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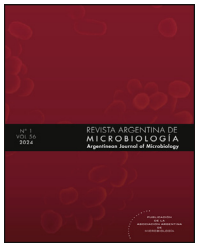

BRIEF REPORT

Sulbactam/avibactam as an alternative strategy for XDR *Acinetobacter baumannii* ventilator-associated pneumonia: A case report

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Abstract Carbapenem-resistant *Acinetobacter baumannii* (CRAB) is a critical global threat, particularly in Latin America and Argentina, where carbapenem resistance exceeds 85%. Treatment options are limited and controversial. This article presents a successful case of a patient with ventilator-associated pneumonia caused by extensively drug-resistant (XDR) CRAB, successfully treated with a combination of ampicillin/sulbactam (AMS) and ceftazidime/avibactam (CAZ/AVI). The CRAB isolate was resistant to multiple antibiotics. *In vitro* testing confirmed that avibactam restored the strain's susceptibility to sulbactam, demonstrating crucial synergy in regions without access to newer drugs. This case highlights the potential of combining AMS and CAZ/AVI as a viable therapeutic strategy for severe CRAB infections, especially XDR strains, offering a valuable alternative where options are limited.

PALABRAS CLAVE
Acinetobacter baumannii;
Carbapenem;
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Avibactam

Sulbactam/avibactam como estrategia terapéutica alternativa para la neumonía asociada a ventilación mecánica por *Acinetobacter baumannii* XDR: informe de un caso

Resumen *Acinetobacter baumannii* resistente a carbapenémicos (CRAB) representa una grave amenaza para la salud global, especialmente en América Latina, y en Argentina la resistencia supera el 85%. Las opciones de tratamiento son limitadas, lo que agrava la problemática.

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Este artículo presenta un caso exitoso de una paciente con neumonía asociada a ventilador por CRAB extremadamente resistente (XDR), tratada con ampicilina/sulbactam (AMS) y ceftazidima/avibactam (CAZ/AVI). El aislado de CRAB era resistente a múltiples antibióticos. Las pruebas *in vitro* confirmaron que el avibactam resensibilizó a la cepa al sulbactam, demostrándose así una sinergia prometedora en regiones sin acceso a nuevos fármacos. Este caso subraya el potencial de la combinación AMS y CAZ/AVI como estrategia terapéutica para infecciones graves por CRAB, especialmente en cepas XDR, y la posiciona como una alternativa valiosa donde las opciones son limitadas.

Acinetobacter baumannii (CRAB) is primarily associated with nosocomial infections in Intensive Care Units (ICUs) and has a high prevalence in Latin America, with carbapenem resistance rates exceeding 60% between 2018 and 2022[1].

Limited therapeutic options are available for severe infections caused by this pathogen[2]. The World Health Organization has included CRAB on its critical priority list for the development of new antimicrobials[3]. In Argentina, the situation is even more concerning, with carbapenem resistance rates above 85% since 2010[4].

The optimal treatment for severe CRAB infections remains controversial[5]. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID)[6] and the Infectious Diseases Society of America (IDSA)[7] offer different recommendations, particularly after the Food and Drug Administration (FDA) approval of sulbactam/durlobactam[8]. The *in vitro* activity of this combination is based on the inhibition of the OXA-type carbapenemases present in almost all CRAB strains by durlobactam, a diazabicyclooctane (DBO) derivative similar to avibactam, leading to the restoration of sulbactam susceptibility[8]. In countries where sulbactam/durlobactam has not yet been approved, sulbactam/avibactam might be a feasible therapeutic alternative, considering that avibactam is usually commercially available in combination with ceftazidime. So the aim of this study is to report a clinical case of CRAB infection successfully treated with the combination of ampicillin/sulbactam (AMS) and ceftazidime/avibactam (CAZ/AVI).

This study describes the case of a 54-year-old female patient hospitalized with newly diagnosed acute myeloid leukemia (AML). On day 12 of hospitalization, she developed neutropenic fever, pulmonary infiltrates, hypoxemia and tested positive for respiratory syncytial virus (RSV) in a respiratory sample. Cefepime was administered but a few days later she was admitted to the ICU with worsening pneumonia, requiring mechanical ventilation. She had signs of septic shock and multiorgan failure, requiring inotropic support and hemodialysis. Meropenem and vancomycin were empirically started and the latter was discontinued after two days of treatment when negative blood culture results were available. The patient had some clinical improvement and meropenem therapy was discontinued on day 8. However, two days later, while she was on ventilatory weaning, she developed a new systemic inflammatory response, with pulmonary infiltrates on the chest-X-ray and respiratory secretions compatible with ventilator-associated pneumonia (VAP). Mini-BAL cultures showed *A. baumannii* growth at >10 000 CFU/ml, considered microbiologically significant. After initial empiric antibiotic treatment with meropenem 1000 mg IV daily, therapy was switched to AMS 3000 mg IV every 12 h and CAZ/AVI 1250 mg IV every 12 h when respiratory sample culture results were reported; these doses were adjusted for the patient's renal function (i.e., extended daily hemodialysis). The dose of sulbactam (1000 mg every 12 h) was particularly considered to reach equivalent doses of 9000 mg per day in patients with normal renal function. At 72 h, the patient experienced clinical improvement with hemodynamic stability, defervescence and reduced ventilatory requirements. A follow-up tracheal aspirate sample conducted 3 days later showed no growth, indicating microbiological cure. The antibiotic regimen was completed at the same dosage for a total of 7 days, maintaining respiratory and clinical stability.

The isolate recovered from the mini-BAL culture was identified as *A. baumannii* using mass spectrometry (VITEK MS, bioMérieux®). Antimicrobial susceptibility testing was performed using an automated system (VITEK 2 Compact, bioMérieux®) and disk diffusion assays, following the guidelines of the Clinical and Laboratory Standards Institute (CLSI M100, 35th ed.) and the protocols of the Argentine National Reference Laboratory. The strain exhibited MIC values for AMS (16/8 μg/ml), amikacin (≥64 μg/ml), cefepime (≥16 μg/ml), ceftazidime (≥64 μg/ml), ciprofloxacin (≥4 μg/ml), piperacillin–tazobactam (≥128/4 μg/ml), imipenem (≥16 μg/ml), meropenem (≥16 μg/ml), trimethoprim–sulfamethoxazole (≥4/76 μg/ml), colistin (≥4 μg/ml, estimated by the colistin drop test), tigecycline (4 μg/ml), and ceftazidime–avibactam (14 μg): 6 mm, categorizing the microorganism as extensively drug resistant (XDR).

The sulbactam MIC was 8 μg/ml, and the AMS disk diffusion test showed a 13-mm inhibition zone. According to IDSA 2024 and the Argentine National Reference Laboratory 2025 criteria, both results correspond to susceptible dose-dependent (SDD) when using high-dose sulbactam combined with a second active agent. Under CLSI 2025 criteria, the isolate is classified as intermediate by MIC and resistant by inhibition-zone diameter.

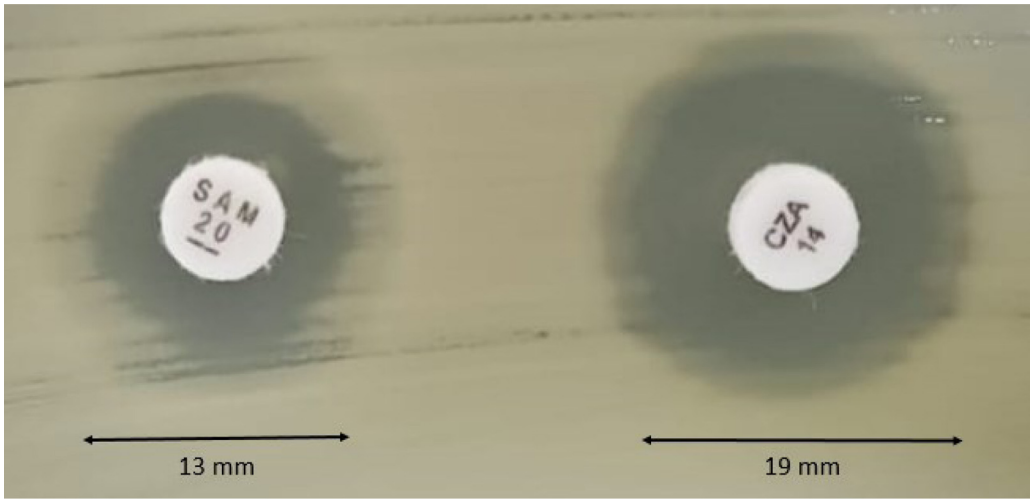

Figure 1 CRAB clinical isolate displaying positive result of the stacking technique using an ampicillin/sulbactam (SAM) (10/10 μg) disk alone and another placed over the ceftazidime/avibactam (CZA) (10/4 μg) one.

PCR detection of *blaOXA-23*-like and *blaOXA-51*-like genes was positive, whereas *mcr-1* and the metallo-β-lactamase genes *bla-VIM*, *bla-IMP*, and *bla-NDM* were not detected. Detection of KPC, NDM, VIM, and IMP by immunochromatography was also negative (O.K.N.V.I – RESIST 5, Britania).

Restoration of sulbactam susceptibility through the addition of avibactam was assessed using the stacking technique with AMS (10/10 μg) and CAZ/AVI (10/4 μg) disks (Fig. 1). The procedure consists in inoculating a Mueller–Hinton agar plate with a 0.5 McFarland suspension of the isolate, placing the AMS disk at the base and vertically overlaying the CAZ/AVI disk, adding 30 μl of sterile water onto the disks, and incubating the plate without inversion for 16–18 h at 35 °C. An inhibition zone ≥13 mm for the AMS (10/10 μg) + CAZ/AVI (10/4 μg) combination is interpreted as a SUL/AVI MIC ≤4 μg/ml[9]. This preliminary cutoff depends on the drug load of the disks and should be applied only after NDM production has been excluded[9]. In this isolate, the stacking inhibition zone measured 19 mm and was therefore interpreted as a SUL/AVI MIC ≤4 μg/ml.

This case report shows the effectiveness of sulbactam/avibactam in a patient with VAP caused by an XDR CRAB isolate, suggesting a potential synergism of this combination. The therapeutic challenges posed by this pathogen have experienced some progress in recent years. In 2023, the FDA approved sulbactam/durlobactam for hospital-acquired pneumonia and VAP caused by CRAB, based on the results from a randomized clinical trial where patients receiving this combination had similar 28-day mortality rates compared to the control group treated with colistin (both with imipenem/cilastatin), but with significantly lower nephrotoxicity[8]. Cefiderocol is another agent with activity against CRAB that has been approved by the FDA in 2020 for the treatment of carbapenemase-resistant Gram-negative bacilli including CRAB. However, due to increased early mortality observed in a clinical trial, this agent should be used with caution for CRAB infections. Despite these advances, sulbactam/durlobactam and cefiderocol remain unavailable in many resource-limited regions with a high prevalence of CRAB infections, such as Latin America, where therapeutic options are largely restricted to agents like colistin, tigecycline, fosfomycin, and sulbactam. In this setting, the IDSA guidelines recommend high-dose ampicillin/sulbactam in combination with at least another active agent (i.e., colistin, minocycline, tigecycline or cefiderocol)[7].

Sulbactam's bactericidal activity against *A. baumannii* is secondary to its inhibitory action on PBP-1a/1b and PBP-3; however, this effect is diminished by the hydrolytic action of OXA-type carbapenemases usually present in CRAB clones[10]. A pharmacokinetic/pharmacodynamic pneumonia model study showed that a sulbactam dose of 9 g/day (as 3 g three times per day in 4-h infusions) was required to achieve adequate epithelial lining fluid concentration for CRAB isolates with a sulbactam MIC of up to 8 μg/ml[11]. However, even though the safety of high-dose AMS administration has been demonstrated, clinical data comparing high-dose sulbactam with other regimens for severe CRAB infections are scarce. A literature review analyzed studies comparing high-dose sulbactam with colistin in combination with other antimicrobials for CRAB infections showed no statistically significant differences in all-cause mortality, although the authors concluded that high-dose sulbactam combined with other agents (including colistin) might be a favorable therapeutic option for CRAB infections[12].

Recent studies have confirmed the *in vitro* activity of sulbactam/avibactam against CRAB, with 91% restoration of sulbactam susceptibility observed following the addition of avibactam in strains producing the OXA-23 carbapenemase[10]. In this regard, the Argentine National Reference Laboratory recently reported that an inhibition diameter ≥13 mm (using 14-μg CZA disks) obtained with the stacking technique shows good correlation with sulbactam–avibactam MIC values ≤4 μg/ml among CRAB isolates lacking NDM production. Since this CRAB isolate exhibited a 19-mm inhibition diameter, it can be inferred that it belongs to this susceptible category and would likely not require maximum doses of 9 g/day to achieve therapeutic success when combined with avibactam, although

no clinical studies are currently available to support these findings.

In the case presented here, the combination of AMS with CAZ/AVI was selected because the XDR CRAB isolate was resistant to colistin and tigecycline. Although pharmacokinetic/pharmacodynamic models predict an almost 100% probability of target attainment when using 9 g/day of sulbactam for isolates with a sulbactam MIC of 8 μg/ml[11], the available clinical evidence remains insufficient to support high-dose sulbactam monotherapy for severe infections caused by isolates with sulbactam MICs of 8 μg/ml[12]. Furthermore, because the patient was undergoing hemodialysis, the actual sulbactam concentration at the infection site was uncertain, as pharmacokinetic data to guide sulbactam dosing in patients with renal impairment are limited[13]. The addition of a DBO carbapenemase inhibitor – such as durlobactam or avibactam – significantly reduces sulbactam MICs, restoring its activity against the aforementioned PBPs and increasing the likelihood of therapeutic success. Therefore, in settings where sulbactam/durlobactam is not available, combining sulbactam with another DBO β-lactamase inhibitor such as avibactam, may represent a valuable alternative. Clinical success with this combination was reported in a critically ill 2-year-old burn patient[14], as well as in two additional cases of bacteremia and VAP during a CRAB outbreak in a burn ICU, both of which occurred after microbiological failure of cefiderocol therapy[15]. In these cases, *in vitro* synergy between sulbactam and avibactam was demonstrated with MICs of ≤4 μg/ml[15]. More recently, a case of a patient with CRAB bacteremia was successfully treated with the sulbactam–avibactam as salvage therapy after sulbactam–colistin clinical failure[16].

Sulbactam/avibactam combination appears to be a promising alternative for severe CRAB infections in regions where sulbactam/durlobactam is not available, although further prospective clinical data are still required.

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Conflict of interest

The authors declare having no conflict of interest.

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