

TITLE: ANALYSIS OF FREQUENCY OF COLISTIN-RESISTANCE AND PRESENCE OF *mcr* GENES IN *Enterobacter cloacae* complex AND *Klebsiella aerogenes* RECOVERED FROM CLINICAL ISOLATES IN BRAZIL

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ABSTRACT:

Enterobacter cloacae complex and *Klebsiella aerogenes* (previously known as *Enterobacter aerogenes*) are opportunistic pathogens that cause several infections such in the urinary, gastrointestinal, respiratory tracts and blood. They are a member of the ESKAPE group of significant bacterial pathogens in humans. The increased carbapenem resistance in this group of bacteria has limited therapeutic options. In this way, colistin (polymyxin E) and polymyxin B have been recommended as last-line therapeutic option. Nevertheless, resistance to polymyxins has been reported by mutations in two-component systems (TCSs) PhoPQ and PmrAB and the acquisition of the newly described plasmidial *mcr* genes. These mechanisms cause modifications of LPS and alter their affinity for polymyxins. This study aimed to evaluate the frequency of polymyxin resistance and presence of the *mcr* genes among *E. cloacae* complex and *K. aerogenes* isolates received by Laboratório de Pesquisa em Infecção Hospitalar (IOC/Fiocruz) from January 2016 to December 2018 from different Brazilian states. In screening of 128 isolates (38 *K. aerogenes* and 90 *E. cloacae* complex), 35 (27,3%) were resistant to colistin by Broth Microdilution Method with MIC of 4mcg/mL to 128mcg/mL (MIC₅₀=64 mcg/mL and MIC₉₀=128 mcg/mL). The colistin resistance rate was higher in *K. aerogenes* (42,1%, n=16) than *E. cloacae* complex (21,1%, n=19). By disk-diffusion method, the taxa of non-susceptibility to carbapenems among colistin-resistant *E. cloacae* complex isolates were 74%, 42% and 32% to ertapenem, meropenem and imipenem, respectively. Whereas 81%, 75% and 75% of colistin-resistant *K. aerogenes* isolates were non-susceptible to ertapenem, meropenem and imipenem, respectively. The lowest rates of resistance were for gentamicin (94% to *K. aerogenes* and 74% to *E. cloacae* complex). The PCR was performed to *mcr* 1 – 5 genes but none isolate was positive. The presence of carbapenemase gene *bla*_{KPC} was detected in 40% of isolates (9 *K. aerogenes* and 5 *E. cloacae* complex) and 8% positive for the *bla*_{NDM} gene (2 *K. aerogenes* and 1 *E. cloacae* complex). In this way, this study demonstrates high frequency of colistin resistance among *E. cloacae* complex and *K. aerogenes* isolates. The clinical significance and mechanisms of colistin-resistance should be elucidated for the appropriate use of polymyxins.

Keywords: Polymyxin resistance; *Enterobacter* spp; *Klebsiella aerogenes*; *mcr*.

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