

Title: DETECTION OF *aac(6')-Ie-aph(2'')*-Ia GENE IN PENICILLIN-RESISTANT *Enterococcus faecalis* ISOLATES WITH HIGH-LEVEL GENTAMICIN RESISTANCE

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Abstract:

The therapy for severe enterococcal infections requires the use of synergistic combinations of a cell wall-active agent, such as penicillin or glycopeptide, with an aminoglycoside, which results in bactericidal activity. However, *Enterococcus faecalis* isolates exhibiting cross-resistance to both G-penicillin and gentamicin (high-level) have been emerged worldwide. In general, high-level aminoglycoside resistance in enterococci is mediated by a drug-modifying enzyme encoded by the *aac(6')-aph(2'')*-Ia gene that confer resistant to virtually all of the clinically available aminoglycosides, including gentamicin but not streptomycin. Therefore, this study aimed to investigate the presence of the *aac(6')-aph(2'')*-Ia gene in penicillin-resistant *E. faecalis* isolates. The isolates were recovered from patients at a Brazilian tertiary hospital from 2006 to 2014. The minimum inhibitory concentration (MIC) for beta-lactams (penicillin and ampicillin) and aminoglycosides (gentamicin and streptomycin) was determined by broth dilution test according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Detection of the *aac(6')-aph(2'')*-Ia gene was performed by PCR. A total of 87 *E. faecalis* isolates were evaluated, 49 were penicillin-resistant (MIC ranged of 16 to 32 µg/mL) and 38 were penicillin-susceptible (MIC ranged of 2 to 8 µg/mL). The isolates were recovered from various clinical samples such as wounds, urine, blood, and secretions. Among the 49 penicillin-resistant isolates, 44 (90%) showed high-level gentamicin resistance (HLGR) (MIC ≥ 500 µg/mL) and 37 (75%) contained the gene *aac(6')-aph(2'')*-Ia; 2 (4%) showed high-level streptomycin resistance (HLSR) (MIC ≥ 1000 µg/mL). Among the 38 penicillin-susceptible isolates, 16 (42%) showed HLGR and 12 (32%) contained the gene; 16 (42%) showed HLSR. In conclusion, the findings of this study demonstrate that the aminoglycoside resistance gene, *aac(6')-Ie-aph(2'')*-Ia, is prevalent among the Brazilian penicillin-resistant *E. faecalis* isolates which usually exhibit cross-resistance to gentamicin (high-level). Notably, some HLGR isolates studied did not contain the *aac(6')-Ie-aph(2'')*-Ia gene. Therefore, further studies are necessary to evaluate the presence of other genes that could confer high-level aminoglycoside resistance in those multidrug-resistant *E. faecalis* isolates.

Keywords: *aac(6')-Ie-aph(2'')*-Ia gene, *Enterococcus faecalis*, high-level gentamicin resistance, multidrug-resistant enterococci, penicillin resistance.

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