27th ECCMID Vienna, Austria 22 – 25 April 2017

The congress of ESCMID

Session: OS097 Biofilms: novel methods in treatment & prevention

Category: 9c. Preclinical biofilm studies

23 April 2017, 17:48 - 17:58
OS0506

Anti-biofilm efficacy and cytotoxicity of novel antimicrobial topical formulations against multidrug resistant wound isolates

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Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug resistant (MDR) Gram negative bacteria such as MDR-*Pseudomonas aeruginosa* (MDR-PA) and MDR-*Acinetobacter baumannii* (MDR-AB) are biofilm forming organisms that can cause wound infections. These infections can lead to high morbidity and high medical resource consumption. Biofilms are inherently resistant to therapy and to the host's immune system, which add complexity in treating MDR infections. Recently we developed a novel, translational, *ex vivo* porcine vaginal mucosa (PVM) biofilm model. We used this model to assess efficacy and cytotoxicity of experimental antimicrobial formulations (n=72) containing octenidine (n=39) or polyhexamethylene biguanide (PHMB) (n=33) and Prontosan® Wound Gel [0.1% PHMB], a commercially available antimicrobial comparator. The study objective is to develop a novel broad spectrum MDR-organism anti-biofilm topical treatment for wounds.

Material/methods: To determine cytotoxicity of the treatments, *ex vivo* PVM 5mm explants (consisting of stratified squamous epithelium) were incubated with 100uL treatment for 24h then transferred to a 96 well microplate. An MTT assay was performed and toxicity was quantified using a microplate photometer. To quantify the efficacy of the treatments, *ex vivo* PVM 5mm explants were incubated with clinical wound isolates including MRSA (n=4), MDR-AB (n=2) and MDR-PA (n=2) for 72h to ensure biofilm formation (confirmed by fluorescent microscopy). Infected PVM explants were treated with 100uL of formulation and incubated 24h. Explants were transferred to neutralizing solution and samples were serially diluted and plated (or plated neat) for enumeration of bacteria.

Results: Treatment with octenidine or PHMB containing formulations and Prontosan resulted in viabilities of 8.3 ±11.20%, 36.6 ±23.26% and 66.3 ±1.7% respectively when compared to an untreated control. Experimental PHMB containing formulations had significantly higher efficacy against MRSA (LAC) with an average log reduction from growth control of 4.4 ±2.31 compared to Prontosan with a log reduction from growth control of 1.6 ±0.08 ($p=0.044$) and octenidine containing formulations with a log reduction from growth control of 2.7 ±1.94 ($p<0.0001$). Lead experimental formulations were selected for high efficacy against MRSA and low toxicity on mucosal tissue. All contained PHMB, (n=4) and had a log reduction from growth control of 3.8 ±0.20 against MRSA (n=4), MDR-PA (n=2) and MDR-AB (n=2) clinical wound isolates, (significant from Prontosan 1.4 ±0.17 ($p<0.0001$)) and a viability of 58.8 ±11.80%. Data presented are means ± SEM.

Conclusions: PHMB containing formulations were most effective against MRSA (LAC) biofilm and were least toxic to the *ex vivo* tissue. Octenidine containing formulations were less effective against MRSA (LAC) biofilms and were toxic to mucosal tissue. Lead PHMB containing formulations (n=4) are promising MDR-organism anti-biofilm treatment candidates, and potentially effective alternatives to Prontosan Wound Gel, because of their comparable cytotoxicity and significantly increased efficacy against tested clinical MDR wound isolates (n=8).