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P2806 *In vitro* activity of ivermectin in combination with colistin against Gram-negative bacilli

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Background: The number of colistin-resistant isolates of GNB has increased in the last years. The need of new therapeutic approaches has promoted the use of drug repurposing. Ivermectin, an antihelmintic drug used for human onchocerciasis, has presented antibacterial activity against *Staphylococcus aureus*. The aim of this study was to analyse the activity of ivermectin in combination with colistin against colistin susceptible (Col-S) and colistin-resistant (Col-R) *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*.

Materials/methods: Col-S reference strains of *A. baumannii* ATCC 17978, *P. aeruginosa* PAO1 and *K. pneumoniae* CECT997, and thirteen Col-R clinical strains of *A. baumannii*, *P. aeruginosa* and *K. pneumoniae* were used. Microdilution assay was performed to examine the activity of ivermectin without colistin. Checkerboard and time-kill curves were performed to determine the synergy between both drugs. In order to identify the ivermectin mechanism of action, membrane permeabilization by fluorescence impermeant indicator Ethidium Homodimer-1 and outer membrane proteins (OMPs) profiles by SDS-PAGE were determined.

Results: Ivermectin alone showed MICs ≥128-256 µg/mL for Col-S and Col-R *A. baumannii, P aeruginosa and K. pneumoniae* strains. Checkerboard analysis showed that colistin in combination with 4-8 µg/mL of ivermectin increased the susceptibility of colistin against Col-S and Col-R strains by 4-256 folds. Time kill curve analysis showed that 4 µg/mL of ivermectin (for *A. baumannii*) and 8 µg/mL of ivermectin (for *P aeruginosa and K. pneumoniae*), combined with colistin sub-MIC concentrations, decreased the bacterial count of Col-S and Col-R *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae* strains at 24h of growth by >2 $\log_{10}$ CFU/mL of difference respect to colistin alone. None of the Col-S and Col-R strains treated with 4 or 8 µg/mL of ivermectin during 24h undergo changes in the membrane permeabilization. Otherwise, OMPs profile after 24h of incubation with ivermectin presented changes in Col-S and Col-R strains of all pathogens, indicating that ivermectin produce changes in the OMP expression.

Conclusions: Ivermectin has potentiated the antibacterial effect of colistin against Col-S and Col-R *A. baumannii*, *P. aeruginosa* and *K. pneumoniae*. This effect might be due to the modification of OMPs being an attractive alternative for the treatment of GNB infections.