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 Streptomyces, 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. MICs were generally similar to previous Enterobacteriaceae with defined resistance patterns.

Methods.
72 sensitive, MDR and XDR Escherichia coli (29), Klebsiella pneumoniae (33) and Enterobacter cloacae (10) with defined genotypes were tested against fosmidomycin, colistin, tigecycline and rifampicin using Liofilchem® 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. Fosmidomycin MICs did not alter according to the sensitive, MDR and XDR phenotype indicating no cross-class resistance.

Results.
Data is shown in the Table below. Fosmidomycin gave ranges of less than 4 mg/l apart from one isolate of E. cloacae which had an MIC of >256 mg/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. Results data is also shown in the Table below. Fosmidomycin shows strong activity against the Enterobacteriaceae studied, with MIC50 and MIC90 values similar to those of tigecycline and colistin. The reproducibility of reading the MICs in triplicate was 96.5% when taken from one isolate of E. caviae, which had an MIC of >256 mg/l; and 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.

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. Two isolates demonstrated synergy involving either tigecycline and colistin, or tigecycline and rifampicin. The reproducibility from performing the MTS in triplicate was 96.5% when taken 70% inhibition difference in MIC.