Title: CO-EXISTENCE OF THE *qnrS* AND *aac(6`)-Ib-cr* GENES WITH MUTATIONS IN *gyrA* AND *parC* AMONG FLUOROQUINOLONE-RESISTANT *Pseudomonas aeruginosa* ISOLATED OF COMMUNITY AND NOSOCOMIAL INFECTIONS IN BRAZIL

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Abstract:
Pseudomonas aeruginosa is one of the most important opportunistic pathogen. The presence of plasmid-mediated quinolone resistance (PMQR) determinants can stimulate mutations in genes encoded by DNA gyrase and topoisomerases IV, promoting high levels of resistance to quinolones. This study evaluated the co-existence of PMQR determinants with mutations in the quinolone resistance-determining regions (QRDRs) and class 1 integron genes in 40 fluoroquinolone-resistant *Pseudomonas aeruginosa* isolates. Plasmid analysis and specific PCRs were performed for *qnrA, qnrB, qnrC, qnrD, qnrS, qepA*, *aac(6')-Ib-cr* and *intI1,* and these were associated to mutations previously performed by sequencing of QRDRs. Antimicrobial susceptibility testing results were analyzed, 37.5% (15/40) and 50% strains (20/40) were characterized as multidrug (MDR) and extensively drug-resistant (XDR) isolates, respectively. The resistance rates for isolates to carbapenem, cefepime, piperacillin/tazobactam, and aminoglycosides were 80%, 72.5%, 57.5% and 55%, respectively. Thirty four isolates (85%) harboured the *aac(6')-Ib-cr* and one isolate concurrently presented both genes, *qnrS* and *aac(6')-Ib-cr*. The presence of the class 1 integron gene was observed in 90% of isolates, and negative strains for integron did not show PMQR genes. None of the isolates contained *qnrA, qnrB, qnrC, qnrD, qnrS* and *qepA.* Of the 34 PMQR positive *Pseudomonas aeruginosa* isolates, 20 were evaluated for QRDRs mutations in *gyrA* and *parC*, these 18 had co-existence of PMQR and QRDRs mutations (90% *aac(6´)-Ib-cr* + Thre83Ile; 93.7% *aac(6´)-Ib-cr* + Thre83Ile + Ser87Leu). These results provide additional evidence that chromosomal QRDRs mutation in sequences encoding *gyrA* and *parC* plus the presence of PMQR determinants play an essential role in fluoroquinolone resistance, reflecting the high rates of resistance found. Another surprising finding shows a high frequency of isolates with co-existence of these resistances was characterized as extensively drug-resistant (77.8%). In conclusion, these results have shown the presence of the PMQR determinants in *Pseudomonas aeruginosa* addition to the high frequency of these co-existing with mutations in *gyrA* and *parC* genes. Our results also contribute to indicate the wide dissemination of class 1 integrons genes in these environments and the association of this with reduced susceptibility of *Pseudomonas aeruginosa* to antimicrobial currently prescribed.

Keywords: Plasmid mediated quinolone resistance; QRDRs mutations; *Pseudomonas aeruginosa.*

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