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ACETOHYDROXAMIC ACID INTERACTS WITH THE CATALYTIC SITE OF *PROTEUS* SPP. UREASE WITH AFFINITY EQUIVALENT TO THAT OF UREA

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Introduction: Urease is an essential virulence factor in *Proteus* spp., contributing to urinary tract infections through the hydrolysis of urea as an energy source and by alkalinizing the environment. Acetohydroxamic acid (AHA) is a reversible urease inhibitor, clinically approved in some countries for the treatment of chronic infections caused by urease-positive bacteria such as *Proteus mirabilis*.

Objective: To investigate the binding mode of AHA to the apo and holo forms of urease from clinical isolates of *Proteus* spp., evaluating its interactions with catalytic residues, determining whether these residues are conserved among isolates, and assessing the contribution of Ni²⁺ metal coordination.

Methods: Structural models were predicted using AlphaFold3, cofactors were added with AlphaFill, and molecular docking was performed with AutoDock Vina. Interactions were analyzed with ChimeraX (v1.10), and residue conservation was verified through multiple sequence alignment.

Results: AHA exhibited predicted affinities of -4.2 kcal/mol (apo) and -4.4 kcal/mol (holo), slightly higher than those of urea (-3.811 and -4.078 kcal/mol). In the apoenzyme, AHA formed hydrogen bonds with His134, His136, His219, His246, Asp360, and Ala363. In the holoenzyme, in addition to maintaining interactions (His219 and Ala363), AHA directly coordinated with both Ni²⁺ ions, an exclusive feature of the holo form of urease. The interactions of AHA with the holo form are strengthened by both Ni²⁺ ions and lysine carboxylation (KCX). The involvement of the modified lysine highlights its functional role not only in metal stabilization but also in ligand anchoring through hydrogen bonding.

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Conclusion: Taken together, these findings confirm the inhibitory potential of AHA against *Proteus* urease and reinforce its clinical relevance as an anti-virulence strategy through competitive inhibition of urea.

Keywords: *Proteus*, Urease, Interactions, Apoenzyme, AHA.

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ETHYLENEDIAMINETETRAACETIC ACID AS A STRATEGY TO INHIBIT BIOFILMS OF *ACINETOBACTER BAUMANNII* DERIVED FROM HOSPITAL INFECTION

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Introduction/Objective: The gram-negative coccobacillus *Acinetobacter baumannii* has frequently been associated with infections occurring after the hospitalization of patients in intensive care units. Its dissemination in hospitals has been favored by its ability to form biofilms, a matrix composed of carbohydrates, proteins, nucleic acids, and other macromolecules, on surfaces and medical devices. Studies have shown that mechanisms related to reduced microbial susceptibility tend to promote cross-resistance among antibiotics, biocides, and disinfectants, contributing to longer hospital stays and increased resistance to available antimicrobials. In addition, few biocides are available on the market, and some already have intrinsic resistance documented and exacerbated by incorrect use and concentration. Even so, progress in the

development of strategies for new compounds acting on devices and surfaces remains limited.

Methods: The study was conducted with clinical isolates from a hospital in southern Brazil. The ability to form microbial biofilms was determined as proposed by Halicki et al. (2019). Subsequently, in polystyrene plates, 10^6 CFU/mL of each isolate was exposed to three concentrations of EDTA (12, 0.6, and 0.3 mM). After incubation for 24 hours at 37°C, the inhibitory capacity of biofilm formation was evaluated using 0.4% crystal violet as an indicator.

Results: Half of the isolates (5/10) were classified as moderate biofilm formers. Regarding the biofilm inhibition potential of EDTA, which has a high capacity for metal ion chelation, it was observed that the mean inhibition was 90.8% at a concentration of 12 mM, 82.2% at 0.6 mM, and 22% at 0.3 mM.

Conclusion: The ability of the chelating agent EDTA to interact with cations that maintain the structural stability of the bacterial outer membrane may make it more susceptible to the entry of antimicrobial agents and to cell lysis, thereby inhibiting the initial stages of biofilm formation. In this context, EDTA demonstrates potential to inhibit this important virulence mechanism of *A. baumannii*, highlighting the relevance of further studies exploring its mechanism of action and potential as a biocidal agent.

Keywords: Biocide, Chelating agents, Virulence, Infection.

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THE IMPORTANCE OF THE CLINICAL PHARMACIST IN MANAGING THE SAFE USE OF CEFTAZIDIME/AVIBACTAM AND THE IMPACT OF THE SMART-CAZ/AVI ALGORITHM

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Background: The treatment of infections caused by gram-negative bacteria has been associated with reports of resistance through different mechanisms of action. Therefore, CAZ/AVI should be reserved for multidrug-resistant infections, and rational use is essential to ensure safe antibiotic therapy and minimize adverse events. In this context, the clinical pharmacist plays a key role in the stewardship of CAZ/AVI, with a strategic role in promoting safety in prescribing and administration.

Aim: The aim of this study was to evaluate pharmaceutical interventions related to the use of CAZ/AVI and the impact of implementing a time-out tool on the frequency and acceptability of interventions.

Methods: Descriptive, quantitative, retrospective study conducted between January 2022 and December 2024 in a private hospital in Rio de Janeiro. Pharmaceutical interventions related to electronic prescription errors of CAZ/AVI were analyzed. These errors were classified as decision or writing errors, and further subdivided according to the PRAT tool. In

August 2023, the SMART-CAZ/AVI algorithm was implemented to standardize prescription analysis, using the time-out as a monitoring tool (CAAE: 77108523.5.0000.5533).

Results: A total of 56 pharmaceutical interventions were performed, with 98.2% classified as decision errors and 1.8% as writing errors. Among decision errors, 74.5% were overdoses according to creatinine clearance (ClCr), 14.5% were underdoses according to ClCr, 9.1% were due to treatment duration requiring suspension, and 1.8% were due to inappropriate scheduling. In writing errors, 100% involved inappropriate units of measurement. Of the interventions performed, 70.2% were accepted by the medical team. After implementation of the SMART-CAZ/AVI tool, there was a 103.03% increase in the number of interventions and a 12.31% increase in the acceptance rate.

Conclusion: The role of the clinical pharmacist was essential for ensuring the safe use of CAZ/AVI, particularly in dose adjustment according to renal function. The SMART-CAZ/AVI tool contributed to increased detection of prescription errors and acceptance of interventions, highlighting the positive impact of standardization and systematization of pharmaceutical care, optimizing the stewardship of rational CAZ/AVI use, and promoting safe antibiotic therapy for patients.

Keywords: Ceftazidime/Avibactam, Antimicrobial stewardship, Clinical pharmacy service, Rational drug use.

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N-ACETYLCYSTEINE EXHIBITS POTENTIAL TO INHIBIT THE ACTIVE SITE OF UREASE FROM CLINICAL ISOLATES OF KLEBSIELLA SPP.

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Introduction: Urease is a nickel-dependent enzyme linked to the pathogenesis of several bacterial species[1], including carbapenemase-producing *Klebsiella*, which are often associated with hospital infections and multidrug resistance to antimicrobials. N-acetylcysteine (NAC), a clinically approved compound with mucolytic properties, has also shown *in vitro* inhibitory activity against *Klebsiella pneumoniae* urease[2] and other bacteria[3].

Objective: This study evaluated the binding of NAC to the immature (apoenzyme) and mature (holoenzyme) forms of urease from clinical isolates of *Klebsiella* spp.

Methods: Sequences were aligned, and structural models were generated with AlphaFold3 (apoenzyme) and AlphaFill (holoenzyme), with insertion of Ni^{2+} ions. Docking was performed with AutoDock Vina, and interactions were evaluated using the Protein–Ligand Interaction Profiler (PLIP). The obtained affinities were compared with those of urea as the reference natural substrate.