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Successful Treatment of Bloodstream Infection Due to Metallo-β-Lactamase-Producing *Stenotrophomonas maltophilia* in a Renal Transplant Patient

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This Journal section presents a real, challenging case involving a multidrug-resistant organism. The case authors present the rationale for their therapeutic strategy and discuss the impact of mechanisms of resistance on clinical outcome. An expert clinician then provides a commentary on the case.

***Stenotrophomonas maltophilia* is an emerging multidrug-resistant (MDR) opportunistic pathogen for which new antibiotic options are urgently needed. We report our clinical experience treating a 19-year-old renal transplant recipient who developed prolonged bacteremia due to metallo-β-lactamase-producing *S. maltophilia* refractory to conventional treatment. The infection recurred despite a prolonged course of colistimethate sodium (colistin) but resolved with the use of a novel drug combination with clinical efficacy against the patient's *S. maltophilia* isolate.**

Stenotrophomonas maltophilia is a Gram-negative, nonfermentative, environmental bacillus that has emerged as an important cause of nosocomial infections in immunocompromised hosts (1, 2). *S. maltophilia* characteristically manifests a multidrug-resistant (MDR) phenotype. Intrinsic antibiotic resistance is mediated by the expression of aminoglycoside-modifying enzymes; *qnrB*-like quinolone-resistant determinant, multidrug efflux pumps; and two β-lactamases (L1 and L2). The L1 inducible metallo-β-lactamase (MBL) hydrolyzes carbapenems and other β-lactams, with the exception of the monobactam aztreonam (ATM), and is resistant to all clinically available β-lactamase inhibitors (1, 3, 4). The L2 β-lactamase is a chromosomally encoded, inducible cephalosporinase that confers resistance to extended-spectrum cephalosporins and ATM but can be inhibited by commercially available serine-β-lactamase inhibitors such as clavulanic acid (1, 2, 5). Here, we report our experience treating an immunocompromised patient with unrelenting MDR *S. maltophilia* bacteremia.

CASE PRESENTATION

A 19-year-old male with end-stage renal disease secondary to autosomal recessive polycystic kidney disease, two renal transplants, asplenia, adrenal insufficiency, and a history of *S. maltophilia* bacteremia (21 months before) developed persistent, MDR *S. maltophilia* bacteremia. The patient's immunosuppressive regimen consisted of tacrolimus, mycophenolate, and physiologic dosing of hydrocortisone undergoing a slow taper because of adrenal insufficiency. His prophylactic antimicrobials included trimethoprim-sulfamethoxazole (TMP-SMX) at 160/800 mg thrice weekly (against *Pneumocystis jirovecii*), penicillin VK at 250 mg twice daily (asplenia), and ciprofloxacin at 750 mg daily (secondary prophylaxis after sepsis from ascending cholangitis) for the first 2 weeks of every month.

On day 1 of bacteremia, the patient presented with fever without focal symptoms of infection. Linezolid and cefepime were administered after blood cultures were obtained. A peripherally inserted central catheter (PICC) was placed on day 2. After 62 h of incubation, blood cultures grew Gram-negative rods. Final identification of the organism and susceptibilities was delayed because of slow growth of the isolate. The preliminary antibiotic susceptibility testing suggested an MDR phenotype with apparent susceptibility to aminoglycosides, and so, the empirical antibiotic regimen was changed to gentamicin on day 6. On day 8, the organism was identified as *S. maltophilia* that showed resistance to TMP-SMX, ceftazidime (CAZ), minocycline, meropenem, and levofloxacin (Table 1). The resistance profile of this isolate may have been related to the long-term antimicrobial prophylaxis post-

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TABLE 1 Culture results

Day(s)	Culture result	Time (h) to positivity	Drug(s) (MIC[s] [μg/ml])[a]			
			Susceptible	Intermediate	Resistant	No breakpoint
PI	*S. maltophilia*[b]	19	TMP-SMX (<0.25/4.75)	Minocycline (6)	CAZ (>256), levofloxacin (>32), ticarcillin-clavulanate (256), meropenem (>32)	Amikacin (8), tobramycin (1.5)
1	*S. maltophilia*[b]	62		Minocycline (6)	ATM (>256), cefepime (>256), ciprofloxacin (>256), TMP-SMX (>32/608)	Colistin (0.09), tigecycline (12)
4	*S. maltophilia*	85		Minocycline (8)	TMP-SMX (>32/608), meropenem (>32)	Colistin (0.09), tigecycline (16)
6–9	NG[d]					
10	*S. maltophilia*	118		Minocycline (6)	TMP-SMX (>32/608), meropenem (>32)	Colistin (0.047)
11	*S. maltophilia*	53	Minocycline (4)		TMP-SMX (>32/608), meropenem (>32)	Rifampin (>32)
13–15	NG					
39	*S. maltophilia*	75			TMP-SMX (>32/608), minocycline (16), CAZ (>256), meropenem (>32)	Colistin (0.38), tigecycline (24)
43	*S. maltophilia*	160	Same as day 39	Same as day 39	Same as day 39	
	S. maltophilia[b,c]	80		Minocycline (8)	TMP-SMX (>32/608), CAZ (>256), meropenem (>32)	
44	*S. maltophilia*	58	Same as day 43	Same as day 43	Same as day 43	
	S. maltophilia	56		Minocycline (8)	TMP-SMX (>32/608), CAZ (>256), meropenem (>32)	
	S. maltophilia[c]	56	Minocycline (3)		TMP-SMX (>32/608), CAZ (>256), meropenem (>32)	
45	*S. maltophilia*[b]	57	Same as day 44	Same as day 44	Same as day 44	
	S. maltophilia	61	Same as day 44	Same as day 44	Same as day 44	
47, 49	NG					
50	*S. maltophilia*[b,c]	64		Minocycline (6)	TMP-SMX (>32/608), CAZ (>256), meropenem (>32)	
53	NG					
57	*S. maltophilia*	71		Minocycline (8)	TMP-SMX (>32/608), CAZ (>256), meropenem (>32)	
58	*S. maltophilia*	84	Same as day 57	Same as day 57	Same as day 57	
66	NG					

[a] Isolates with similar identifications obtained from the same site within 72 h had susceptibility testing referred to the most recent prior isolate.
[b] Isolate submitted for PFGE.
[c] Isolate submitted for CZA-ATM *in vitro* susceptibility testing.
[d] NG, no growth.

transplantation (TMP-SMX, penicillin, ciprofloxacin). The patient was transitioned to intravenous (i.v.) colistimethate sodium (2.5 mg/kg once daily, dose adjusted on day 15 to 1.5 mg/kg every 36 h because of reduced creatinine clearance). Repeat blood cultures on day 10 showed growth of a Gram-negative bacillus, prompting removal of the PICC. After removal of the PICC, all blood cultures remained without growth. The patient was treated for 14 days with i.v. colistimethate, during which a new PICC was placed to complete treatment at home. The PICC was removed upon completion of therapy.

On day 39 after the initial bacteremia, he developed fever, hypotension, and tachycardia. A new PICC was placed, and intravenous colistimethate and linezolid were reinitiated empirically; blood cultures on admission demonstrated growth of *S. maltophilia*. Repeat cultures of blood taken on days 43, 44, and 45 also demonstrated growth of *S. maltophilia*. The MIC of colistimethate

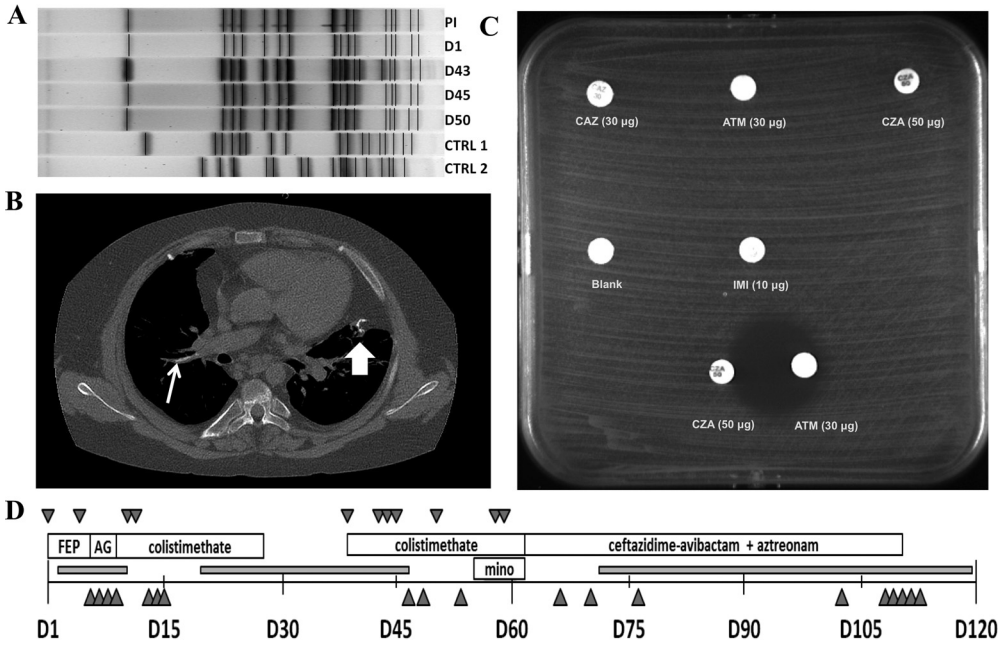

FIG 1 Synopsis of the treatment of bacteremia due to MDR *S. maltophilia*. (A) PFGE of *S. maltophilia* clinical isolates using Xba1. CTRL 1 and 2, contemporaneous control isolates of *S. maltophilia* from different patients. Isolates obtained on day (D1), day 45, and day 50 (primary cluster) are indistinguishable on PFGE. The PI is different by one band, suggesting that it is probably the same strain as the primary cluster. The isolate obtained on day 43 has up to four bands different from the primary cluster, suggesting that it may be related to the primary cluster. The two control clusters are significantly different from the strains isolated from the patient. (B) Noncontrast chest CT scan demonstrating an intravascular calcific lesion. Line arrow, area of calcification in the right pulmonary artery, the suspected site of an endovascular focus. Block arrow, calcification at a prior surgical site of a lung biopsy. (C) Disk diffusion susceptibility testing of the MDR *S. maltophilia* isolate in Mueller-Hinton agar. Note the synergy between CZA and ATM. IMI, imipenem. (D) Time line of bacteremia, antimicrobial therapy, and indwelling vascular devices. FEP, cefepime; AG, aminoglycoside; mino, minocycline. Downward triangles represent positive blood cultures for *S. maltophilia*. Upright triangles represent blood cultures without growth. Gray boxes indicate times when indwelling vascular devices were present.

increased nearly 4-fold for isolates obtained from the first episode of bacteremia to those from the second bacteremic episode (Table 1). Pulsed-field gel electrophoresis (PFGE) was performed to assess the genetic similarity of the isolates from the separate bacteremic events (6). Results noted indistinguishable PFGE band patterns on samples obtained on days 1, 45, and 50 (Fig. 1A). A similar PFGE restriction band pattern was noted for an *S. maltophilia* isolate (past isolate [PI]) obtained 21 months prior to day 1 of the current episode, suggesting earlier infection with the same strain of *S. maltophilia* in this patient.

Given persistent bacteremia, the PICC was removed on day 47. Culture of the catheter tip was without growth. However, cultures from day 50 still grew *S. maltophilia*. A transthoracic echocardiogram on day 48 did not reveal evidence of vegetations on the cardiac valves. A computed tomography (CT) scan of the chest performed on day 54 revealed a calcified focus in the right main pulmonary artery (Fig. 1B) that was suspicious for a thrombus possibly serving as a nidus of infection. Minocycline (loading dose of 200 mg twice daily for 2 doses, followed by 100 mg twice daily) was added to the therapy with i.v. colistimethate on day 55. Repeat blood cultures on days 57 and 58 again demonstrated growth of *S. maltophilia* despite the absence of indwelling lines or other devices. As the bacteremia persisted during therapy with i.v. colistimethate and minocycline, alternative antibiotic options were considered and additional *in vitro* susceptibility testing, including determination of synergistic activity, was performed with several of the patient's recent isolates to identify drug combinations with potential efficacy against this MDR organism.

CHALLENGE QUESTION

Which antimicrobial(s) would be appropriate to treat the patient whose case is described?

A. Colistimethate (i.v.) and gentamicin
B. Ticarcillin-clavulanate (i.v.) and minocycline
C. Oral fosfomycin and extended-infusion meropenem
D. Oral TMP-SMX and ceftolozane-tazobactam (i.v.)
E. CAZ-avibactam (AVI) (CZA) (i.v.) and aztreonam (ATM)
F. Meropenem and colistimethate (i.v.)

TREATMENT AND OUTCOME

The presence of L1 and L2 β-lactamases was confirmed by PCR in all isolates. Disc diffusion susceptibility testing revealed *in vitro* resistance to CAZ, CZA, ATM, and imipenem (zone diameter, >6 mm). However, 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. This was interpreted as evidence of a synergy between CZA and ATM (Fig. 1C).

On day 63, the patient's antibiotic regimen was changed to CZA (2.5 g i.v. every 8 h) in combination with ATM (2 g i.v. every 8 h). Repeat blood cultures up to 113 days after completion of CZA-ATM therapy were without growth. He received a total of 48 days of therapy with CZA-ATM for the treatment of a presumptive endovascular infection in the pulmonary outflow tract caused by *S. maltophilia* (Fig. 1D). Since discontinuation of antibiotic therapy with CZA-ATM, further episodes of *S. maltophilia* bacte-

remia have not occurred (>90 days of observation). The answer to the challenge question is E.

Infections caused by *S. maltophilia* pose a therapeutic challenge because of intrinsic and acquired resistance to many agents (7). Exposure to β-lactams induces *S. maltophilia* to express two chromosomal β-lactamases, L1 and L2, which together confer resistance to all β-lactams and cannot be inhibited by commercially available inhibitors. CZA is a novel combination of the extended-spectrum cephalosporin CAZ with the diazabicyclooctane AVI, a non-β-lactam β-lactamase inhibitor that was recently approved for complicated intraabdominal and urinary infection in adults (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm435629.htm).

CZA demonstrates *in vitro* activity against bacteria possessing class A and C β-lactamases, such as extended-spectrum β-lactamases (ESBLs), *Klebsiella pneumoniae* carbapenemase, and AmpC cephalosporinases, as well as activity against some class D β-lactamases (e.g., OXA-48). Of important note, CZA does not demonstrate *in vitro* activity against isolates containing MBLs.

We hypothesized that a "triple combination" of antibiotics may be effective against MDR *S. maltophilia* if each one of its two β-lactamases were "occupied" with the right counterpart, leaving a third agent "free" to reach its target. The combination of CZA and ATM could target L2 with AVI, thus protecting ATM and CAZ from hydrolysis. The L1 MBL hydrolyzes CAZ and is not inhibited by AVI but cannot hydrolyze ATM. With coadministration of CZA and ATM, CAZ would serve as the primary substrate for L1, while AVI would inhibit L2 and allow ATM to bypass inactivation and successfully reach the penicillin-binding proteins (PBPs) of *S. maltophilia*, likely PBP3.

The results of molecular analysis and *in vitro* susceptibility testing supported our reasoning. Genes encoding L1 and L2 were detected by PCR, consistent with the observed *in vitro* resistance to CZA and ATM; synergy between CZA and ATM was demonstrated by disc diffusion testing, ultimately predicting therapeutic success. Unfortunately, methods to identify potentially synergistic drug combinations are not readily available (8, 9).

It is conceivable that ATM partnered with AVI (without CAZ) might have also been effective in treating this infection, although this combination has not been extensively tested *in vitro* against *S. maltophilia*. The coformulation of ATM and AVI has demonstrated *in vitro* and *in vivo* activity against *Enterobacteriaceae* producing MBLs; however, the activity of the ATM-AVI combination against *Pseudomonas aeruginosa* harboring MBLs is not as predictable (10, 11). Regardless, ATM-AVI is only in the early stages of clinical development (ClinicalTrials.gov Identifier: NCT01689207). Moreover, CAZ may contribute antimicrobial activity against certain MBLs, and the potential benefit of "dual β-lactam therapy" provided by ATM and CAZ cannot be discounted (12, 13). Therefore, in the absence of alternatives, the coadministration of CZA and ATM may offer an option for the treatment of serious infections caused by some carbapenem-resistant Gram-negative bacteria with a complex background of resistance determinants that includes the simultaneous production of MBLs and class A and C cephalosporinases.

COMMENTARY

S. maltophilia is an increasingly important pathogen in immunocompromised patients or those with cystic fibrosis. Characteristically displaying an MDR phenotype, including being inherently resistant to carbapenems, infections with *S. maltophilia* are difficult to treat, and there are sparse data providing guidance on the optimal regimen when commonly used antibiotics fail (1). Because of a combination of host factors and limited treatment options, the mortality rate associated with infections caused by *S. maltophilia* exceeds 30% (14). Additionally, as highlighted by this case, *S. maltophilia* can persist for years given the correct host (in this case, bacteremia recurred nearly 2 years after treatment), adding an additional layer of complexity to the treatment of *S. maltophilia* infections. The case presented here highlights these difficulties routinely encountered by clinicians in the treatment of patients with *S. maltophilia* infections and provides promising information on a novel "repurposing" of two marketed antibiotics, ATM and CZA.

In this case, neither the gold-standard therapy, TMP-SMX, nor any alternative agents (including levofloxacin, minocycline, and colistimethate sodium) were options because of *in vitro* resistance or clinical failure. The intrinsic resistance of *S. maltophilia* to most commercially available β-lactams is mediated by two chromosomally encoded inducible β-lactamases, L1 and L2. L1 is an MBL that, characteristically of all MBL enzymes, does not hydrolyze ATM. L2 is a clavulanate-sensitive Ambler class A cephalosporinase that complements the activity of L1 by hydrolyzing ATM in addition to extended-spectrum cephalosporins (1, 15). The authors hypothesized that the novel broad-spectrum β-lactamase inhibitor AVI (which inhibits Ambler class A and C β-lactamases) would inhibit the L2 β-lactamase, leaving ATM free to interact with the PBPs of *S. maltophilia* (10). As demonstrated by evidence of *in vitro* synergy of CZA and ATM by the double-disk diffusion test and the clinical response, this hypothesis was well founded. Despite recalcitrant bacteremia of several weeks duration, the combination of ATM and CZA led to rapid and sustained clearance of blood cultures through several months following the completion of therapy.

The methods used by the authors to identify synergy between ATM and CZA is worth noting. A double-disk synergy test requires no special equipment or training and can be routinely performed in many clinical microbiology labs to provide timely, clinically useful information. Overlaid E tests may provide similarly useful information with the added benefit of quantifying the degree of synergy observed (16). It is important to note that CZA is likely the only currently available β-lactam–β-lactamase inhibitor combination with this potential for synergy with ATM. While L2 is inhibited by clavulanate and the combination of ATM and ticarcillin-clavulanate is synergistic *in vitro*, ticarcillin-clavulanate is no longer commercially available (17). In contrast to other class A β-lactamases, tazobactam and sulbactam are less potent inhibitors of L2 with little to no benefit when combined with ticarcillin against *S. maltophilia* (18). As oral amoxicillin-clavulanate is the sole means of obtaining clavulanate in the United States, CZA appears to be the only viable option for synergism with ATM for serious *S. maltophilia* infections.

As discussed by the authors, the combination of ATM and CZA has utility extending beyond *S. maltophilia* and has significant potential in the management of infections caused by other MBL-producing Gram-negative organisms. MBL enzymes, including NDM, VIM, and IMP, have now been identified worldwide in diverse members of the family *Enterobacteriaceae* and *P. aeruginosa* (among others) (19). Although ATM is active against organisms harboring only MBL enzymes, these organisms frequently

possess one or more ESBLs, carbapenemases, or AmpC-type enzymes, which readily hydrolyze ATM and limit its utility as a single agent to rare cases. AVI potently inhibits these class A and C enzymes, and the ATM-AVI combination is nearly universally active *in vitro* against MBL-producing *Enterobacteriaceae* (10, 19). In contrast, the addition of AVI to ATM provides only minimal benefit against MBL-producing *P. aeruginosa* and *Acinetobacter baumannii*, perhaps because of the prevalence of OXA-type enzymes or non-β-lactamase-mediated β-lactam resistance in these organisms. Since ATM-AVI is in early-phase clinical trials, CZA plus ATM is presently the only means to achieve this potentially effective combination against the increasingly prevalent MBL-producing *Enterobacteriaceae*. Additionally, the possibility of *in vitro* synergy or activity resulting from the CAZ component may result in additional salutary benefit beyond the inhibition of β-lactamases by AVI (12, 13). However, given the limited clinical data available on the utility and safety of ATM-CZA, the combination should be further studied prior to widespread use (13, 20).

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