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In vitro prevention of the emergence of fosfomycin resistance in methicillin-resistant *Staphylococcus aureus* (MRSA)

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Background

Fosfomycin (FOS) has been shown to be effective against MRSA. However, its main drawback is the rapid emergence of *in vitro* resistance

Objective

Aim of the study was to evaluate if the selection of FOS-resistant MRSA strain could be prevented *in vitro* by combining FOS with rifampin (RIF), daptomycin (DAP), levofloxacin (LEV) and vancomycin (VAN).

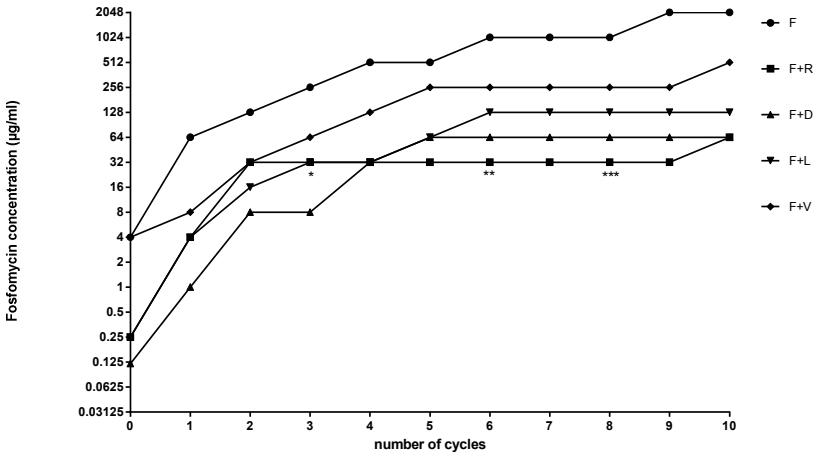
Methods

A reference MRSA strain (ATCC 43300) was used. The frequency of spontaneous resistance to FOS was tested by incubating for 24h 10^9 CFU/ml of MRSA inoculated on FOS-containing agar plates. For progressive emergence of resistance, bacteria (10^5 CFU/ml) were exposed to two-fold increasing concentrations of FOS alone and with 0.5xMIC of RIF, DAP, LEV and VAN for a total of 10 consecutive days. The stability of resistance to FOS was performed by subculturing FOS-resistant strain on antibiotic-free agar for 5 days. Susceptibility to RIF was determined at day 3,6,9 and 10 by gradient strip diffusion test.

Results

	FOS	RIF	LVX	DAP	VAN
MIC (BD)	4 µg/ml	0.008 µg/ml	0,25 µg/ml	0.5 µg/ml	1 µg/ml

Antimicrobial susceptibility test of MRSA ATCC 43300 performed by macrobroth dilution



*: E-test for Rifampin: 0.006mcg/ml
** : E-test for Rifampin: 0.19 mcg/ml
*** : E-test for Rifampin: 0.47-0.64 mcg/ml

Selection of FOS-resistant MRSA after serial exposure to FOS alone or in combination with 0.5xMIC of RIF, LVX, DAP and VAN.

•FOS resistance emerged rapidly and could not be prevented by the addition of LEV and VAN.

•The addition of RIF and DAP delayed the increase in the MIC of FOS.

•The MIC of RIF at day 10 was 0.19 µg/ml.

Conclusions

- FOS resistance rapidly developed *in vitro*.
- Addition of RIF and DAP only delayed the emergence of FOS resistance.
- FOS prevented the emergence of RIF resistance up to 10 days of progressive exposure to sub-inhibitory RIF concentrations.