Title: MOLECULAR AND PHENOTYPIC RESISTANCE TO FLUORQUINOLONES IN *Staphylococcus aureus* ISOLATES PRESENTING DIFFERENT GENETIC BACKGROUND

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Abstract:

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important pathogen, and fluorquinolones are an alternative choice for the clinical treatment of MRSA infections. However, these isolates can present mutations at the Quinolone Resistance-Determining Region (QRDR) of *gyrA*, *gyrB*, *parC* and *parE* genes. The aim of this study was to determine minimum inhibitory concentrations (MIC) for fluorquinolones in 70 MRSA isolates from different clonal lineages and evaluate the presence of mutations at the QRDR of *gyr* and *par* genes. MIC for ciprofloxacin and moxifloxacin were determined by the microdilution broth method and the clonal lineages were assessed by PFGE and SCC*mec* typing by multiplex PCR. Punctual mutations at *gyrA*, *gyrB*, *parC* and *parE* genes were detected on41 randomly chosen MRSA isolates by DNA sequencing. The MIC_{50} and $MIC_{90}$for ciprofloxacin were32 and 256 μg/mL, and for moxifloxacin were 2 and 32 μg/mL, respectively. Overall, 44% (31/70) of the isolates belonged to USA100/SCC*mec*II lineage, 18.5% (13/70) belonged to the Brazilian Epidemic Clone (BEC)/SCC*mec*III, 18.5% (13/70) to the USA400/SCC*mec*IV, 13% (9/70) were named as USA 800/SCC*mec*IV and four isolates carrying the SCC*mec* type IV were related to sporadic clones. It was possible to associate specific mutation patterns with the different clonal lineages, and this association was related to the MIC values (p<0.05). The USA800/SCC*mec*IV isolates presented low fluorquinolones MICs and was related to the unique mutations at codons 80 (ser→phe) and 88 (glu→gli) at *parC* and *gyrA* genes, respectively. Similarly, BEC/SCC*mec*III isolates had low MICs and were related to mutations at the genes *parC* (80:ser→phe) and *gyrA* (84: ser→leu). On the other hand, USA400/SCC*mec*IV isolates with MICs of ≥128 μg/mL showed double mutations at the *parC (*80:ser→tir and 84:glu→lis/gli) and *gyrA* (84: ser→leu) genes. Among USA100/SCC*mec*II isolates, with MIC values >128 μg/mL for ciprofloxacin double mutations were detected at *parC* (80:ser→tir and 84: glu →lis/gli) and *gyrA* (84: ser→leu and 88: glu→lis) genes. No isolate presented mutation at the *parE* gene, while only one BEC isolate showed a *gyrB* mutation. Our results indicate a strong association of MRSA specific genetic backgrounds with the type of QRDR mutation present. We also observed a relationship between the type of mutation and the fluorquinolones MIC values among the MRSA isolates analyzed.

Key-words: *Staphylococcus aureus,* MRSA, fluorquinolones, *QRDR*

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