clinical outcome of patients with *S. maltophilia* BSI [28]. Detailed analysis of the complete cohort results is currently underway.

Bibliographic Research

To identify clinical reports of patients with *S. maltophilia* BSI receiving cefiderocol treatment beyond the setting of clinical trials, we searched Embase and Medline for all English written reports published up to 18 March 2024, using the search terms "cefiderocol" or "S-649266" AND "*Stenotrophomonas maltophilia*". This study only included reports detailing patients aged 18 years and above who were treated with cefiderocol for a minimum of 72 h due to BSI caused by *S. maltophilia*.

Definitions

Patient outcomes were classified as either clinical success or failure at the end of the follow-up period. This period began on the index date and concluded on the date of death or the last documented clinical visit up to October 2024 for our four patients. For cases sourced from the medical literature, follow-up ended as per the clinical details provided in the respective reports.

A successful clinical outcome was defined as the complete resolution of signs and symptoms attributable to *S. maltophilia* infection, without the need for additional antibiotic therapy targeting *S. maltophilia* during the follow-up period, except when de-escalation therapy was required. Microbiological resolution was evaluated only for patients with a follow-up blood culture and was defined as obtaining negative follow-up cultures during cefiderocol therapy. Clinical failure was defined as an absence of clinical response, recurrence, and/or all-cause in-hospital mortality.

Microbiological Procedures

The identification of *S. maltophilia* and in vitro antibiotic susceptibility testing were performed at participating hospitals using local routine methods. Susceptibility patterns were reported according to the 2023 EUCAST recommendations or, for antibiotics without EUCAST recommendations (e.g., levofloxacin, chloramphenicol), the 2023 CLSI Performance Standards.

Cefiderocol Administration

Cefiderocol was administered according to the prescribing information at a dosage of 2 g intravenous over 3 h repeated every 8 h. Dose adjustments were required only for patients with moderate to severe renal dysfunction [creatinine clearance (CLCr) < 60 mL/min] or for those with augmented renal clearance (CLCr ≥ 120 mL/min).

Ethics

The study was approved by the institutional review board of the coordinating center (Comitato Etico interaziendale, City of Health and Sciences, Turin, pratica no. 202/2023, PROT.N. 0066633) and was conducted in accordance with the Declaration of Helsinki. Informed consent was deemed unnecessary due to the retrospective nature of the study. STROBE recommendations were followed.

RESULTS

Clinical Cases of *S. maltophilia* BSI Treated with Cefiderocol

Case 1. A 47-year-old female with no significant medical history was admitted to the intensive

care unit (ICU) due to viral myocarditis complicated by cardiogenic shock and hemophagocytic lymphohistiocytosis. She received immunosuppressive therapy with high-dose steroids, etoposide, and cyclosporine. On the 60th day of hospitalization, she developed central venous catheter (CVC)-related BSI caused by *S. maltophilia*. She was treated with cefiderocol plus levofloxacin for 3 days, and her CVC was also removed. Empirical antibiotic therapy was switched to TMP-SMX, which was administered for additional 14 days. No significant adverse events were reported during treatment, and negativization of the blood cultures was achieved after the first 2 days of antimicrobial therapy with cefiderocol plus levofloxacin. The patient was discharged after 215 days with no reported infection relapse.

Case 2. An 82-year-old female patient presented to the emergency department with complaints of melena and rectal bleeding. Her medical history revealed a diagnosis of acute lymphoblastic leukemia undergoing treatment with imatinib, previous breast cancer treated with chemotherapy, and severe aortic stenosis. Following a nearly month-long hospitalization in the medical unit, she was diagnosed with a CVC-related BSI caused by *S. maltophilia*. Initially, she received empirical treatment with piperacillin/tazobactam for 3 days, which was subsequently switched to cefiderocol for 7 days based on microbiological identification. Follow-up blood cultures were negative for *S. maltophilia* after 3 days of cefiderocol therapy. Her hospital stay lasted a total of 43 days. At the time of discharge, there were no clinical signs of recurrent infection, and blood cultures remained negative.

Case 3. A 21-year-old man was admitted to the hospital due to extensive burns covering 90% of his body surface. On the 70th day of hospitalization, he developed sepsis, and blood cultures revealed the presence of *S. maltophilia*. He received a 14-day course of combination therapy with cefiderocol and TMP-SMX. Additionally, he underwent multiple surgical debridements to excise infected necrotic tissue. Microbiological eradication was successfully achieved after 7 days of antibiotic treatment, and no infection relapses were reported. Unfortunately, he succumbed to his critical condition on the 91st day of admission.

Case 4. An 18-year-old man was admitted to the hospital for an allogeneic hematopoietic stem cell transplant due to refractory T-cell lymphoblastic lymphoma. On the 47th day of his hospitalization, while in a neutropenic phase, he developed a CVC-related BSI caused by *S. maltophilia*. Initial treatment with cefiderocol monotherapy was initiated, but removal of the vascular catheter was not feasible. Unfortunately, the patient passed away on the 4th day of treatment. Follow-up blood cultures were not performed.

Cumulative Summary of Our Cases and Published Cases in the Medical Literature

A systematic PubMed search identified five cases of *S. maltophilia* BSI treated with cefiderocol [25–27, 29]. However, one case was excluded due to the patient being a newborn (5 weeks old) [25]. This resulted in a total of eight cases reviewed, including the four cases from our cohort. The clinical characteristics of the study population are summarized in Table 1.

Patient Demographics

Patients' age ranged from 18 to 82 years (median 52.5 years; Q1–Q3 27.5–61.0), with 50.0% being male. Cardiovascular disease was the most common underlying condition (66.7%, 4 out of 6 patients for whom information was available), followed by onco-hematological disease (50.0%, 4 out of 8). Multiple underlying conditions were present in 50.0% of the cases, and the median Charlson comorbidity index, calculated for 6 out of 8 cases, was 3.5 (Q1–Q3 0.5–5.8). At the onset of *S. maltophilia* BSI, 87.5% of patients (7 out of 8) had a CVC in place, and 75.0% (6 out of 8) had a urinary bladder catheter (Table 1).

Infection Sources and Pathogen Profile

The most frequent infection sources were the CVC (5/8; 62.5%) and the lower respiratory tract (2/8; 25.0%). The remaining patient had

Table 1 Baseline characteristics and clinical outcomes of the study population following treatment with cefiderocol

	Study population (*n* = 8; *n*/*N*)
Median age, (Q1–Q3)[a]	52.5 (27.5–61.0)
Male gender[a]	3/6 (50.0%)
Hospital ward admission[a]	
Intensive care unit	3/6 (50.0%)
Internal medicine	1/6 (16.7%)
Onco-haematology unit	1/6 (16.7%)
Other	1/6 (16.7%)
Underlying disease	
Cardiovascular disease[a]	4/6 (66.7%)
Onco-hematologic disease	4/8 (50.0%)
Chronic kidney disease[a]	3/6 (50.0%)
Hematopoietic stem cell transplantation	1/8 (12.5%)
Solid organ transplant	1/8 (12.5%)
Diabetes[a]	1/6 (16.7%)
Neurological disease[a]	1/6 (16.7%)
Gastrointestinal disease[a]	1/6 (16.7%)
Median Charlson Comorbidity Index, (Q1–Q3)[a]	3.5 (0.5–5.8)
Predisposing conditions	
Central venous catheter	7/8 (87.5%)
Urinary bladder catheter	6/8 (75.0%)
Continuous renal replacement therapy	2/8 (25.0%)
Intermittent hemodialysis	1/8 (12.5%)
Surgery, within previous month	1/8 (12.5%)
Source of infection	
CVC-related BSI	5/8 (62.5%)
HAP/VAP	2/8 (25.0%)
Burn infection	1/8 (12.5%)
Presentation with sepsis/septic shock[a]	4/6 (66.7%)
Cefiderocol treatment	
First line therapy[b]	7/8 (87.5%)
Combination therapy	5/8 (62.5%)
Length of treatment, days (median, interquartile range)	14 (6.2–16.0)
Need for ICU admission for *S. maltophilia* infection[c]	0/3 (0%)
Successful clinical outcome	5/8 (62.5%)
Clinical failure[d]	3/8 (37.5%)
Microbiological failure	0/7 (0%)
Length of hospital stay (days), median (range)	96 (30–215)

BSI Bloodstream Infection, *CVC* Central Venous Catheter, *HAP* Hospital-associated pneumonia, *VAP* ventilator-associated pneumonia

[a]Information available in 6 out of 8 patients

[b]Only molecules with activity against *S. maltophilia* were considered

[c]Information was available for six patients, three of whom were already in the ICU at the time they developed *S. maltophilia* bloodstream infections

[d]Clinical failures were due to deaths in all cases; however, only 1 out of 3 deaths was attributable to *S. maltophilia*

a BSI secondary to a burn wound infection (Table 1). Notably, 66.7% of the patients presented with sepsis or septic shock, while two patients (25.0%) had polymicrobial BSI, with one involving extended-spectrum beta-lactamase (ESBL)-producing *E. coli* and the other an unspecified pathogen. In all cases, appropriate treatment was administered based on the judgment of the attending physicians.

As for antibiotic susceptibility profiles, approximately 90.0% of *S. maltophilia* isolates (7/8) were susceptible to TMP-SMX at elevated dosages according to EUCAST criteria, while only 37.5% were reported to be susceptible to levofloxacin per CLSI guidelines (3/8).

Susceptibility data for other antibiotics with established CLSI clinical breakpoints (minocycline, ceftazidime and ticarcillin–clavulanic acid) were unavailable for our cases and in the published literature. Cefiderocol susceptibility was reported in 6 out of 8 cases; in five of these, broth microdilution was performed, whereas disk diffusion testing was used in the remaining case. Regardless of the methodology used, cefiderocol demonstrated in vitro activity against all tested isolates.

Therapeutic Approaches and Source Control

Seven of the eight patients (87.5%) received cefiderocol as first-line therapy, while one patient (12.5%) was treated with cefiderocol as a second-line option. In this case, prior antibiotic therapy included levofloxacin administered for 9 days (Table 2).

The mean duration of cefiderocol therapy was 14 days (Q1–Q3 6.2–16.0 days). Combination antibiotic therapy was given in five out of eight patients (62.5%), with TMP-SMX and levofloxacin each used in two cases (25.0%), and tigecycline in one (12.5%). Lock therapy with TMP-SMX was combined with systemic cefiderocol treatment in a single case (Table 2). Infection source control was deemed necessary in 6 patients (75.0%). Information regarding adequate source control was available in 5 out of 6 patients and it was achieved in 2 out of 5 cases (40.0%).

Clinical Outcomes Overall

Five patients (62.5%) achieved a successful clinical outcome at the end of treatment (Table 1). Follow-up blood cultures were performed in 7 of 8 patients (87.5%), with microbiological eradication achieved in all of these cases. Clinical failure occurred in three patients (37.5%) and was due to death in all cases, of which only one was attributable to *S. maltophilia* infection. There was no statistically significant difference in clinical success between those receiving cefiderocol as monotherapy versus combination therapy [66.7% (2/3) vs. 60.0% (3/5); $P = 1.0$] or as primary versus second-line therapy [57.1% (4/7) vs. 100% (1/1); $P = 1.0$].

DISCUSSION

To the best of our knowledge, this study represents the largest real-world case series investigating the use of cefiderocol for the treatment of *S. maltophilia* BSI. A notable strength of our study is that it addresses a critical gap in the literature, as patients with *S. maltophilia* BSI are often underrepresented in randomized clinical trials.

In recent years, the incidence of *S. maltophilia* BSI has been increasing, largely driven by the growing population of at-risk patients [3, 30–33]. This trend is likely attributable to advancements in cancer therapies, the increased use of invasive medical devices, and the widespread administration of broad-spectrum antibiotics [30, 31, 34]. Notably, *S. maltophilia* has emerged as the leading cause of carbapenem-resistant Gram-negative BSI in the United States, with approximately 45% of cases originating in the community [6].

In this context, therapeutic options for managing *S. maltophilia* BSI are limited to a few antibiotics, including levofloxacin, TMP-SMX, minocycline, and tigecycline [35]. However, these agents present significant limitations, including a high risk of toxicity and side effects, increasing rates of both in vitro and in vivo resistance development, and challenges in achieving optimal pharmacokinetic/pharmacodynamic targets [14–21]. Furthermore, despite multiple studies comparing various therapeutic regimens, no clinical evidence currently supports any single antibiotic as the definitive treatment for *S. maltophilia* BSI [36–41].

Cefiderocol, a catechol-substituted siderophore cephalosporin approved for the treatment of severe infections caused by Gram-negative bacilli with limited or no therapeutic options [22], has demonstrated high in vitro efficacy against *S. maltophilia*, with susceptibility rates exceeding 95–98% of isolates tested [42, 43]. Despite these promising in vitro findings, clinical experience with cefiderocol for *S. maltophilia* infections, particularly BSI, remains limited [26, 27].

Table 2 Clinical presentations, antibiotic treatment, clinical course

Patient, ref	Age (year)	Type of infection	Polymicrobial infection	Antibiotic treatment before cefiderocol	Cefiderocol susceptibility	Cefiderocol treatment	Treatment after cefiderocol	Source control potentially achievable/achieved	Microbiological eradication	In-hospital mortality	SM infection relapse
Case 1	47	CVC-BSI	No	No	Microdilution method MIC = 0.016 mg/L	Cefiderocol + levofloxacin for 3 days	TMP-SMX for 15 days	Yes (CVC removal, performed)	Yes	No	No
Case 2	82	CVC-BSI	No	Piperacillin/tazobactam for 3 days	Microdilution method MIC = 0.016 mg/L	Cefiderocol for 7 days	No	Yes (CVC removal, not performed)	Yes	No	No
Case 3	21	Wound infection in a severely burned patient	No	No	Microdilution method MIC ≤ 2 mg/L	Cefiderocol + TMP-SMX for 14 days	No	Yes, multiple surgical debridement performed	Yes	Yes	No
Case 4	18	CVC-BSI	No	No	Microdilution method MIC = 0.062 mg/L	Cefiderocol for 4 days	No	Yes (CVC removal, not performed)	Unknown	Yes	No

Table 2 continued

Patient, ref	Age (year)	Type of infection	Polymicrobial infection	Antibiotic treatment before cefiderocol	Cefiderocol susceptibility	Cefiderocol treatment	Treatment after cefiderocol	Source control potentially achievable/achieved	Microbiological eradication	In-hospital mortality	SM infection relapse
Case 5, Medioli et al. [27]	62	CVC-BSI complicated with septic thrombosis	No	Piperacillin/tazobactam + daptomycin for 2 days; levofloxacin for 9 days	Disk diffusion method MIC = 25 mm	Cefiderocol + levofloxacin for 22 days + intralock therapy with TMP-SMX for 14 days	Minocycline plus the lock therapy with TMP-SMX as a chronic suppressive therapy	Yes (CVC removal, not performed)	Yes	No	No
Case 6, Fratoni et al. [29]	58	Bacteriemic VAP	Yes; SM + ESBL-producing *E.coli*	No	Microdilution method MIC = 0.125 mg/L	Cefiderocol for 14 days + tigecycline for 10 days	No	No	Yes	Yes	No
Case 7, Lupia et al. [26]	NA	Bacteriemic HAP	No	No	Disk diffusion method, but MIC not reported	Cefiderocol for 22 days	No	No	Yes	No	No
Case 8, Lupia et al. [26]	NA	CVC-BSI	Yes; SM + isolated pathogen not specified	No	Disk diffusion method, but MIC not reported	Cefiderocol + TMP-SMX for 14 days	No	Yes (Unknown)	Yes	No	No

BSI blood stream infection, *CVC* central venous catheter, *CVC-BSI* central venous catheter reated BSI, *MIC* minimum inhibitory concentration, *NA* not available, *SM S. maltophilia*, *SSssTI*, *TMP-SMX* trimethoprim- sulfamethoxazole, *VAP* ventilator-associated pneumonia

In the APEKS-NP trial, among cefiderocol-treated patients, there was a single case of non-bacteremic pneumonia caused by *S. maltophilia* that achieved both clinical cure and microbiological eradication [24]. Conversely, in the CREDIBLE-CR trial, five patients with *S. maltophilia* infections (none of whom had bacteremia) were treated with cefiderocol, but none achieved clinical cure or microbiological eradication [23]. In the present study, which included a population of patients with multiple comorbidities, we observed significantly higher cure rates compared to the pooled results from clinical trials (1 out of 6 patients; 16%). Specifically, we achieved a clinical success rate of 70%, aligning with real-world outcomes observed for other non-fermenting microorganisms treated with cefiderocol [44–46].

In the CREDIBLE trial, all patients with *S. maltophilia* infections treated with cefiderocol had nosocomial pneumonia, and 60% of them exhibited a fourfold increase in MIC values during treatment [23]. In contrast, in our study, which exclusively included patients with BSI, no increase in cefiderocol MICs was observed as all patients with available follow-up blood cultures (7 out of 8) demonstrated microbiological clearance following cefiderocol administration. While directly comparing our findings with clinical trial data is challenging, it is important to consider that, in the context of HAP-VAP, the development of in vivo resistance could reflect exposure to subtherapeutic concentrations of cefiderocol at the pulmonary level, potentially facilitating MIC increases [47]. However, further studies are needed to explore this hypothesis in greater detail.

In our study, all clinical failures were associated with all-cause in-hospital mortality, with no evident benefit observed for combination therapy over monotherapy or for first-line therapy compared to subsequent treatments. Notably, even when applying a broader mortality criterion (in-hospital mortality) that included patients who died more than 3 months after the diagnosis of bacteremia, the mortality rate in our cohort remained lower than the approximately 60% reported in the literature [3, 30–33]. However, accurately attributing mortality directly to *S. maltophilia* BSI is challenging, as these infections may act more as an indicator of patient severity rather than a primary cause of death [3, 30–33]. This hypothesis is further supported by the clinical profiles of the three patients who died in our study, all of whom had critical underlying conditions, including severe burn injuries, terminal-stage oncohematologic diseases, and prolonged intensive care unit stays.

In our study, cefiderocol was administered for a duration of up to 22 days. Although we did not specifically address safety issues, none of the patients required treatment discontinuation due to adverse events, confirming the drug's good tolerability, consistent with findings from previous studies [23, 24].

This study has several limitations. The most significant is the small sample size, as we were able to include only eight patients, which limits the generalizability of our conclusions. Second, the decision to initiate cefiderocol therapy, the use of concomitant antibiotics, and the duration of treatment were determined by the treating physicians rather than predefined criteria. This lack of uniformity may complicate the interpretation of cefiderocol's role in the treatment of BSI. Third, although four patients were derived from a large retrospective database, the remaining four were included from previously published studies, introducing the potential for publication bias. Additionally, the retrospective nature of the data collection and the reliance on case reports from existing literature result in significant gaps in information, including details of patients' medical histories and susceptibility profiles of the isolates. For example, MIC values were not reported for most cases. Lastly, the follow-up duration was inconsistent and limited to only a few days after cefiderocol withdrawal, which may have hindered the detection of recurrences or the evaluation of the long-term effects of treatment in this population.

CONCLUSIONS

The results of our analysis support the use of cefiderocol as an effective therapeutic option for managing BSI caused by multidrug-resistant *S. maltophilia,* including in frail, critically ill, or

medically unstable patients. However, larger studies addressing the role of combination therapy are needed.

ACKNOWLEDGEMENTS

Members of the OPERA SITA GIOVANI study group: Accurso Giuseppe; Bavaro Davide Fiore; Chiappetta Stefania; Faliero Domenico; Fumarola Benedetta; Geremia Nicholas; Giovannenze Francesca; Maccaro Angelo; Marino Andrea; Merli Marco; Pagani Gabriele; Sardanelli Alessia; Scaglione Vincenzo; Tontodonati Monica; Vassia Veronica. Accurso Giuseppe, Bavaro Davide Fiore, Chiappetta Stefania, Faliero Domenico, Fumarola Benedetta, Geremia Nicholas, Giovannenze Francesca, Maccaro Angelo, Marino Andrea, Merli Marco, Pagani Gabriele, Sardanelli Alessia, Scaglione Vincenzo, Tontodonati Monica, Vassia Veronica

Author Contributions. Conceptualization: Antonio Vena, Matteo Bassetti; Methodology: Antonio Vena, Laura Mezzogori, Nadia Castaldo, Silvia Corcione, Renato Pascale; formal analysis: Antonio Vena, Laura Mezzogori, Nadia Castaldo, Silvia Corcione, Renato Pascale; Data curation: Antonio Vena, Laura Mezzogori, Nadia Castaldo, Silvia Corcione, Renato Pascale, Maddalena Giannella, Simone Mornese Pinna, Daniele Roberto Giacobbe, Davide Fiore Bavaro, Vincenzo Scaglione, Benedetta Fumarola, Gabriele Pagani, Francesco Giuseppe De Rosa, Michele Bartoletti, Matteo Bassetti Curation: Antonio Vena, Laura Mezzogori, Nadia Castaldo, Silvia Corcione, Renato Pascale, Maddalena Giannella, Simone Mornese Pinna, Daniele Roberto Giacobbe, Davide Fiore Bavaro, Vincenzo Scaglione, Benedetta Fumarola, Gabriele Pagani, Francesco Giuseppe De Rosa, Michele Bartoletti, Matteo Bassetti; Writing—original draft preparation: Antonio Vena, Laura Mezzogori, Nadia Castaldo, Silvia Corcione; Writing—review and editing: Antonio Vena, Laura Mezzogori, Nadia Castaldo, Silvia Corcione, Renato Pascale, Maddalena Giannella, Simone Mornese Pinna, Daniele Roberto Giacobbe, Davide Fiore Bavaro, Vincenzo Scaglione, Benedetta Fumarola, Gabriele Pagani, Francesco Giuseppe De Rosa, Michele Bartoletti, Matteo Bassetti.

Funding. This study was supported by an independent medical grant from Pfizer, Shionogi & Co., Ltd and Tillotts Pharma, AG. The funders have no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. The funds required for the publication of the study will be drawn from the budget of our affiliated universities and hospitals, specifically allocated for this type of expense.

Data Availability. The data presented in this study will be available from the corresponding author on reasonable request and provided all regulatory and privacy requirements are fulfilled.

Declarations

Conflict of Interest. Outside the submitted work, Antonio Vena reports research grants and/or personal fees for advisor/consultant and/or speaker/chairman from Gilead, Menarini, MSD, Pfizer, Astella and Shionogi. Outside the submitted work, Matteo Bassetti reports research grants and/or personal fees for advisor/consultant and/or speaker/chairman from BioMérieux, Cidara, Gilead, Menarini, MSD, Pfizer and Shionogi. Outside the submitted work, Daniele Roberto Giacobbe reports investigator-initiated grants from Pfizer Inc., Shionogi, BioMérieux and Gilead Italia, and personal fees for advisor/speaker from Pfizer Inc., Menarini and Tillotts Pharma. Laura Mezzogori, Nadia Castaldo, Silvia Corcione, Renato Pascale, Maddalena Giannella, Simone Mornese Pinna, Davide Fiore Bavaro, Vincenzo Scaglione, Benedetta Fumarola, Gabriele Pagani, Francesco Giuseppe De Rosa and Michele Bartoletti have nothing to declare. Matteo Bassetti and Daniele Roberto Giacobbe are Editorial Board members of Infectious Diseases and Therapy. Matteo Bassetti and Daniele Roberto Giacobbe were not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethical Approval. The study was approved by the institutional review board of the coordinating centre (Comitato Etico interaziendale, City of Health and Sciences, Turin, pratica no. 202/2023, PROT.N. 0066633) and was in accordance with the declaration of Helsinki. Informed consent was deemed unnecessary due to the retrospective nature of the study. STROBE recommendations were followed.

REFERENCES

1. Chang YT, Lin CY, Chen YH, Hsueh PR. Update on infections caused by *Stenotrophomonas maltophilia* with particular attention to resistance mechanisms and therapeutic options. Front Microbiol. 2015;6:893. https://doi.org/10.3389/fmicb.2015.00893.

2. Mojica MF, Humphries R, Lipuma JJ, et al. Clinical challenges treating *Stenotrophomonas maltophilia* infections: an update. JAC Antimicrob Resist. 2022;4(3):dlac040. https://doi.org/10.1093/jacamr/dlac040.

3. Paez JI, Costa SF. Risk factors associated with mortality of infections caused by *Stenotrophomonas maltophilia*: a systematic review. J Hosp Infect. 2008;70(2):101–8. https://doi.org/10.1016/j.jhin.2008.05.020.

4. Osawa K, Shigemura K, Kitagawa K, Tokimatsu I, Fujisawa M. Risk factors for death from *Stenotrophomonas maltophilia* bacteremia. J Infect Chemother. 2018;24(8):632–6. https://doi.org/10.1016/j.jiac.2018.03.011.

5. Jeon YD, Jeong WY, Kim MH, et al. Risk factors for mortality in patients with *Stenotrophomonas maltophilia* bacteremia. Medicine (Baltimore). 2016;95(31): e4375. https://doi.org/10.1097/MD.0000000000004375.

6. Cai B, Tillotson G, Benjumea D, Callahan P, Echols R. The burden of bloodstream infections due to *Stenotrophomonas maltophilia* in the United States: a large, retrospective database study. Open Forum Infect Dis. 2020;7(5):ofaa141. https://doi.org/10.1093/ofid/ofaa141.

7. Jian J, Xie Z, Chen L. Risk factors for mortality in hospitalized patients with *Stenotrophomonas maltophilia* bacteremia. Infect Drug Resist. 2022;15:3881–6. https://doi.org/10.2147/IDR.S371129.

8. Hu RM, Huang KJ, Wu LT, Hsiao YJ, Yang TC. Induction of L1 and L2 beta-lactamases of *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother. 2008;52(3):1198–200. https://doi.org/10.1128/AAC.00682-07.

9. Bassetti M, Ariyasu M, Binkowitz B, et al. Designing a pathogen-focused study to address the high unmet medical need represented by carbapenem-resistant gram-negative pathogens—the international, multicenter, randomized, open-label, phase 3 CREDIBLE-CR study. Infect Drug Resist. 2019;12:3607–23. https://doi.org/10.2147/IDR.S225553.

10. Okazaki A, Avison MB. Aph(3')-IIc, an aminoglycoside resistance determinant from *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother. 2007;51(1):359–60. https://doi.org/10.1128/AAC.00795-06.

11. Sanchez MB, Martinez JL. The efflux pump SmeDEF contributes to trimethoprim-sulfamethoxazole resistance in *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother. 2015;59(7):4347–8. https://doi.org/10.1128/AAC.00714-15.

12. Bostanghadiri N, Ghalavand Z, Fallah F, et al. Characterization of phenotypic and genotypic diversity of *Stenotrophomonas maltophilia* strains isolated from selected hospitals in Iran. Front Microbiol. 2019;10:1191. https://doi.org/10.3389/fmicb.2019.01191.

13. Biagi M, Lamm D, Meyer K, et al. Activity of aztreonam in combination with avibactam, clavulanate, relebactam, and vaborbactam against

multidrug-resistant *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother. 2020. https://doi.org/10.1128/AAC.00297-20.

14. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the treatment of ampc beta-lactamase-producing enterobacterales, carbapenem-resistant acinetobacter baumannii, and Stenotrophomonas maltophilia infections. Clin Infect Dis. 2022;74(12):2089–114. https://doi.org/10.1093/cid/ciab1013.

15. Giles A, Foushee J, Lantz E, Gumina G. Sulfonamide allergies. Pharmacy (Basel). 2019. https://doi.org/10.3390/pharmacy7030132.

16. Huang YW, Liou RS, Lin YT, Huang HH, Yang TC. A linkage between SmeIJK efflux pump, cell envelope integrity, and sigmaE-mediated envelope stress response in *Stenotrophomonas maltophilia*. PLoS One. 2014;9(11): e111784. https://doi.org/10.1371/journal.pone.0111784.

17. Wu CJ, Chiu TT, Lin YT, Huang YW, Li LH, Yang TC. Role of smeU1VWU2X operon in alleviation of oxidative stresses and occurrence of sulfamethoxazole-trimethoprim-resistant mutants in *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother. 2018. https://doi.org/10.1128/AAC.02114-17.

18. Yahav D, Lador A, Paul M, Leibovici L. Efficacy and safety of tigecycline: a systematic review and meta-analysis. J Antimicrob Chemother. 2011;66(9):1963–71. https://doi.org/10.1093/jac/dkr242.

19. Bassetti M, Vena A, Battaglini D, Pelosi P, Giacobbe DR. The role of new antimicrobials for Gram-negative infections in daily clinical practice. Curr Opin Infect Dis. 2020;33(6):495–500. https://doi.org/10.1097/QCO.0000000000000686.

20. Bassetti M, Castaldo N, Fantin A, Giacobbe DR, Vena A. Antibiotic therapy for nonfermenting Gram-negative bacilli infections: future perspectives. Curr Opin Infect Dis. 2023;36(6):615–22. https://doi.org/10.1097/QCO.0000000000000984.

21. Lasko MJ, Gethers ML, Tabor-Rennie JL, Nicolau DP, Kuti JL. In vitro time-kill studies of trimethoprim/sulfamethoxazole against *Stenotrophomonas maltophilia* versus *Escherichia coli* using cation-adjusted Mueller-Hinton Broth and ISO-Sensitest Broth. Antimicrob Agents Chemother. 2022;66(3): e0216721. https://doi.org/10.1128/aac.02167-21.

22. Highlights of prescribing information: Fetroja (Cefiderocol). 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209445s000lbl.pdf. Accessed 26 Feb 2025.

23. Bassetti M, Echols R, Matsunaga Y, 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;21(2):226–40. https://doi.org/10.1016/S1473-3099(20)30796-9.

24. Wunderink RG, Matsunaga Y, Ariyasu M, 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;21(2):213–25. https://doi.org/10.1016/S1473-3099(20)30731-3.

25. Hsu AJ, Simner PJ, Bergman Y, Mathers AJ, Tamma PD. Successful treatment of persistent *Stenotrophomonas maltophilia* bacteremia with cefiderocol in an infant. Open Forum Infect Dis. 2023;10(4):ofad174. https://doi.org/10.1093/ofid/ofad174.

26. Lupia T, Carnevale-Schianca F, Vita D, et al. *Stenotrophomonas maltophilia* infections in haematological malignancies and hematopoietic stem cell transplantation: a case series including cefiderocol-based regimens. Medicina (Kaunas). 2024. https://doi.org/10.3390/medicina60010088.

27. Medioli F, Casali E, Viscido A, Pistolesi V, Venditti M, Oliva A. First case of persistent *Stenotrophomonas maltophilia* bacteraemia due to septic thrombosis successfully treated with a cefiderocol-containing regimen. J Glob Antimicrob Resist. 2023;34:5–8. https://doi.org/10.1016/j.jgar.2023.05.013.

28. Tamma PD, Heil EL, Justo JA, Mathers AJ, Satlin MJ, Bonomo RA. Infectious Diseases Society of America 2024 guidance on the treatment of antimicrobial-resistant gram-negative infections. Clin Infect Dis. 2024. https://doi.org/10.1093/cid/ciae403.

29. Fratoni AJ, Kuti JL, Nicolau DP. Optimised cefiderocol exposures in a successfully treated critically ill patient with polymicrobial *Stenotrophomonas maltophilia* bacteraemia and pneumonia receiving continuous venovenous haemodiafiltration. Int J Antimicrob Agents. 2021;58(3): 106395. https://doi.org/10.1016/j.ijantimicag.2021.106395.

30. Paez JI, Tengan FM, Barone AA, Levin AS, Costa SF. Factors associated with mortality in patients with bloodstream infection and pneumonia due to *Stenotrophomonas maltophilia*. Eur J Clin Microbiol Infect Dis. 2008;27(10):901–6. https://doi.org/10.1007/s10096-008-0518-2.

31. Denton M, Kerr KG. Microbiological and clinical aspects of infection associated with *Stenotrophomonas maltophilia*. Clin Microbiol Rev.

1998;11(1):57–80. https://doi.org/10.1128/CMR.11.1.57.

32. Al-Jasser AM. *Stenotrophomonas maltophilia* resistant to trimethoprim-sulfamethoxazole: an increasing problem. Ann Clin Microbiol Antimicrob. 2006;5:23. https://doi.org/10.1186/1476-0711-5-23.

33. Gracia-Paez JI, Ferraz JR, Silva IA, Rossi F, Levin AS, Costa SF. Smqnr variants in clinical isolates of *Stenotrophomonas maltophilia* in Brazil. Rev Inst Med Trop Sao Paulo. 2013;55(6):417–20. https://doi.org/10.1590/S0036-46652013000600008.

34. del Toro MD, Rodriguez-Bano J, Herrero M, et al. Clinical epidemiology of *Stenotrophomonas maltophilia* colonization and infection: a multicenter study. Medicine (Baltimore). 2002;81(3):228–39. https://doi.org/10.1097/00005792-200205000-00006.

35. Mojica MF, Bonomo RA, van Duin D. Treatment approaches for severe *Stenotrophomonas maltophilia* infections. Curr Opin Infect Dis. 2023;36(6):572–84. https://doi.org/10.1097/QCO.0000000000000975.

36. Samonis G, Karageorgopoulos DE, Maraki S, et al. *Stenotrophomonas maltophilia* infections in a general hospital: patient characteristics, antimicrobial susceptibility, and treatment outcome. PLoS One. 2012;7(5): e37375. https://doi.org/10.1371/journal.pone.0037375.

37. Watson L, Esterly J, Jensen AO, Postelnick M, Aguirre A, McLaughlin M. Sulfamethoxazole/trimethoprim versus fluoroquinolones for the treatment of *Stenotrophomonas maltophilia* bloodstream infections. J Glob Antimicrob Resist. 2018;12:104–6. https://doi.org/10.1016/j.jgar.2017.09.015.

38. Nys C, Cherabuddi K, Venugopalan V, Klinker KP. Clinical and microbiologic outcomes in patients with monomicrobial *Stenotrophomonas maltophilia* infections. Antimicrob Agents Chemother. 2019. https://doi.org/10.1128/AAC.00788-19.

39. Junco SJ, Bowman MC, Turner RB. Clinical outcomes of *Stenotrophomonas maltophilia* infection treated with trimethoprim/sulfamethoxazole, minocycline, or fluoroquinolone monotherapy. Int J Antimicrob Agents. 2021;58(2): 106367. https://doi.org/10.1016/j.ijantimicag.2021.106367.

40. Zha L, Zhang D, Pan L, et al. Tigecycline in the treatment of ventilator-associated pneumonia due to *Stenotrophomonas maltophilia*: a multicenter retrospective cohort study. Infect Dis Ther. 2021;10(4):2415–29. https://doi.org/10.1007/s40121-021-00516-5.

41. Wang YL, Scipione MR, Dubrovskaya Y, Papadopoulos J. Monotherapy with fluoroquinolone or trimethoprim-sulfamethoxazole for treatment of *Stenotrophomonas maltophilia* infections. Antimicrob Agents Chemother. 2014;58(1):176–82. https://doi.org/10.1128/AAC.01324-13.

42. Karakonstantis S, Rousaki M, Vassilopoulou L, Kritsotakis EI. Global prevalence of cefiderocol non-susceptibility in Enterobacterales, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*: a systematic review and meta-analysis. Clin Microbiol Infect. 2024;30(2):178–88. https://doi.org/10.1016/j.cmi.2023.08.029.

43. Longshaw C. The activity of cefiderocol and comparator agents against rare Gram-negative isolates collected from 2020 to 2022 as part of the SENTRY antimicrobial surveillance program. European Congress of Clinical Microbiology and Infectious Disease, Copenhagen, Denmarck. 2023;P1374

44. Meschiari M, Volpi S, Faltoni M, et al. Real-life experience with compassionate use of cefiderocol for difficult-to-treat resistant Pseudomonas aeruginosa (DTR-P) infections. JAC Antimicrob Resist. 2021;3(4):dlab188. https://doi.org/10.1093/jacamr/dlab188.

45. Chou A, Ramsey D, Amenta E, Trautner BW. Real-world experience with cefiderocol therapy for *Pseudomonas aeruginosa* and other multidrug resistant gram-negative infections within the Veterans Health Administration, 2019–2022. Antimicrob Steward Healthc Epidemiol. 2023;3(1): e90. https://doi.org/10.1017/ash.2023.165.

46. Falcone M, Tiseo G, Leonildi A, et al. Cefiderocol-compared to colistin-based regimens for the treatment of severe infections caused by carbapenem-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother. 2022;66(5): e0214221. https://doi.org/10.1128/aac.02142-21.

47. Gatti M, Bartoletti M, Cojutti PG, et al. A descriptive case series of pharmacokinetic/pharmacodynamic target attainment and microbiological outcome in critically ill patients with documented severe extensively drug-resistant *Acinetobacter baumannii* bloodstream infection and/or ventilator-associated pneumonia treated with cefiderocol. J Glob Antimicrob Resist. 2021;27:294–8. https://doi.org/10.1016/j.jgar.2021.10.014.