P0235
24th ECCMID
Barcelona

Efficacy of Fosmidomycin alone and in combination with colistin, tigecycline and rifampicin against multi-drug resistant and extensively drug resistant Enterobacteriaceae

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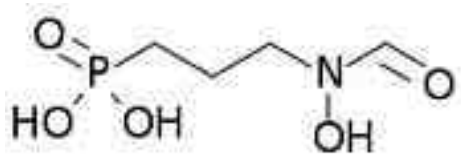
Introduction. With the advent of multi-drug resistant (MDR and extensively drug resistant (XDR) Enterobacteriaceae, older drugs are being explored more for the efficacious potential. Fosmidomycin, originally isolated from Streptomyyces, a structural analogue of 2-C-methyl-D-erythrose-4-phosphate that specifically inhibits bacterial DXP reductoisomerase. We examined the activities of fosmidomycin against 72 genetically defined Enterobacteriaceae and compared it to colistin, tigecycline and rifampicin alone and in combination.

Fig. 1. Structure of fosmidomycin



Methods. 72 sensitive, MDR and XDR *Escherichia coli* (29), *Klebsiella pneumoniae* (33) and *Enterobacter cloacae* (10) with defined genotypes were tested against fosmidomycin, colisitin, tigecycline and rifampicin using Liofilchem® (Liofilchem, Italy) minimal inhibition concentration (MIC) testing strips (MTS) and verified by microbroth dilution. Fosmidomycin was used with glucose-6-phosphate and trailing read at 70% inhibition. Isolates were an international non-clonal collection; MDR were ESBL positive and XDR were also ESBL positive and contained at least one of KPC, OXA-48 and NDM carbapenemases. FIC values for combination testing was carried out by Liofilchem® MTS synergy applicator system. Results where possible were interpreted according to EUCAST v 2.0 clinical breakpoints. Data are expressed as MIC ranges, MIC50 and MIC90 where the MIC inhibits 50% and 90% of the population, respectively. Synergy was when the FICs were <0.5.

Results. Data is shown in the Table below. Fosmidomycin gave ranges of less than 4mg/l apart from one isolate of E. cloacae which had an MIC of >256mg/l; and MIC50 and MIC90 of 0.5-1 and 1-1.5, respectively, for all isolates. Tigecycline and colistin gave lower MICs than fosmidomycin, and rifampicin MICs were generally much higher. Microbroth dilution and MTS were in good agreement with no major errors and few minor errors.

Table. MIC values of fosmidomycin, colisitin, tigecycline and rifampicin against 72 Enterobacteriaceae with defined genotypes.

	Fosmidomycin			Colistin			Tigecycline			Rifampicin		
	range	MIC50	MIC90	range	MIC50	MIC90	range	MIC50	MIC90	range	MIC50	MIC90
E.coli (29)	0.064-4	0.5	1	0.5-0.75	0.75	1	0.094-1	0.38	0.75	2->256	16	>256
Klebsiella (33)	0.38-3	0.75	1.5	0.5-8	0.75	1	0.094-0.75	0.5	0.75	6->256	16	>256
E. cloacae (10)	0.064->256	1	1	0.75-1	0.75	1	0.38-1	0.5	0.5	12->256	16	>256

The fosmidomycin MICs did not alter according to the sensitive, MDR and XDR phenotype indicating no cross-class resistance.

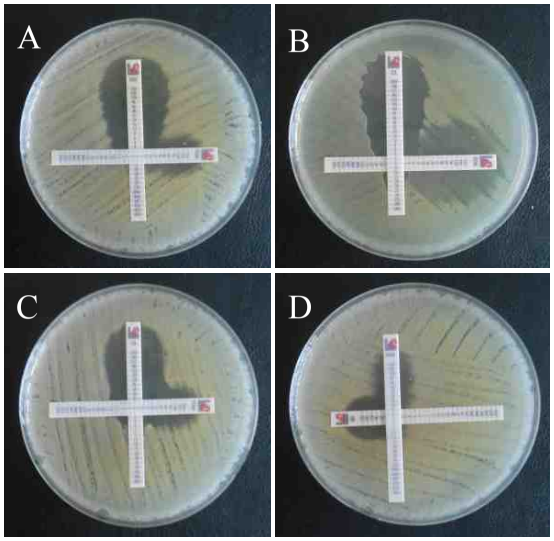
Fig. 2. Examples of antibiotic combination testing using MTS synergy platforms.

A) tigecycline and fosmidomycin – no effect.

B) colisitin and fosmidomycin – additive effect.

C) colistin and fosmidomycin – synergistic effect.

D) rifampicin and fosmidomycin – no effect.



Two isolates demonstrated synergy involving either tigecycline and colistin. The reproducibility from performing the MTS in triplicate was 96.5% when taken as ±1 $\log^2$ dilution difference in MIC.

Conclusions. Using the MTS method, fosmidomycin shows strong activity against Enterobacteriaceae with MIC50 and MIC90 values similar to tigecycline and colistin. The lack of synergy was surprising given its unique target. Although lacking guidelines and breakpoints, forgotten drugs like fosmidomycin require further consideration.

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