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Escherichia coli clinical isolates harboring mcr-1 and mcr-1.3 genes recovered from a university hospital in Buenos Aires, Argentina

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Background: Polymyxins (colistin, polymyxin B), although introduced in the antibiotic armamentarium in the 1950's, have been considered until recently to be too nephrotoxic and too neurotoxic for their regular use for treating infections in humans. Due to the paucity of remaining antibiotics for treating infections, polymyxins have become the last resort in particular for treating infections associated to carbapenem-resistant Enterobacteriaceae (CRE). Transferable polymyxins resistance mediated by the plasmid-borne *mcr-1* gene has recently been described in Enterobacteriaceae, raising a considerable concern. Other two variants, MCR-1.2 and MCR-2 have been reported. Colistin resistant *E. coli* emerged in a University Hospital in Buenos Aires, Argentina in 2014 (0.2%) and reach 2% in 2016. In Argentina only the mcr-1 gen has been described. The aim of this study is to analyze colistin resistant *Escherichia coli* clinical isolates, recovered between 2014 and 2016 in a University Hospital of Buenos Aires, Argentina.
Material/methods: Ten clinical *E. coli* isolates resistant to colistin were studied. The isolates were recovered from the urine of 5 inpatients and 5 outpatients. Whole genome sequencing was performed using an Illumina MISeq platform. Plasmid characterization and mating-out assay was done using *E.coli* J53 as receptor strain. Susceptibility testing and minimal inhibitory concentration (MIC) determination, following EUCAST recommendations, were done using the clinical isolates and the transconjugants of *mcr-1*.
Results: Sequencing analysis revealed the presence of *mcr-1-like* gene in six out of the 10 clinical isolates. Only 4 isolates presented an *mcr-1* allele that was identical to the prototype *mcr-1* reference

gene (accession number KP347127). The other 2 isolates presented a novel allele of *mcr-1* gene, named *mcr-1.3* gene. MCR-1.3 presented a Tyr instead of a His at the position 452 in the amino acids sequence. All the clinical isolates presented MICs values in the range of 4-16 mg/l. All the isolates harboring *mcr-1* or *mcr-1.3* genes presented MICs of 4 mg/l. Transconjugants were obtained for MCR-1 and MCR-1.3 producing strains, with MICs of 4 mg/l. The *mcr-1*-like genes for 5 out of the 6 isolates, were located on plasmids similar to the prototype IncI2-type differing by some small deletions and insertions of insertion sequences. Only one isolate presented a plasmid carrying mcr-1-like gene on a different IncI2 backbone.

Conclusions: A progressive increase in the rate of colistin resistant *E. coli* was observed, being associated to the presence of plasmids harboring mcr-1-like genes in 60% of the colistin resistant isolates. This is the first report of a novel variant named MCR-1.3.