TITLE: *STENOTROPHOMONAS MALTOPHILIA* IN A CYSTIC FIBROSIS PATIENT: PHENOTYPIC AND GENOMIC ANALYSIS OF RESISTANCE

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ABSTRACT:

The recurrent use of antimicrobials in Cystic Fibrosis (CF) patients lead to colonization by multidrug-resistant (MDR) microorganisms such as *Stenotrophomonas maltophilia*. Although this microorganism is not yet being considered a classic virulent pathogen, it presents a range of intrinsic and acquired resistance mechanisms to most antimicrobials. The purpose of this study was to identify the phenotypic resistance profile and genomic analysis of resistance of *S. maltophilia* isolates obtained from sputum of a single pediatric patient, persistently colonized by *S. maltophilia* assisted at a reference center in Rio de Janeiro. Whole Genome Sequencing (WGS) was performed on a MiSeq benchtop instrument (Illumina, USA). The minimal inhibitory concentration (MIC) was determined for 4 isolates collected in 2012, 2013 and 2014 to ciprofloxacin (CIP), ceftazidime (CAZ) and trimethoprim/sulfamethoxazole (TMP-SXT). All isolates were susceptible to SXT (MIC ranged from 0.25 to 1ug/mL) and resistant to CAZ (MIC =128 ug/mL) and CIP (MIC ranged from 4 to 16 ug/mL). The Rapid Annotation using System Technology (RAST) v. 2.0 server (http://rast.nmpdr.org) and BLASTP searches against GenBank were used for genome annotation. The results reveal that all isolates carry the gene bla_{L1} (metalo-beta-lactamase) and the operon *ampR*-bla_{L2} responsible for resistance to all clinically available beta-lactams. Three RND (resistance-cell-regulation) efflux pumps, such as, SmeABC, SmeDEF and SmeVMX were also identified in all isolates. SmeABC and regulators are encoded by the operon *smeABC* and *smeRS*, respectively and are involved in acquired resistance to beta-lactams. In addition, SmeABC results in decreased susceptibility to fluoroquinolones. We have also identified the SmeDEF and VMX efflux pumps operons and their regulators, *smeT* and *smeRv*, respectively. SmeDEF is the most described and important mechanism associated with low-level fluoroquinolone intrinsic and acquired resistance. Otherwise, overexpression of SmeVWX is associated with high-level (MIC > 32 ug/mL) fluoroquinolones acquired resistance. Besides that, we also identified two genes (*smqnr, qnr* family and *smrA,* ABC-ATP binding cassette) involved in the intrinsic and acquired resistance to fluoroquinolones. The Multilocus Sequence Typing analysis showed that all samples belong to the same sequence type. Overall, our result suggest that *S. maltophilia* can successfully adapt to a highly stressful environment such as CF lung.

Keywords: *Stenotrophomonas maltophilia*, Cystic Fibrosis, antimicrobial resistance, genome sequencing

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