

## XIX CONGRESO DE LA SOCIEDAD ARGENTINA DE MICROBIOLOGÍA GENERAL

22 al 25 de octubre del 2024

Centro cultural y Pabellón Argentina de la Universidad Nacional de Córdoba, Córdoba, ARGENTINA.



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## PHENOTYPIC AND GENOTYPIC VARIATIONS OF *Staphylococcus aureus* UNDER CFTR MODULATOR TREATMENT IN CYSTIC FIBROSIS

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*Staphylococcus aureus* (SA) is one of the most isolated pathogens from the lungs of pediatric patients diagnosed with cystic fibrosis (PPCF). To persist in these environments, SA has evolved mechanisms to withstand various stressors, including immune responses, microbial competition, and exposure to antibiotics and other CF-related therapies. Recently, Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) modulators have been introduced into the treatment regimen for CF patients in Argentina. Our hypothesis is that within SA infections, the presence of competitors like *Pseudomonas aeruginosa* (PA) or the use of CFTR modulators selects for specific genetic variants, resulting in phenotypes advantageous in this microenvironment. In this study, we analyzed 20 genomes from two PPCF, corresponding to a patient mono-infected with SA and another to a SA-PA coinfecting patient. These genomes were sequenced using the Illumina HiSeq platform, before and after the initiation of CFTR modulator therapy. Our results showed that most isolates belonged to sequence type 398 (ST398), a methicillin sensitive SA (MSSA) lineage recently observed in Argentina, characterized by clones with high virulence and distinct phenotypes compared to other SA lineages. Additional isolates were identified within clonal complexes CC30, CC5, CC1, and CC22, typically associated with Methicillin Resistant SA (MRSA), exhibiting unique virulence profiles. Notably, 17 out of the 20 isolates carried the *bla<sub>Z</sub>* gene, displaying significant nucleotide variability comparing to the reference strain USA300 (ST8). Particularly, in the coinfecting patient, most isolates belonged to ST398 and were MSSA, regardless of the sampling time, except for one isolate, which belongs to CC30. In contrast, the mono-infected patient exhibited greater genetic diversity throughout the study. Pre-modulator therapy isolates were predominantly ST398. Post-therapy isolates, however, diverged into two distinct groups: one associated with CC5 and CC22 (collected 2 months after the start of treatment), and one associated

with CC1 (collected 6 months after). Phenotypically, the isolates, except for those belonging to CC1, show high production of staphyloxanthin, high DNase activity, low hemolytic activity, and greater resistance to PA compared to USA300 (ST8). The isolates belonging to CC1 show reduced staphyloxanthin production, diminished DNase activity, an absence of hemolytic activity, and heightened resistance to PA. In conclusion, our study identifies ST398 as the predominant lineage, particularly in the PA-SA co-infected patient, suggesting that its high virulence and immune evasion capabilities may confer a selective advantage in the presence of both the CFTR modulator therapy and PA competition. Furthermore, the genetic variability observed in the mono-infected patient indicates the possible emergence of modulator-resistant variants, which may be selected over time as therapy is prolonged.

Palabras clave: Staphylococcus – Pseudomonas – GENOMES – MODULATOR – FIBROSIS