TITLE: CHARACTERIZATION OF CARBAPENEM NON-SUSCEPTIBLE *Pseudomonas aeruginosa* BETWEEN 2019 AND 2021: INCREASED RESISTANCE

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Pseudomonas aeruginosa is an opportunistic pathogen associated with nosocomial infections that has demonstrated antimicrobial resistance, including carbapenems, one of the main therapeutic options against infections caused by this microorganism. Epidemiological studies help to elucidate the evolution and dissemination of resistance mechanisms, as well as the use of empirical antimicrobials for treatment. The Adolfo Lutz Institute has public health surveillance laboratories that receive microbiological isolates of Gram negative pathogens causing hospital-acquired infections, for identification and epidemiological study. A total of 1,546 bacterial isolates were received between 2019 August and 2021 August, from which 81 (5%) were identified as carbapenem non-susceptible (carbaNS) *Pseudomonas aeruginosa.* After excluding duplicate patients' samples, a total of 59 isolates from different patients, from 13 different hospitals in state of São Paulo, were analyzed. Isolates were submitted to multiplex PCR for carbapenemases (KPC, NDM, OXA-48, SPM, IMP and VIM), from which 19 (32%) were positive for bla_{IMP} gene, 3 (5%) for the bla_{VIM} gene, 2 for bla_{SPM} and 1 for bla_{KPC}. The high number of bla_{IMP}-positive isolates was found to be due to the occurrence of a monoclonal outbreak in the year 2020, in a kidney transplant patients' hospital, as characterized by pulsed field. Through the sensitivity test performed by the disk-diffusion method, 53 (90%) isolates were either non-susceptible for ciprofloxacin, cefepime and levofloxacin, while 39 (66%) were susceptible for aztreonam and 26 (44%) for tobramycin. In the microdilution test for polymyxin B, 5 (8%) isolates of carbaNS were resistant (MIC≥4ug/mL), excluding another possible therapeutic option. Out of the 59 carbaNS *P. aeruginosa* isolates, 34 (58%) did not present carbapenemase production, likely indicating the resistance mediated by AmpC hyperexpression +/- porin loss. In these cases the use of new drug combination like ceftazidime/avibactam and meropenem/varbobactam could be an important therapeutic option. In summary, we observed that non-carbapenemase mediated resistance to carbapenems is quite important in drug-resistant *P. aeruginosa*, opening opportunities to the use of novel beta-lactam/beta-lactamase inhibitors. Nevertheless, outbreaks due metallo-beta-lactamases-producing strains can also occur, which demands the correct identification of mechanisms associated with resistance phenotypes.

Keywords: antimicrobial resistance; carbapenem non-susceptible; ceftazidime/avibactam; *Pseudomonas aeruginosa*

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