

27th **ECCMID**

Vienna, Austria
22 – 25 April 2017

The congress of  ESCMID

Session: EV023 Pharmacoepidemiology, improved prescribing and antibiotic stewardship

Category: 5a. Mechanisms of action, preclinical data & pharmacology of antibacterial agents

22 April 2017, 08:45 - 15:30
EV0439

Synergistic antimicrobial combinations based on eucalyptol analytical standard against antibiotic resistant *Staphylococcus epidermidis* strains isolated from wound infections

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Background: Seen as a new and important opportunistic pathogen, *S. epidermidis* seems to be an important reservoir of antibiotic resistance genes at the epithelial level, widespread in nosocomial infections etiology, with higher rates than *S. aureus*. The purpose of this study was assessing the synergy between the analytical standard eucalyptol and conventional clinically used antibiotics with a sequential algorithm used for the investigation of its antimicrobial activity and potential use as an innovative pharmaceutical product.

Material/methods: 30 clinical isolated *S. epidermidis* methicillin resistant strains from patients with severe wound infections were identified by using Vitek2 automatic system. The antibiotic resistance profile was obtained by disc diffusion method. Three specific combinations have been used: eucalyptol: erythromycin (EE), eucalyptol: ceftiofur (EC) and eucalyptol: clindamycin (ECL). The co-

solubilisation method was used for obtaining the antimicrobial combinations. The quantitative analysis of the antimicrobial activity was performed by the serial microdilution technique establishing the minimum inhibitory concentrations (MIC) for the single compounds and combinations. The fractional inhibitory concentrations/ index (FIC/ FICI) were calculated, identifying the synergism/ antagonism of action between the tested compounds. The flow cytometry assay was carried out in order to evaluate the possible mechanism of action of the tested extracts. The tested concentrations for the flow cytometry assay were those corresponding to the MIC and MIC/ 3.

Results: The antibiotics concentration used in combination with eucalyptol was 7.5 µg/mL, a concentration up to 8 to 10 times lower than the antibiotic MIC *per se*. The same situation applies for eucalyptol: antibiotics that was 5 to 8 times lower than the MIC of eucalyptol alone (up to 62.5 µg/mL). The tested mixtures revealed FICI values in the range of 0.5 – 5, specifically interpreted by using Mun et al., 2014 algorithm. The synergic effects on 23 % of tested strains, the additive effects on 54 % of the tested strains were observed for EE. EC exhibited additive effects on 23% of the strains, as well as antagonistic effects on 23 % of the strains, also 38 % of the strains showed an indifferent effect. ECL showed additive effects up to 15 % of the tested strains, as well as indifferent effects on 69% of the tested strains. The possible mechanisms of action revealed by flow cytometry were the cellular wall permeabilization and inhibition of efflux pumps activity.

Conclusions: These results show the potential use of the eucalyptol and erythromycin as a novel strategy with decreased antibiotic concentrations and high anti-inflammatory and antimicrobial potency. The synergism between the natural compound eucalyptol and conventional antibiotics could increase efficiency in the treatment of wound infections. Further formulation studies should be made, for obtaining the proper formulation for the actives' release in a new, innovative product.