TITLE: COLISTIN RESISTANCE IN *Klebsiella pneumoniae* ISOLATES MEDIATED BY *mgrB* INSERTIONAL INTERRUPTION

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ABSTRACT:
Infections caused by carbapenem-resistant *Klebsiella pneumoniae* lead to limitations of therapeutic options. Therefore, polymyxins were reintroduced into clinical practice and its increased use led to emergence of resistant bacterial isolates. Recently, an increase in prevalence of *K. pneumoniae* colistin-resistant was observed in a public university hospital in Recife, Brazil. This study aimed to evaluate the genetic relationship and mechanisms involved in colistin resistance in these isolates. The MIC values were determined by automated system and interpreted according to CLSI (2017). The clonal relationship was analyzed by PFGE and sequence types were determined through MLST. Resistance to colistin was evaluated regarding to the presence of *mcr* gene and *mgrB* gene integrity, by PCR followed by sequencing. Sixteen isolates of *K. pneumoniae* were identified, which were collected from 2013 to 2016, from different samples and anatomical sites. Among them, nine isolates (56.25%) were extensively resistant (XDR), six isolates (37.5%) were pandrug resistant (PDR) and one isolate (6.25%) was multidrug resistant. Most showed susceptibility to amikacin and tigecycline. The PFGE indicated three major clonal groups (A, B and C) and two smaller groups (A1 e A2). Group A and subgroups A1 and A2 comprised 12 isolates and accounted for ten ST11, one for ST340 and one for a new ST (ST3990). ST11 and ST340 are part of the clonal complex 258 (CC258), which is known to be widespread in the world and closely associated to carbapenem-resistant strains. Groups B and C included the remaining four isolates, which belonged to ST25 and ST423, respectively. Regarding to colistin resistance , the presence of insertion sequences (IS) interrupting the *mgrB* gene was observed in ten isolates. The ISs identified (ISKpn13, IS903 and IS903b) belong to the IS5 family, which have already been reported in isolates of *K. pneumoniae* resistant to colistin. In the six isolates that showed intact *mgrB*, resistance to colistin is probably mediated by other mechanisms, such as changes in Two Component Systems (*pmrAB* and *phoPQ*), which will be evaluated later. The *mcr* gene was not detected in any of the isolates. These results highlight the high frequency of insertional interruption of *mgrB* mediating the resistance to colistin in *K. pneumoniae* isolates belonging to different STs, indicating this is probably the most common and easily stablishing mechanism to colistin resistance in this species.

Keywords: *Klebsiella pneumoniae*, colistin, MDR, *mgrB* insertional interruption, IS5 family

Development Agency: FACEPE, CAPES and CNPq