TITLE: MULTI-STATE SURVEY OF *Klebsiella pneumoniae* CARBAPENEMASE (KPC)-PRODUCING FROM WHOLE-GENOME SEQUENCING RESISTOME ANALYSIS IN BRAZIL

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ABSTRACT

The spread of carbapenem resistant *Klebsiella pneumoniae* is an emerging clinical problem of great relevance in Brazil and in the world. In this study, we explored the resistome and clonal dissemination of 10 *Klebsiella pneumoniae* carbapenemase (KPC)-producing strains, using whole-genome sequencing analysis of a representative isolates of seven Brazilian states, and the Federal District collected between the years 2009 to 2016. Genotyping was done by Pulsed Field Gel Electrophoresis (PFGE) and carbapenemases genes were identified by PCR for 21 strains. PFGE results showed that KPC-producing was clustered into seven pulsotypes (A-G), all positive for *bla*$_{KPC}$ gene and none presented the *bla*$_{IMP}$, *bla*$_{VIM}$, *bla*$_{NDM}$ and *bla*$_{GES}$ genes; however, the presence of the same clone was observed in different regions. All strains that were sequencing harboring plasmid-mediated quinolone resistance (PMQR) and *bla*$_{KPC-2}$ genes and 70% had *bla*$_{CTX-M-15}$. It was also observed in lower frequency, the presence of *bla*$_{CTX-M-2}$, *bla*$_{CTX-M-131}$, and *bla*$_{CTX-M-8}$ genes; however, only two strains harbored more than one *bla*$_{CTX-M}$. In addition, was observed for the first time in Brazil the *Klebsiella pneumoniae* carbapenemase (KPC)-producing harboring *bla*$_{CTX-M-3}$ gene. ST11 may be the major sequence type circulating in different regions of Brazil, favoring the dissemination of *bla*$_{KPC-2}$ and *bla*$_{CTX-M-15}$ genes in this country, although the minor species clone has begun to be observed (ST443). A troubling finding was the detection of the same clone (F and F1), belonging to the identical sequence type (ST11), in a strain recovered from the Federal District and a strain resistant to colistin isolated in Uberlandia, in 2016 and 2015, respectively. There was an inter-state cross-transmission of KPC-producing, and the isolates presented the coexistence of multiple resistance genes, including mainly *bla*$_{CTX-M}$, *bla*$_{KPC}$ and PMQR determinants. ST11 was associated with the clonal spread of *K. pneumoniae bla*$_{CTX-M-15}$-producing in this study. Surveillance of the horizontal transfer of both carbapenemase and ESBL genes among *K. pneumoniae* strains is important for preventing a worldwide increase in antimicrobial drug's resistance, mainly in Brazil.

Keywords: *Klebsiella pneumoniae,* KPC-2, Brazil, *Pulsed Field Gel Electrophoresis,* Whole genome sequencing.

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