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*Case Report*

# Synergistic combination of aztreonam and ceftazidime/avibactam against resistant *Stenotrophomonas maltophilia* on pancreatitis

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## Abstract

Introduction: *Stenotrophomonas maltophilia* is a Gram-negative, opportunistic pathogen associated with a high morbidity and mortality rate. We report our clinical experience in treating a patient with infected pancreatic necrosis caused by multidrug-resistant (MDR) *S. maltophilia* with a novel drug combination.

Case report: A 65-year-old male with history of type II diabetes was admitted with acute pancreatitis, voluminous ascites, and signs of sepsis after undergoing an echo-endoscopy procedure with pancreas biopsy to investigate a Wirsung duct dilatation. Retroperitoneal fluid culture revealed *S. maltophilia* resistant to colistin and with intermediate susceptibility to trimethoprim-sulfamethoxazole and levofloxacin. The synergy between aztreonam (ATM) and ceftazidime/avibactam (CZA) was demonstrated using the combined disk pre-diffusion test.

Conclusions: There are sparse data providing guidance on the optimal regimen against MDR *S. maltophilia* infections. Although in this case a surgical excision was essential, combination of ATM and CZA provided effective synergistic antimicrobial treatment with clinical cure of severe acute pancreatitis infected with *S. maltophilia*. The combined disk pre-diffusion test with ATM and CZA requires no special equipment and can be routinely performed in clinical microbiology labs. Combination of ATM with CZA should be considered for cases of MDR *S. maltophilia* infections with limited treatment options.

**Key words:** *Stenotrophomonas maltophilia*; bacterial resistance; nosocomial infection.

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## Introduction

*Stenotrophomonas maltophilia* is a Gram-negative opportunistic pathogen with increasing incidence in hospital settings and is associated with high morbidity and mortality rate [1]. *S. maltophilia* is characterized by multidrug resistance (MDR), which is due to intrinsic resistance to aminoglycosides, tetracycline, phosphomycin, and most β-lactams, in addition to the ability to develop other resistance mechanisms during antibiotic therapy [2–4]. These characteristics worry health care professionals, since therapeutic options for the treatment of infections caused by this bacterium are scarce. Consequently, in many cases, there is a delay in starting effective treatment, or there is a need for high doses of antimicrobials and, therefore, a greater risk of therapeutic failure or toxicity [2,3].

*S. maltophilia* naturally produces two β-lactamases, enzymes classified according to their structure and functional group: L1, a B3 metallo-β-lactamase (MβL) that hydrolyzes all β-lactams (penicillins, cephalosporins, and carbapenems) with the exception of aztreonam (ATM), and confers resistance against all available β-lactamase inhibitors; and L2, a Class A cephalosporinase, which expresses resistance to the extended-spectrum cephalosporins and ATM, although it is sensitive to serine-β-lactamase inhibitors such as clavulanate and avibactam (AVI). In this scenario, there is an urgency for discovering new combinations of antimicrobials that are efficient against *S. maltophilia* [2,5,6].

Recent studies have indicated, through in vitro tests, that the combination of ATM-AVI promotes a promising synergistic mechanism of action effective against isolated strains of Gram-negative pathogens that are producers of serine-β-lactamase, MβL, and cephalosporinases. It is considered that the inhibitory effects of ATM on L1, produced by *S. maltophilia*, and its consequent potential bactericidal activity, could be reestablished from the association with AVI, which is active against L2. However, there are no commercially available drugs with combination ATM-AVI formulations worldwide; currently, only isolated

formulations of ATM and ceftazidime/avibactam (CZA) are available in the pharmaceutical market. Therefore, this combination of antimicrobials may be clinically useful for the treatment of infections caused by multidrug-resistant, β-lactamase-producing microorganisms [3,5,7].

Simple microbiological tests, based on the antimicrobial gradient method that incorporates the principle of disk diffusion and agar dilution tests, allow evaluating the potential synergism of the combination of ATM and CZA and its bactericidal effect against multidrug-resistant bacteria [7–9]. Lima *et al.* demonstrated the successful application of a modified pre-diffusion disc test to predict the in vitro efficacy of the ATM-AVI combination against MβL-producing Enterobacterales. Discs impregnated with CZA and ATM antibiotics were used to conduct this test. The method presented is simple, low cost, and requires no special equipment to be performed [9].

Considering that there are few reports described in the literature on the therapeutic success of antimicrobial association against MDR *S. maltophilia*, this case report presents the clinical experience of treating a patient with infected pancreatic necrosis caused by MDR *S. maltophilia*. It was a serious clinical condition which required complex therapeutic management, but clinical success was achieved using a combined therapy of CZA and ATM.

## Case Report

A 65-year-old male with history of type II diabetes was admitted with acute pancreatitis (ICD: K85), voluminous ascites, and signs of sepsis after undergoing an echo-endoscopy procedure with pancreas biopsy to investigate a Wirsung duct dilatation. He had elevated laboratory infectious parameters, C-reactive protein (CRP) of 25.25 and leukocytes of 12560. The patient's previous treatment in another institution included metronidazole, ceftriaxone, and then, the initial doses of meropenem. Once admitted, antibiotic therapy was followed up with meropenem 1 g every 8 hours and linezolid 600 mg every 12 hours. A percutaneous drainage of the abdominal collection was conducted on the eighth-day due to a probable pancreatic fistula. A sample of the retroperitoneal fluid was taken to culture, which revealed a MDR *Stenotrophomonas maltophilia*. Results of the isolate's susceptibility testing are shown on Table 1. The in vitro synergy between ATM and CZA was demonstrated using a modified combined disk pre-diffusion test.

In this scenario, antibiotic therapy was followed up with simultaneous administration of ATM 1g every 8h, with 1h infusion, and CZA 2/0.5 g every 8 hours, with 2 h infusion, along with teicoplanin 400 mg for Gram-positive additional coverage. After this adjustment, his laboratory tests showed some improvement, indicating a reduction in the infectious process. On the day of antibiotic therapy change, his CRP was 13.71 and leukocytes were 11000, on the following day there was a significant reduction to 8.97 and 8710, respectively, as shown in Figure 1. In addition, six days after the antibiotic therapy modification, an abdominal computer tomography (CT) scan showed some reduction in the volume of abdominopelvic inflammatory changes related to pancreatitis. Despite this, the patient had pancreatic necrosis, requiring partial pancreatectomy. This procedure took place on the 37$^{th}$ day of hospitalization.

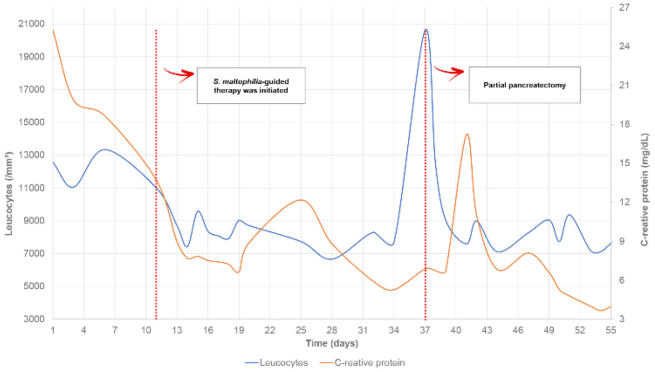
A sample of pancreatic drainage was taken to conduct fungus and bacteria culture. The fungus culture identified *Candida lusitaniae* sensitive to fluconazole. There was no bacterial growth. The samples of pancreatic necrosis were used to conduct a bacterioscopy, the acid-fast bacillus test, and mycobacterial culture; the results were all negative.

**Table 1.** Antimicrobial susceptibility test of *S. maltophilia* isolated from patient's biological sample.

| Antibiotics | Sensitive | Intermediate | Resistant |
|---|---|---|---|
| TMP-SMX | | ■ | |
| Levofloxacin | | ■ | |
| Colistin | | | ■ |
| Tigecycline | ■ | | |
| ATM-CZA | ■ * | | |

Black squares indicate the test result. Methods: E-tests and/or microdilution and disk pre-diffusion test; ATM-CZA: aztreonam and ceftazidime/avibactam; TMP-SMX: trimethoprim-sulfamethoxazole; *Synergism detected.

**Figure 1.** Patient's laboratory parameters throughout the hospitalization period.




C-reactive protein detection method: Ultrasensitive Immunoturbidimetry.

After the partial pancreatectomy there was still an increase in CRP, which was 6.71 two days after the procedure, and increased to 17.19 four days later (on the 41st day of hospitalization). However, these changes in laboratory tests were associated with the fungal infection detected. Therefore, five days after surgery, fluconazole 150 mg, once a day, was initiated. Soon after the antifungal treatment was started, the inflammatory and infectious parameters improved, along with a significant clinical recovery. The CRP went from 17.19 to 6.6 in eight days (from the 41st day to the 49th day). The patient's laboratory parameters throughout the hospitalization period are shown in Figure 1.

The patient completed 6 weeks of antimicrobial treatment using ATM in combination with CZA and teicoplanin. He was discharged in good general conditions, with medical prescription of fluconazole 150 mg and levofloxacin 750 mg once a day, for oral administration. The patient underwent laboratory tests for a few months after discharge and there was no remission of the infection.

An informed consent was signed by the patient and the local research ethics committee approved the publication of this case; ethical approval ID: 58856422.6.0000.5461.

## Discussion

It is known that the incidence of nosocomial MDR *S. maltophilia* infections is increasing, affecting mainly immunocompromised individuals, patients in prolonged hospitalization in an intensive care unit (ICU), patients on mechanical ventilation, and using other invasive devices and indwelling catheters. These risk factors are associated with some of *S. maltophilia* characteristics, such as its ability to form biofilm and to colonize these invasive devices, its intrinsic resistance, in addition to the ability to develop other resistance mechanisms [10,11]. The infection occurs through direct contact with contaminated substances, surfaces, medical-hospital material or the hands of health care professionals, especially during invasive procedures, such as the echo-endoscopy procedure with pancreas biopsy which was the case for the patient in this study [1].

Local or systemic infectious complications are responsible for the high mortality and morbidity of severe acute pancreatitis, and approximately one-third of patients with acute necrotizing pancreatitis subsequently suffer from pancreatic infection [12]. The increasing prevalence of *S. maltophilia* in bloodstream and hepatobiliary infections raises the possibility that it may become a common causative organism of necrotizing pancreatitis in the future [13].

A retrospective study followed the identification of 817 *S. maltophilia* isolates from blood culture samples, respiratory and urine samples; in a tertiary-care teaching hospital in Hungary between 2008 and 2017. Regarding the susceptibility of the isolates to antibiotics, most of isolates were susceptible to some first line antimicrobials recommended to treat this infection, TMP-SMX and levofloxacin (87.4 and 90.5%, respectively [14].

Mönkemüller *et al*. reported a similar case of pancreatic necrosis infected by *S. maltophilia* which was also successfully treated with appropriate antibiogram-based antibiotic therapy and endoscopic drainage. In their case, the isolated strain was sensitive to TMP-SMX, ticarcillin-clavulanate, and piperacillin [15]. *S. maltophilia* resistance to 1st line antimicrobials, namely: TMP-SMX, minocycline, tigecycline, levofloxacin and cefiderocol; and the coexistence of multiple resistance mechanisms are being reported at higher rates in the literature, which reinforces the need for new agents and combinations to be used, such as CZA and ATM [10,16].

Mojica *et al*. reported a case of an immunocompromised patient with a MDR *S. maltophilia* bacteremia, refractory to colistimethate sodium and minocycline, successfully treated with combined therapy of CZA (2.5 g every 8 h) and ATM (2 g every 8 h) for 48 days. Although the bloodstream infection lasted for weeks, this combined antibiotic therapy quickly provided the patient's clinical recovery and negative blood cultures for months after therapy was completed [7]. This successful clinical experience, along with our patient's case, corroborates with the hypothesis reported in previous studies, which considers that ATM's activity against L2 producing *S. maltophilia* might be possible by its association with AVI, that inhibits L2, and therefore, theoretically protects ATM from hydrolysis. It is considered that ATM combined with commercially available CZA might be useful to treat L1 and L2 producing *S. maltophilia* infections [3,5,17], and a recent published guideline, of the Infectious Diseases Society of America (IDSA), suggests the use of this dual therapy for moderate to severe MDR *S. maltophilia* infections [10].

In vitro studies demonstrate the synergistic activity of ATM-AVI against strains producing MβLs or co-producing MβL and *Klebsiella pneumoniae* Carbapenemase (KPC). Experiments from Mojica *et al*. have evidenced that combining AVI with ATM restores

the activity of ATM against the majority of aztreonam-resistant *S. maltophilia* strains [2]. Simple disc diffusion susceptibility testing with MDR *S. maltophilia* isolates revealed in vitro resistance to ceftazidime, CZA, and ATM alone. Yet, when discs of CZA and ATM were placed 20 mm apart, a zone of inhibition was observed on the side of the ATM disk facing CZA [7]. Lima *et al*. elaborated a low cost modified combined disk pre-diffusion test, associating ATM-AVI, and tested MDR *K. pneumoniae* strains susceptibility to those drugs [9]. The application of this method confirmed synergistic activity of ATM-AVI against *S. maltophilia* isolate from our patient, which supported the clinical decision to use ATM-CZA for his treatment.

A study that evaluated the susceptibility of 76 *S. maltophilia* clinical isolates to antibiotics, showed that both CZA and ATM-AVI exerted promising activity. In summary, ATM-AVI was more active in vitro than ATM alone for 94.74 % of the isolates, moreover, its activity stood out among ceftazidime, ATM and CZA [5]. Another study's results of susceptibility testing with *S. maltophilia* isolates demonstrated that ATM-AVI was the most reliably bactericidal combination among others, such as amoxicillin-clavulanate, CZA, meropenem-vaborbactam, and imipenem-relebactam. It was evidenced that AVI produced a significant reduction on ATM's MICs, and also restored susceptibility in most of isolates [17]. Biagi *et al*. also compared the synergic effect of combined antibiotic therapy, including ATM with CZA or meropenem-vaborbactam, which presented activity against 87.5 % and 75 %, respectively, of New Delhi metallo-ß-lactamase (NDM) and serine ß-lactamase-coproducing Enterobacterales strains. These studies show the importance of evaluating potential therapeutic alternatives, to provide clinicians with options to treat severe infections caused by MDR agents [18].

The ATM and CZA combination may also be a promising option against other MDR Enterobacterales, including MβL and carbapenemases-producing strains. A Spanish retrospective study reported the outcomes of 10 patients treated with ATM and CZA from infections caused by MDR *Klebsiella pneumoniae*. There was 60 % clinical success and no adverse events related to the combination therapy as evaluated during the follow-up [19]. A recently reported case showed the successful management of a MDR *K. pneumoniae* bloodstream infection with combined therapy of ATM and CZA, in a neutropenic patient. The isolated strain was a NDM producing *K. pneumonia* [20]. A reported case of a 70-year-old man with severe pyelonephritis infected by an extremely drug resistant *Escherichia coli* also presented clinical success with the combined antibiotic therapy of CZA and ATM. In this case, previous scheme (active in vitro) with gentamicin, colistin, and fosfomycin failed and rapidly deteriorated the renal function. 48 Hours after CZA-ATM initiation, the patient had already presented clinical and renal function improvement, reaching microbiological and clinical cure after 2 months [20].

Our case report is a retrospective study of only one patient, which is one of its limitations. Although the patient had negative culture and clinical recovery results, it is likely that the performance of pancreatectomy played an important role on the infection's resolution. Furthermore, only the antimicrobials available in our institution, which have action against *Stenotrophomonas*, were tested in the antibiogram, as demonstrated on Table 1. Other antimicrobials such as ticarcillin-clavulanic acid and cefiderocol were not tested.

## Conclusions

The aztreonam and ceftazidime/avibactam is a potential antibiotic combination to treat life-threatening infections caused by Gram-negative MβL producers. However, randomized studies with more patients need to be performed in order to define the role of this antibiotic combination in the treatment of infections caused by *S. maltophilia*.

The assessment of in vitro synergistic activity of antibiotics was essential for the adequate antibiotic therapy escalation in the case presented. This test can be routinely performed by the microbiology laboratory and, whenever possible, it should be considered to guide therapeutic decision of infections caused by MDR microorganisms.

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