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Short Communication

First case of persistent *Stenotrophomonas maltophilia* bacteraemia due to septic thrombosis successfully treated with a cefiderocol-containing regimen

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ABSTRACT

Introduction: There is scarce evidence in literature of what should be the best antimicrobial treatment for bloodstream infections (BSIs) sustained by *Stenotrophomonas maltophilia*, a peculiar pathogen that intrinsically withstands to most of the available antibiotics.
Results and conclusion: Here, we describe a challenging case of a persistent *S. maltophilia* BSI due to septic thrombosis successfully treated with the addition of the novel siderophore cephalosporin cefiderocol to an only partially effective levofloxacin regimen. Additionally, an intra-lock therapy with trimethoprim/sulfamethoxazole was selected as a strategy to prevent recurrence of infection since complete source control was not possible. The serum bactericidal assay was also used to corroborate the in vivo efficacy of the adopted combination therapy.

1. Introduction

Stenotrophomonas maltophilia is a non-fermenting Gram-negative environmental and opportunistic pathogen that intrinsically withstands many of the known antimicrobials. Recently, global concern has arisen regarding the progressive increase of hospital acquired infections caused by this bacterium, especially in immunocompromised patients, with high mortality rates [1,2].

Among its varied resistance mechanisms, the most peculiar is the chromosome-inducible β-lactamase production of L1 and L2, a class B metallo-β-lactamase and class A serine-cephalosporinase, respectively (according to Ambler classification), granting this pathogen extensive resistance to most β-lactams compounds, carbapenems included [1,2].

For this reason, the antimicrobials included in the treatment guidelines are trimethoprim/sulfamethoxazole, levofloxacin, and minocycline. Recent studies show that the novel siderophore cephalosporin cefiderocol exhibits high in vitro activity, even better than the classical agents used so far, suggesting that it may represent a powerful weapon against *S. maltophilia* infections, including bloodstream infections (BSI) [2–4].

Cefiderocol has been used against carbapenem-resistant organisms' sustained infections; however, starting with the CREDIBLE-CR study, ambiguous results have been obtained, especially when dealing with *Acinetobacter baumannii* infections. Thus far, only a few cases of *S. maltophilia* infection have been treated with cefiderocol, although cefiderocol has recently been successfully used for the treatment of *S. maltophilia* BSI in an infant [5–7].

To the best of our knowledge, no data regarding the use of this drug in adult *S. maltophilia* BSI exists, granting no clear guidance on cefiderocol use upon this organism in vivo.

2. Method

Herein, we present a complex case presentation of *S. maltophilia* bacteraemia sustained by a haemodialysis catheter-related septic thrombosis of the jugular vein, unresponsive to intravenous levofloxacin but eventually cleared with the addition of intravenous

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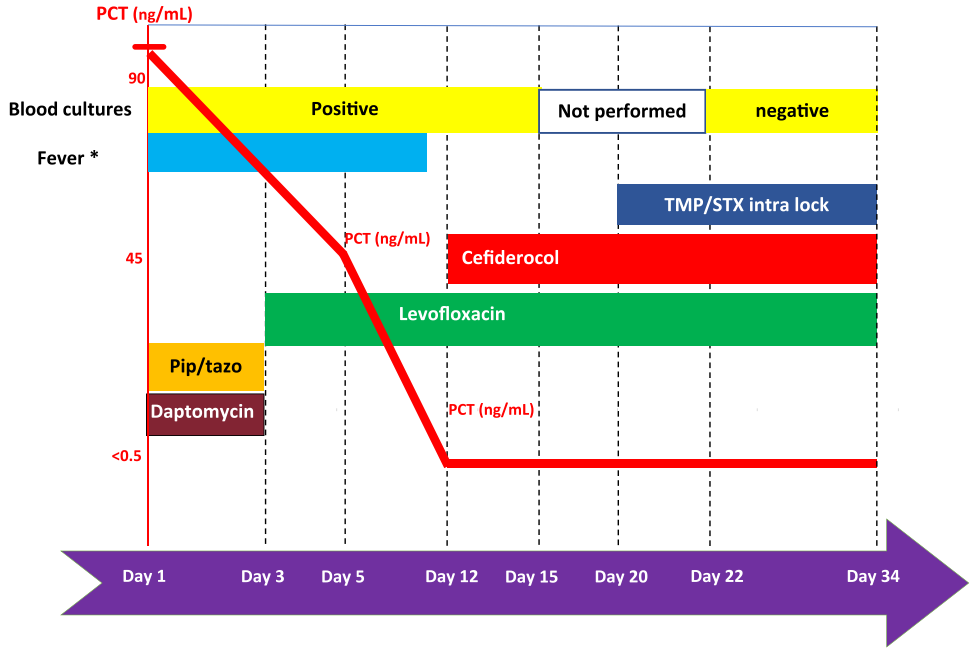

Fig. 1. Clinical evolution of the patient with focus on the antimicrobial therapy deployed.
CRP, C-reactive protein; PCT, procalcitonin; TMP/SMX, trimethoprim/sulfamethoxazole. *Body temperature during fever was always between 37.0°C and 37.5°C.[1]

cefiderocol and intra-lock trimethoprim/sulfamethoxazole administration.

3. Results

A 62-year-old female presented at the end of January 2022 to the Emergency Department (ED) for a reported state of confusion and drowsiness. The medical history of this patient included ischemic/hypertensive cardiomyopathy, end-stage multifactorial chronic kidney failure, uncontrolled insulin-dependent diabetes mellitus, and ischemic multi-district encephalopathy. In 2018 she started dialysis treatment, for which she carried a tunneled central venous catheter (CVC) in the right jugular vein. Since then, she was hospitalized several times for infective causes, the last being a *S. maltophilia* bacteraemia successfully treated with levofloxacin in December 2021.

Upon the present admission to the ED, the general state of the patient was critical: she was slumbering, unresponsive to stimuli, and produced scarce verbal responses. She was moderately tachypneic while resting. Abdominal examination showed no pathological signs. She was slightly pyretic (37.5°C), but other vital parameters stood within normal range. Laboratory exams showed a mild neutrophilic leukocytosis (10.500/mm^3 leukocytes, 67% of which were neutrophiles), 5.7 mg/dL of serum creatinine, 8.33 mEq/L of kaliemia, and 93.91 ng/mL of procalcitonin. Three different sets of blood cultures were collected. Lastly, her nose pharyngeal swab for SARS-CoV2 was positive.

Fig. 1 summarizes the clinical course of the patient. Empirical antimicrobial therapy with piperacillin/tazobactam (2.25 g b.i.d. plus 0.75 g right after every dialysis session) and daptomycin (350 mg after every dialysis session, if the interdialytic time was 48 h; 500 mg instead, if the interdialytic time was 72 h) was started. She was then hospitalized in our Infectious Disease department and, given the rich plethora of risk factors for evolution of COVID-19, she received a dose of casirivimab/imdevimab (SARS-CoV2 antibodies available at that time).

[1] Red line represents PCT trend over time.

Table 1
S. maltophilia antimicrobial susceptibility testing

Tested antibiotics	MIC mcg/mL	S/R/I[a]
Ceftazidime	> 32	R
Levofloxacin	2	I
Minocycline	≤ 2	IE
Trimethoprim/sulfamethoxazole	≤ 1/19	S
Cefiderocol (disk diffusion)	25 mm (zone inhibition)	S[b]

[a] According to the European Committee for Antimicrobial Susceptibility Testing: I, susceptible, increased exposure; IE, insufficient evidence that the species in question is a good target for therapy with the drug; R, resistant; S, susceptible. A MIC with a comment but without an accompanying S, I, or R categorization may be reported.
[b] For *Acinetobacter baumannii* and *Stenotrophomonas maltophilia*, zone diameter cut-off values of susceptibility of ≥ 17 mm and ≥ 20 mm corresponded to MIC values of ≤ 2 and ≤ 0.5 mg/L, respectively.

Two days later, blood culture results revealed *S. maltophilia*. The antimicrobial susceptibility tests, performed with MicroScan WalkAway (Beckman Coulter, Brea, CA), showed a MIC of 2 mcg/mL for levofloxacin, and full susceptibility for trimethoprim/sulfamethoxazole and minocycline (Table 1). Given this, piperacillin/tazobactam and daptomycin were stopped and levofloxacin (750 mg loading dose, continuing with 500 mg every 48 h) was started.

A trans-thoracic echocardiogram showed no presence of endocardial vegetation.

Although the patient became afebrile under levofloxacin, follow-up blood cultures (FUBCs) performed on days 5 and 11 of hospitalization again grew *S. maltophilia*. The microbiology laboratory was then asked to test susceptibility to cefiderocol (as the recently published European Committee for Antimicrobial Susceptibility Testing guidelines suggested [8]). The disk diffusion method was used, and the diameter of inhibition was 25 mm, corresponding to MIC values below the PK-PD breakpoint of S ≤ 2 mg/L [8]. Given that, on day 12, cefiderocol was added (0.75 g b.i.d. after dialysis) to levofloxacin, with prompt improvement of her state

of consciousness and a decrease in inflammatory markers (namely C-reactive protein and procalcitonin) on subsequent days (Fig. 1). Serum Bactericidal Assay (SBA) titers, carried out on day 17 and performed as previously described, before and 3h after cefiderocol administration were 1:8 and 1:64, respectively [9].

A computed tomographic angiography showed that the right jugular vein, where the CVC was in place, was too gravely narrowed by a massive thrombosis. Other potential sites of insertion were excluded because of technical issues. Because removal of the CVC could not be performed, making adequate source control impossible, on day 20, an intra-lock therapy with trimethoprim/sulfamethoxazole was started (10 mg/mL plus 100 units/mL of heparin during every dialytic session). Because of scarce venous reservoir and low patient compliance, FUBCs could be repeated only on day 22 and eventually came out negative (Fig. 1).

Lastly, on day 30, the SARS-CoV2 nose pharyngeal swab came back negative. The patient was discharged home with the recommendation to continue oral minocycline (200 mg first dose, then 100 mg 2 times per day) and the lock therapy with trimethoprim/sulfamethoxazole during each dialysis session as a chronic suppressive therapy. No signs of infection relapse were observed after a six month follow-up observation.

4. Discussion

In this report, we showed that the addition of cefiderocol to an only partly effective levofloxacin regimen induced prompt amelioration of clinical conditions in such a serious condition as *S. maltophilia* septic thrombosis.

S. maltophilia is an intrinsically carbapenem-resistant emerging pathogen that can cause nosocomial pneumonia and bacteraemia in fragile patients, especially in those who are severely and persistently neutropenic and in those subjected to broad-spectrum antibiotic pressure. Recently, it has also been associated with severe SARS-CoV2 disease [1,2,5,10,11].

According to the Infectious Diseases Society of America guidelines, therapeutic choices should be driven by the infection's severity: while mild infections should be treated with a single-regimen therapy based on either trimethoprim/sulfamethoxazole, levofloxacin, minocycline, tigecycline, or cefiderocol, combination therapy with at least two of the aforementioned active molecules may be considered for severe infections [12]. However, clinical data demonstrating superior outcomes over monotherapy are still lacking [13].

Historically, trimethoprim/sulfamethoxazole has been considered the first-choice therapy for infections caused by *S. maltophilia*; however, in a recent study by Sarzynski et al., levofloxacin was associated with a lower death rate in patients with lower respiratory tract infection than trimethoprim/sulfamethoxazole and, eventually, with fewer hospital days between index culture collection and discharge [14]. Moreover, trimethoprim/sulfamethoxazole is associated with a list of treatment-limiting toxicities such as renal and hepatic injury, electrolyte imbalances, and bone marrow suppression, which may lead patients and providers to prefer levofloxacin [2,14]. In consideration of these factors, we chose this latter agent as the initial therapy in our highly fragile patient and, eventually, a combination regimen with cefiderocol was adopted to improve the chances of definite cure of such a severe condition as septic thrombosis. As a matter of fact, the evidence we have so far on this novel cephalosporin highlights a high in vitro activity against *S. maltophilia*, with MICs ranging from 0.004–2.0 mcg/ml [15].

Unfortunately, we were not able to obtain an actual MIC for cefiderocol; rather, we performed the disk diffusion method, which returned a result of 25 mm of diameter inhibition, corresponding to a MIC value below the PK-PD breakpoint of S $\leq$ 2 mg/L, according to the European Committee for Antimicrobial Susceptibility Testing guidelines [8]. However, some evidence of the in vivo efficacy of our combined therapy was provided by the high peak and SBA titers obtained following intravenous cefiderocol administration.

Not surprisingly, in our case disappearance of fever and normalization of procalcitonin were obtained some days before clearance of bacteraemia. This is in line with our previous observations showing that, in the case of Gram-negative septic thrombosis, FUBCs represent the most important indicator of antimicrobial treatment response [16–20]. On the other hand, we could not firmly demonstrate possible clearance of bacteraemia under the levofloxacin plus cefiderocol combined therapy before intra-lock trimethoprim/sulfamethoxazole because of difficulties in performing serial FUBCs due to low patient compliance. As a matter of fact, intra-lock therapy was at least successful in preventing an otherwise rather probable recurrence of the infection, given the impossibility of performing an effective source control by means of catheter removal.

5. Conclusion

We have described an unusual case of *S maltophilia* septic thrombosis that clearly improved with a cefiderocol plus levofloxacin intravenous treatment course. The high SBA titers underline the potential of this therapy against such a severe infection. Definitive cure with no subsequent relapse was eventually obtained by combining trimethoprim-sulfamethoxazole intra-lock therapy.

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Competing interests: The authors have no conflicts of interest to declare.

Ethical approval: The study was approved by the local Ethical Committees (no. 0341/2023). The patient's written consent was obtained upon entry to our department.

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