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Post-surgical Meningitis due to Multi-drug Resistant *Acinetobacter baumannii*. *In Vivo* Synergistic Activity of the Sulbactam/avibactam Association

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Abstract

Acinetobacter baumannii (AB) is a non-fermenting gram-negative bacillus, largely opportunistic, ubiquitous in the environment, with the ability to survive in adverse environmental conditions, promoting its persistence and dissemination in different areas of the hospital. It has been implicated in many outbreaks of healthcare-associated infections such as pneumonia, bacteremia, surgical wound contamination, or urinary tract infections, especially among patients with previous severe illnesses such as those requiring admission to intensive care units (ICU). The most problematic strains are those resistant to carbapenems, resistance caused by chromosomal or plasmid oxacillinase class (bla OXA), and more recently bla NDM-1. The appearance of these strains leaves few active antimicrobials (Colistin, Minocycline, Tigecycline; Amikacin) that are limited in their efficacy and toxic. To this, we must add, as is the case of our patient who presented post-surgical meningitis, the limited diffusion capacity in the central nervous system (CNS) of these last options. One of the therapeutic alternatives is to search for synergistic associations such as sulbactam/avibactam that showed rapid synergistic and bactericidal activity in isolates resistant to ampicillin/sulbactam due to a significant reduction in its MIC, which allows us to administer usual, better-tolerated doses that reach therapeutic concentrations in CNS. Here, we present a patient who developed post-surgical meningitis due to multi-resistant AB.

Keywords: Post-surgical meningitis; Extensively drug-resistant (XDR); Acinetobacter baumannii; Antimicrobial synergistic association sulbactam/avibactam

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Introduction

AB is one of the main multi-resistant microorganisms linked to infections associated with health care and has become a problem of world importance. AB is identified in 13.6% of crops causing nosocomial infections, having 20.9% of the AB resistance to carbapenemic resistance (ABRC) [1]. The European and the United States Disease Control Centers (ECDC and CDC) classify AB resistance into three classes: multiple drug resistant (MDR), extensively resistant (XDR), and pan-resistant (PDR) [2].

In a study on the sensitivity profile of the complex of isolates from intra-hospital infections of the Whonet Net and blood culture, as well as an increase in the percentage of resistance for all antimicrobials and an increase in the number of insulations belonging to the MDR class during the Covid-19 Pandemic [3].

Colistin, minocycline, tigeciclin, and amikacin remain the drugs with the greatest *in vitro* activity against AB, but with a worrying increase in resistance to the first two. Post-surgical meningitis, a complication with high mortality, is aggravated when the cause is a multi-resistant microorganism where therapeutic alternatives are scarce, adding to the difficulties in achieving useful therapeutic concentrations in the CNS. Therapeutic strategies are based on administering antimicrobial associations and optimizing the pharmacokinetic/pharmacodynamic (pk/pd) relationship, those antimicrobials being of choice that maintains some degree of *in vitro* activity. In the patient described, preference was given in the antibiotic scheme to carbapenemic, phosphomycin, rifampicin or considered its intraventricular or intra-ethical use (e.g., aminoglycosides). An interesting alternative is the combination of sulbactam/avibactam which increases the activity of sulbactam against AB resistant to carbapenemic *in-vitro* studies [4].

Clinical Case

The 44-year-old patient who entered the Franchin Sanatorium Intensive Therapy Unit on May 18, 2022, derived from another institution, studying the 4th day of acute subarachnoid hemorrhage Fisher HHV. It had been subjected to a wide left decompressive craniotomy with evacuation of intra-parenchymatous hematoma left temporal, placement of subdural PIC, and drainage. The same day is referred to an interventionist neurosurgery service where angio-tac is carried out by verifying the right Lobar (VCI filter is placed) and embolizes aneurysm of the left medium cerebral artery and leaves

DVE. Samples are taken for crops and empirically start treatment with meropenem and vancomycin. Re-envises the UTI with spontaneous ocular opening, AFEBRIL, with a tendency to HTA, in mechanical respiratory assistance. It was requested TAC of the control brain continued with the same antibiotic scheme. In the surveillance anal swap at the time of re-entry, KP MBL is detected. On May 23, fever presents a lumbar puncture developing AB in the CCP sensitive to tigecycline and colistin-resistant, phosphomycin, ampicillin/sulbactam (AMS), cefotaxima, cefepime, ciprofloxacin, imipenem, meropenem, piperacilin/tazobactam, amikacin, gentamycin, and trimetopriga/sulfamethoxazole (TMS). In blood cultures develop *Enterococcus. faecalis* sensitive to ampicillin. The antimicrobial scheme is broken into vancomycin, meropenem, colistin IV, and intrathecal, despite which persisted febrile. It was decided to perform a lumbar puncture of control and in the CSF and in the subgaleal collection it develops again AB that also presents resistance to cefopezone/tazobactam, ceftazidima/avibactam, aztreonam and rifampicin/amikacin synergy so the therapeutic scheme is modified by receiving tigeciclin + amikacin IV and intrathecal + meropenem + rifampicinade agreement with sensitivity tests. At 72 hours, without changes in its clinical/neurological condition and persisting with daily febrile records and the possibility of not achieving useful therapeutic concentrations with the antibiotics used, it was decided to start with AMS + Ceftazidima/Avibactam at usual doses + tigeciclina in virtue of works published with the synergistic activity shown by Sulbactam + Avibactam [5]. The patient did not return febrile records. After two weeks, he performed lumbar control of control presenting improvement of the physical, chemical, and cytological examination with negative culture, so they suspend antibiotics at 48 hours. He presented bacteremia associated with catheter by candida parapsillosis that was treated and evolved favorably. Finally, I passed to a general room to be referred to a rehabilitation institute.

Discussion

Infections associated with health care by AB MR are related to high mortality, greater than 40% [6]. Infections caused by multiple antibiotic bacteria have increased in frequency, significantly increasing patient morbidity and mortality. AB is a nosocomial pathogen with multiple antibiotics resistance, checking a carbapenemes resistance that exceeds 85% since 2010 by the acquisition of class D. carbapenemsa D. In 2014, the first cases of insulation of abating bearers were detected in the country MBL type NDM [3]. The patient described presented to the 5th-day bacterial meningitis caused by an AB xDR that has emerged as a producer of bugs of severe nosocomial infections, widely documented worldwide and by strains resistant to resistant to carbapenemic. Colistin's use is one of the therapeutic resources, but there is currently an increase in resistance to this antimicrobial [7]. Other antibacterials with activity against AB are minocycline, tigecycline, and amikacin. In the case of the patient who describes the commitment of the CNS, complicated the therapeutic possibilities given the little effectiveness of many antibiotics to cross the hematoencephalic barrier. With bacteriological results, it was decided to continue with vancomycin, meropenem, colistin IV, intrathecal, and tigeciclin. The combination of intrathecal colistin with beta-lactam antibiotics or tigeciclin has been mentioned as effective therapy [8,9].

For the persistence of fever and the development of AB in CSF and in the subgaleal collection with the same pattern of antimicrobial resistance, being also resistant to ceftazidima/avibactam, aztreonam and showing synergy to amikacin + rifampicin, it is decided to rotate to tigeciclin, amikacin IV and it, meropenem and rifampicin. At 72 hours, without changing changes in its general status and for the persistence of fever, it is decided to start with AMS + Ceftazidima/Avibactam at usual doses continuing with tigeciclin. These AB strains with carbapenemic resistance are oxacillinase producers (blah oxa) mediated by plasmids or chromosomal, having also observed in recent times the presence of softm1 [10]. As previously mentioned, the increasing use of colistin in both human and veterinary medicine has resulted in an increase in resistance to it. The broad resistance profile observed in the patient and the location in CNS, the failure in the therapy used, and that none of the combinations of lactamic β and β lactamase inhibitors are useful against AB resistant to carbapenemic, led to the use of an association of beta-lactamase inhibitors (sulbactam + avibactam) according to works that showed synergistic activity with existing presentations [11]. This was proven by Pasteran et al. [4] when they evaluated the activity of sulbactam/avibactam and sulbactam/relabactam compared to 187 strains of AB Mr. A decrease of more than two dilutions in the Sulbactam CIM seobed in 89% of the insulation when evaluated in combination with Avibactam.

Conclusion

It is evident that, with limited therapeutic options for AB xDR, an alternative is the search for synergistic activity of antimicrobials. The indication of ampicillin/sulbactam + ceftazidima/avibactam is a therapeutic alternative to take into account in patients with infectious complications due to AB xDRCon commitment to the CNS.

Conflict of Interest

The authors declare that they have no conflicts of interest. The article was sent with the consent of all authors for their evaluation and publication.

Ethics Statement

Work has been approved by the ethics committee responsible in the workplace, and does not declare means of financing of the work carried out.

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