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Pseudomonas aeruginosa resistant to carbapenems: evaluation of the prevalence of resistance determinants and levels of sensivity to latest generation drugs.

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INTRODUCTION

The spread of carbapenemase-producing strains of Pseudomonas aeruginosa resistant to carbapenems (CRPA) constitutes a problem clinically relevant, as it limits therapeutic choices for potentially serious infections. The aim of the study was to evaluate the prevalence and typology of genes among class A (GES and KPC) and class B (IMP, VIM and NDM) carbapenemases in P. aeruginosa (PA) and identify the drugs with greater efficacy in vitro for the treatment of carbapenem-resistant P. aeruginosa.

METHODS

For the study, 72 isolates of P. aeruginosa resistant to meropenem were selected from clinical and surveillance samples, collected as part of the routine diagnostic activity at the U.O. of Microbiology, IRCCS University Hospital of Bologna, in the period August-December 2023. For each isolate, the following were performed: i) search for carbapenemase production with NG-Test CARBA-5 enzyme immunoassay (Figure 1); ii) molecular test for the detection of class A carbapenemases (GES), through nucleic acid extraction with the ELITe InGenius instrument and amplification with a home-made PCR system; iii) evaluation of the MIC of the following antibiotics, obtained with different methods: - routine antibiogram with MicroScan WalkAway broth microdilution system (Figure 2) for ceftazidime, cefepime, ceftazidime/avibactam, piperacillin/tazobactam, ceftolozane/tazobactam, meropenem, imipenem; -antibiogram with manual method: E-test for imipenem/relebactam, Kirby-Bauer for cefiderocol, Agar-dilution for fosfomycin; all antibiotics were interpreted with Eucast Breakpoint MIC criteria (Version 13.0,2023).

Figure 1. Enzyme immunoassay NG-Test CARBA-5

Figure 2. MicroScan WalkAway

RESULTS

Of the 72 isolates, 20 were from surveillance swabs (rectal mucosal swabs) and 52 from clinical specimens (21 from respiratory material, 16 from urine, 5 from blood and 10 from other sources) (Figure 3). It was found that 29.2% (21/72) of the total CRPA strains analyzed were positive for carbapenemase. 42.8% (9/21) of the total carbapenemase producers were producers of IMP, 33.3% (7/21) of VIM, 19.1% (4/21) of GES and 4.8% (1/21) of NDM (Figure 4). 70.8% (51/72) of the total samples tested are not carbapenemase producers.

Of the 72 samples analyzed, 3/72 (4.2%) were sensitive to imipenem (MIC ≤4), 41/72 (56.9%) sensitive to ceftazidime/avibactam (MIC ≤8). 45/72 (62.5%) samples were sensitive to ceftolozane/tazobactam (MIC< 4); of the 27 isolates found to be resistant to ceftolozane/tazobactam, 19 (70.4%) are carbapenemase producers. 18/72 (25%) samples were sensitive for cefepime (MIC<8), 25/72 (35%) for piperacillin/tazobactam (MIC<16) and 17/72 (24%) for ceftazidime (MIC<8) . For fosfomycin the MIC50 was 64 µg/mL and the MIC90 >256 µg/mL; 64.3% (45/70) of the strains tested for this antibiotic have MIC< 256 µg/mL. 22.2% of the samples tested were sensitive for imipenem/relebactam and 94.4% for cefiderocol.

For many drugs it is possible to observe a statistically significant difference ($p < 0.05$) between the percentage of resistance in the case of CPPA and non-carbapenemase-producing PA. Ceftolozane/tazobactam, for example, shows a large difference between CP-producing and non-producing strains, as does ceftazidime/avibactam. For cefiderocol, the few resistant strains observed are carbapenemase producers (Figure 5).

Figure 3. Clustered bar graph of the type of isolates used for this study.

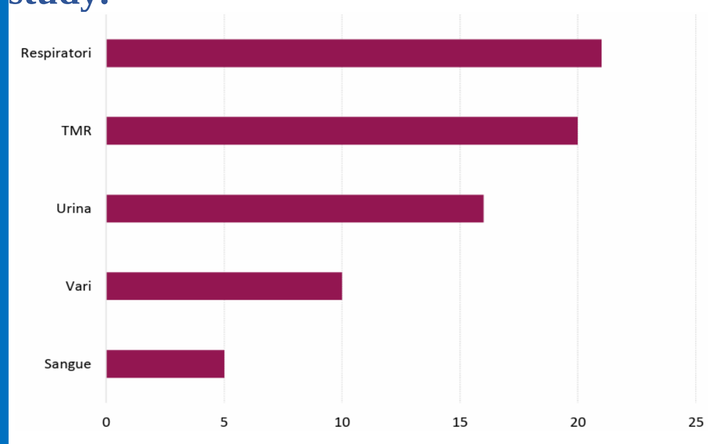
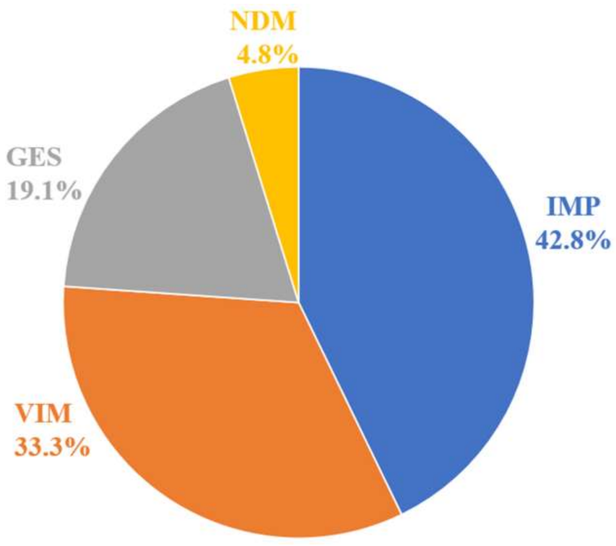
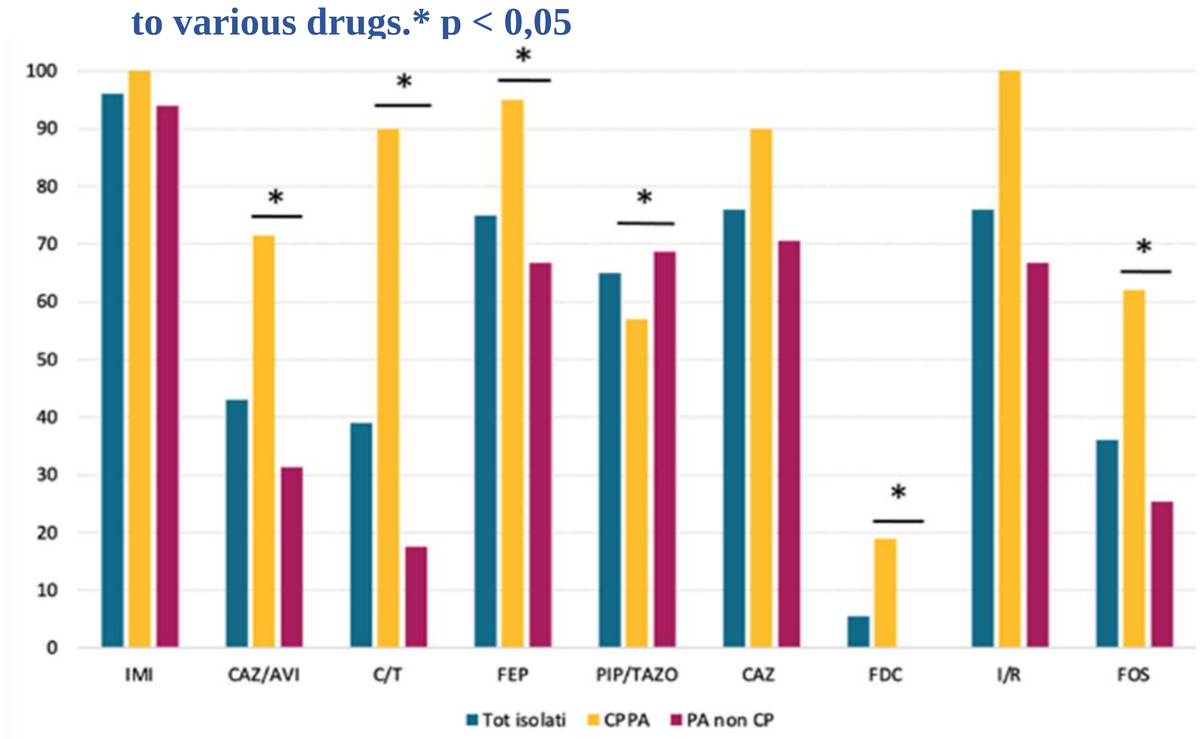


Figure 4. Pie chart of the relative percentages of P. aeruginosa isolates with class B CP (IMP, VIM and NDM) and isolates with GES resistance gene (class A CP) out of the total of those found to produce CP



**CP: carbapenemases*

Figure 5. Summary table comparing the percentages of resistance to various drugs.* p < 0,05



CONCLUSION

The data demonstrate that: i) in the epidemiological context covered by the study, the production of carbapenemases was rather frequent, with a prevalence of the IMP gene; the prevalence of CP in carbapenem-resistant PA isolates was higher than that highlighted in similar studies carried out previously in the Italian epidemiological context and also in the specific Bolognese one; ii) multi-resistance is strictly related to the production of carbapenemases and in general, among the drugs routinely tested, in PA strains that do not produce carbapenemases, ceftolozane/tazobactam and, in second place, ceftazidime/avibactam retain greater sensitivity while cefiderocol is the drug that overall provides the best guarantee of effectiveness.