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Short Communication

Aztreonam plus ceftazidime-avibactam as treatment of NDM-1-producing *Klebsiella pneumoniae* bacteraemia in a neutropenic patient: Last resort therapy?

Paola Bocanegra-Ibarias, Adrián Camacho-Ortiz, Elvira Garza-González, Samantha Flores-Treviño, Hyojin Kim, Eduardo Perez-Alba*

Hospital Universitario "Dr. José Eleuterio González", Universidad Autónoma de Nuevo León, Madero y Gonzalitos s/n, Colonia Mitras Centro, Monterrey, Nuevo León C.P. 64460, Mexico

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ABSTRACT

Objectives: We report the successful treatment of a bloodstream infection caused by *Klebsiella pneumoniae* harbouring NDM-1 using aztreonam-ceftazidime-avibactam in a neutropenic patient in whom colistin and meropenem therapy had previously failed.
Methods: A clinical isolate was evaluated to determine the presence of NDM, TEM, SHV, CTX, and CMY, and the killing kinetics of aztreonam (ATM; 4 μg/mL), aztreonam-avibactam (ATM-AVI; 4/4 μg/mL), and colistin (2 and 4 μg/mL) were tested.
Results: ATM-AVI showed in vitro activity against the *Klebsiella pneumoniae* harbouring NDM-1, whereas colistin allowed re-growth.
Conclusions: This report supports reconsideration of use of colistin for treatment of infections caused by *K. pneumoniae* harbouring NDM. CZA/ATM use should be kept in mind as a treatment option, perhaps earlier than colistin.

1. Introduction

Although carbapenems are widely used as first-line agents for treatment of severe Gram-negative infections, the worldwide spread of carbapenem-resistant enterobacteria has led clinicians to a therapeutic dead-end compelling the use of non-β-lactam antibiotics. New Delhi metallo-β-lactamases (NDM) pose a particular challenge because of their broad hydrolysing activity that includes penicillins, cephalosporins, and carbapenems [1]. While aztreonam (ATM) is capable of evading hydrolysis by metallo-β-lactamases (MBL), serine β-lactamases render ATM ineffective leading to its combination with β-lactam inhibitors [2].

We present the case of a patient with neutropenia after haematopoietic cell transplantation (HCT) and bacteraemia caused by *Klebsiella pneumoniae* harbouring NDM, in whom therapy with colistin had failed previously, who was successfully treated with ceftazidime-avibactam (CZA) plus aztreonam (CZA/ATM).

2. Case presentation

A 35-year-old man from Honduras was referred to a hospital in Monterrey, Mexico, to undergo evaluation for HCT. The patient suffered from aplastic anaemia diagnosed 18 months prior to admission, and was treated with cyclosporin and prednisone unsuccessfully. He had been hospitalized in Honduras two weeks before his referral for the treatment of gastrointestinal bleeding. Upon his arrival in Mexico, the patient was diagnosed with *Salmonella* spp. disseminated disease and the HCT was postponed. He was treated with IV ceftriaxone for seven days and afterward received PO levofloxacin for another week as an outpatient.

One month later, he underwent preparation for HCT with a nonmyeloablative regimen (fludarabine, cyclophosphamide, and anti-thymocyte globulin). One week later, he received total body irradiation that was followed by the HCT. Only 24 h after the procedure and with an absolute neutrophil count (ANC) of 1210 cells/μL, the patient had a fever. Blood cultures were obtained, and imipenem 1 g TID and filgrastim were started, after which euthermia was achieved for two days. On day +4, ANC was 180 cells/μL, blood cultures were negative, and the patient's temperature was 39.5 °C. Thus, new blood cultures were obtained,

* Corresponding author.
E-mail address: eduardo.perezlb@uanl.edu.mx (E. Perez-Alba).

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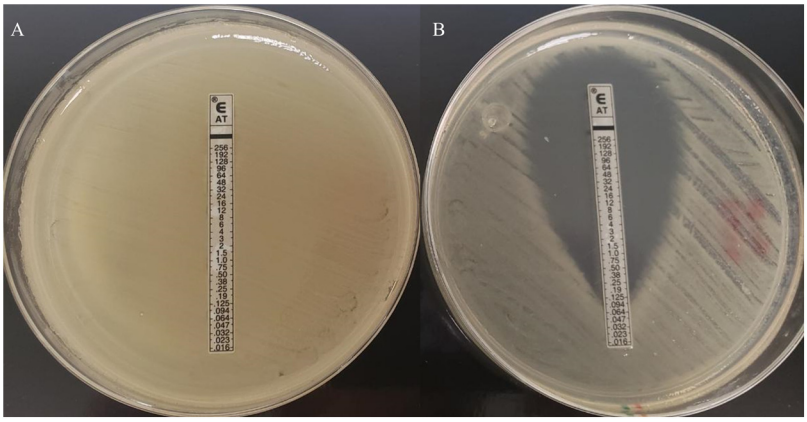

Fig. 1. Aztreonam MIC for *Klebsiella pneumoniae* isolate before (A) and after (B) exposure to avibactam.

vancomycin was empirically added to the current regimen, and other potential infectious and non-infectious causes of fever were sought.

The patient persisted as febrile, and on day +6, blood cultures grew *K. pneumoniae* after 48 h of incubation. The isolate was susceptible to colistin by broth microdilution (minimum inhibitory concentration [MIC] 0.25 μg/mL) and resistant to cefepime, ceftazidime, imipenem, meropenem, levofloxacin, piperacillin/tazobactam, gentamicin, amikacin, trimethoprim/sulfamethoxazole, and CZA by disk diffusion.

The administration of imipenem and vancomycin were stopped, and meropenem 2 g TID was started combined with colistin with a loading dose of 300 mg, after which 150 mg TID followed. The latter approach was attempted as meropenem MIC was unknown at the time and, evidence suggests that there is a lower mortality rate in patients with carbapenemase-producing *K. pneumoniae* bloodstream infections treated with carbapenem-containing combinations [3].

The patient persisted as febrile and neutropenic. The MIC for meropenem was found to be ≥32 μg/mL and by day +12 the decision was made to stop the meropenem and colistin combination and start ATM 2 g TID and CZA 2−0.5 g TID. By day +14, the patient's clinical condition improved, he became afebrile, and two days later, neutropenia resolved. There were no side effects with the new antibiotic therapy which was administered for 10 days. He was discharged and was last seen as an outpatient on day +80 free of symptoms that suggested infection, but later succumbed to his haematological disease.

3. Results

The carbapenemase-encoding gene (NDM) and the extended-spectrum β-lactamase encoding genes (TEM, SHV, CTX, and CMY) were positive by PCR. NDM-1 was detected by sequencing. KPC, GES, IMP, VIM, and OXA-48 like genes were not detected [4].

Further laboratory studies included in vitro synergy of AVI and ATM against the *K. pneumoniae* isolate using an E-test method and a time to kill assay. AVI was incorporated into Mueller-Hinton agar plates to a final concentration of 4 μg/mL. Plates were inoculated with a *K. pneumoniae* suspension with an optical density equivalent to a 0.5 McFarland standard, and an ATM E-test strip (bioMérieux, Marcy-l'Étoile, France) was applied to it, which reduced the MIC of ATM from >256 to ≤0.094 μg/mL. The combination of aztreonam-avibactam (ATM-AVI) reduced the MIC to less than the susceptibility breakpoint of aztreonam (≤4 μg/mL) (Fig. 1). The killing kinetics of ATM, ATM-AVI, and colistin were assessed using a standard time-kill methodology and by viable bacterial counts as previously reported [5,6].

The antibiotic concentrations of ATM, AVI, and colistin were adjusted to the susceptible breakpoint concentration of the antibiotics recommended by the Clinical and Laboratory Standards Institute [7]. The killing kinetics of ATM (4 μg/mL), ATM-AVI (4/4 μg/mL), and colistin (2 and 4 μg/mL) [5] showed that ATM-AVI had bactericidal activity, decreasing at least three Log at 8 h, with no regrowth at 48 h of incubation (Fig. 2).

Instead, colistin at 2 μg/mL was initially bactericidal against the *K. pneumoniae* strain, and bacterial regrowth was observed after 8 h of incubation. Colistin at 4 μg/mL inhibited the bacterial growth from 2 h completely.

4. Discussion

Treatment of infections by Enterobacteriaceae harbouring NDM remains a challenge. In this report, we present evidence of the successful use of CZA/ATM for management of bacteraemia caused by *K. pneumoniae* harbouring NDM in a patient with neutropenia after an HCT.

The in vitro activity of ATM-AVI has been demonstrated with promising results [8]. In a study that included 267 Enterobacteriaceae positive for MBL genes isolates from 40 countries, all strains were inhibited with the monobactam/non-β-lactam β-lactamase inhibitor [2]. The clinical experience is far more limited as the drug combination is not yet available for clinical use. Currently, there are two clinical studies under way: a phase III study to determine the efficacy, safety, and tolerability of ATM-AVI versus best available therapy in the treatment of infections caused by MBL producing Gram-negative bacteria (ClinicalTrials.gov registration no. NCT03580044), and a phase I study aiming to investigate the safety and pharmacokinetics of CZA/ATM (ClinicalTrials.gov registration no. NCT03978091). Although ATM-AVI is not available

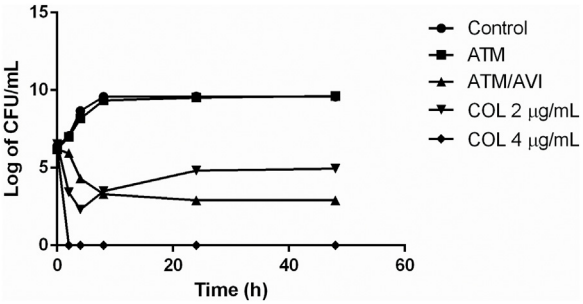

Fig. 2. Time-kill curves showing the effects of unsupplemented broth (control) and broth supplemented with either aztreonam (4 μg/mL), aztreonam-avibactam (4/4 μg/mL), or colistin (2 and 4 μg/mL).

for clinical use, successful use of CZA/ATM as prophylaxis in a patient undergoing solid organ transplant with a previous infection caused by an NDM-producing *K. pneumoniae* has been reported [9].

Regarding treatment with CZA/ATM, there is evidence of 14 patients receiving this combination, with five of them dying as a result of causes other than infection and the rest achieving clinical cure [10–13]. Although all these patients had important comorbidities or immunosuppression, our case also adds evidence of its successful use in the context of neutropenia after an HCT, a clinical scenario that has not been extensively explored [12].

The in vitro activity of ATM with other β-lactamase inhibitors against MBL-producing Enterobacteriaceae has been reported, with susceptibility restored for 86%, 50%, and 20% of the isolates when combined with CZA, amoxicillin-clavulanate, and ceftolozane-tazobactam, respectively [14]. In this report, clavulanate was as efficient as AVI in many cases. At present, there is no evidence of an in vivo effect; and an intravenous formulation is not available.

Meropenem-vaborbactam (MEM-VAB) has also been tested in vitro in combination with CZA/ATM against MBL-producing strains. Based on MIC test results, CZA restored ATM susceptibility in ATM-resistant strains more consistently than MEM-VAB and the latter proved inactive against an OXA-232 producing strain [15]. Thus, ATM plus MEM-VAB may not be the best option for empiric treatment of NDM-producing Enterobacteriaceae either.

Because of the lack of available results for use of CZA/ATM against extensively drug-resistant strains, the treatment of NDM-producing Enterobacteriaceae with non-β-lactam antibiotics is still recommended, and polymyxins head the list [1]. Different studies have evaluated the activity of colistin against *K. pneumoniae*, with evidence of prompt initial killing followed by regrowth of strains (with MICs higher or lower than 2 μg/mL) [16,17]. The case presented here provides evidence that colistin, in combination with meropenem may not be the best option to treat infections caused by *K. pneumoniae* harbouring NDM. Revision of the current susceptibility breakpoint for colistin has been suggested, because no difference in mortality has been detected between colistin-susceptible and colistin-resistant Enterobacteriaceae when the 2 μg/mL breakpoint is used [16].

In conclusion, our report supports reconsideration of use of colistin for treatment of infections caused by *K. pneumoniae* harbouring NDM, even in combination with a carbapenem. CZA/ATM use should be kept in mind as a treatment option, perhaps earlier than colistin.

Funding

None.

Competing interests

None declared.

Ethical approval

Not required.

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