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O0392 Contribution of beta-lactamases, porins and efflux pumps to carbapenem resistance in *Acinetobacter baumannii*

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Background: *Acinetobacter baumannii* is recognized as one of the most challenging nosocomial pathogens, whose infections are often associated with epidemic spread of multidrug-resistant strains. *A. baumannii* strains resistant to carbapenems are an emergent threat as they limit the range of therapeutic alternatives and pose a considerable threat to clinical patient care and public health. Here, we investigated the role of efflux pumps in carbapenem resistance using 16 MDR *A. baumannii* clinical isolates as proof of concept.

Materials/methods: Drug susceptibility was assessed by disc diffusion. All isolates were screened for genes encoding IMP, VIM, SIM, GES, KPC, NDM, TEM, SHV, OXA-23, OXA-24, OXA-51, OXA-58, and OXA-143 β-lactamases and ISAba1. The contribution of efflux mechanisms to carbapenem resistance was assessed by synergism assays with efflux inhibitors (EIs), ethidium bromide real-time efflux activity evaluation, and the expression analysis of efflux pump genes and porins in response to imipenem. *A. baumannii* ATCC19606 was used as control.

Results: All strains presented a multidrug resistant phenotype characterized by resistance to carbapenems, fluoroquinolones and aminoglycosides. The β-lactamases OXA-23 were detected in three strains and OXA-24 in 13. OXA-51 were detected in all strains but ISAba1 was not detected upstream this oxacillinase excluding its contribution to carbapenem resistance. The results showed the existence of synergistic interactions between EIs and carbapenems and ethidium bromide extrusion. Efflux assays demonstrated that these strains have significantly increased efflux activity that can be inhibited in the presence of EIs, mainly thioridazine. The efflux pumps genes *adeB*, *adeJ*, *adeG*, *craA*, *amvA*, *abeS* and *abeM* were overexpressed in response to carbapenems. An association between carbapenems resistance and the expression of the porins *ompA*, *carO* or *oprD* was not found.

Conclusions: This study demonstrates the contribution of efflux pumps to carbapenem resistance in MDR *A. baumannii* clinical strains. Clinical carbapenem resistance is a combination between increased efflux activity and β-lactamases production such as OXA-23 or OXA-24. Overexpression of efflux pumps may impact the clinical outcome of *A. baumannii* infections and treatment should consider alternative therapeutic combinations such as the use of EIs.

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