

TITLE: COLISTIN RESISTANCE EMERGES IN MULTIDRUG-RESISTANT *Klebsiella pneumoniae* IN RIO DE JANEIRO, BRAZIL

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ABSTRACT:

Klebsiella pneumoniae is an important human pathogen, among the most frequently causing infections worldwide, able to accumulate and disseminate a variety of antimicrobial resistance genes. Resistance to colistin (COL), one of the last therapeutic options for multidrug-resistant (MDR) bacteria, has been increasingly reported. COL-resistant *K. pneumoniae* (COLRKp) emerged in two hospitals in Rio de Janeiro state, Brazil, in 2016. The aim of this study was to characterize COLRKp isolates according to antimicrobial susceptibility and resistance gene content. Twenty-nine isolates were successively recovered from blood (n=15) and urine specimens (n=10), and surveillance screening anal swab cultures (n=4) from 21 patients from November 2016 to September 2018. We determined susceptibility to COL by broth minimum inhibitory concentration (MIC) and to amikacin (AMI), amoxicillin-clavulanate (AMC), aztreonam (ATM), cefepime (CPM), cefotaxime (CTX), ceftazidime (CAZ), chloramphenicol (CHL), ciprofloxacin (CIP), ertapenem (ETP), fosfomycin (FOS), gentamicin (GEN), meropenem (MEM), tetracycline (TET), and trimethoprim-sulfamethoxazole (SXT) by disk-diffusion (CLSI 2019). Resistance genes were identified by PCR and sequencing. COL MIC ranged from 4 to ≥ 256 $\mu\text{g/mL}$ (mode=64 $\mu\text{g/mL}$). All isolates were resistant to AMC, CPM, CTX, ATM, and CIP. Twenty-eight (97 %) were resistant to CAZ; 26 (90 %) to MEM; 25 (86 %) to FOX, ETP, and SXT; 21 (72 %) to CHL; 14 (48 %) to GEN; 12 (41 %) to AMI; 6 (21 %) to TET; and one (3 %) to FOS. A variety of antimicrobial resistance genes was found in the COLRKp isolates. Twenty-five (86%) isolates had *bla*_{TEM} beta-lactamase encoding gene, 24 (83%) had *sul* genes which confer resistance to sulphonamides; 22 had *bla*_{KPC-2} carbapenemase encoding gene; and 22 had *bla*_{CTX-M} ESBL encoding gene. Although phenotypic resistance to tetracycline was found only in 6 isolates, 21 carried *tet* genes of type A, B, D, E, and G. Plasmid-mediated quinolone-resistance genes (*qnr*) were found in 9 (31%) isolates. Five (17%) isolates carried an additional carbapenemase encoding gene: four had *bla*_{OXA-48-like} and one *bla*_{OXA370}. Two isolates carried *bla*_{GES} beta-lactamase encoding gene. COL resistance emerged amid highly resistant strains, further restricting the number of drugs available to treat severe infections.

Keywords: *Klebsiella pneumoniae*; multidrug-resistance; colistin resistance; extended spectrum beta-lactamase; carbapenemases;

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