Resistance and tolerance/persistence to meropenem-vaborbactam, imipenem-relebactam, and cefiderocol among carbapenem-resistant Klebsiella pneumoniae

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Introduction: Newer antibiotics, such as beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations, such as meropenem-vaborbactam (MEV), imipenem-relebactam (I/R), and aztreonam-avibactam (AZA); and cefiderocol (FDC), have been proposed for treating KPC-producing carbapenem-resistant *Klebsiella pneumoniae* (CRKp) infections, mainly caused by extensively drug-resistant (XDR) and difficult-to-treat (DTR) isolates. Those antibiotics may also be therapeutic alternatives against isolates producing KPC variants, which confer resistance to ceftazidime-avibactam (CZA) and have been increasingly detected. **Objectives:** To evaluate resistance and tolerance/persistence to FDC and newer BL/BLI among CRKp. **Material and Methods:** 53 CRKp isolated from blood cultures between June and December 2022 were studied. Bacterial identification was performed by MALDI-TOF, and the initial antimicrobial susceptibility test was performed by VITEK 2®. Disk diffusion test was used to evaluate susceptibility to FDC and the newer BL/BLI combinations, including MEV, I/R, and AZA. Tolerance Disk Test (TDtest) was used to assess the tolerance/persistence to those antibiotics. Whole-genome sequencing was used to evaluate beta-lactamase-encoding genes and porin mutations. **Results and discussion:** 32/53 CRKp were categorized as FDC-resistant, and the other 21 isolates were tolerant/persistent to this antibiotic. Although FDC susceptibility was evaluated only by the disk diffusion test, EUCAST guidelines were considered for interpreting the results. All FDC-resistant isolates harbored *cirA* mutations. 9/53 isolates were resistant to MEV, and 7/53 were resistant to I/R. The 7/53 I/R-resistant isolates were also resistant to MEV, due to porin alterations (OmpK35/OmpK36). Tolerance/persistence to MEV and I/R was detected for all the isolates previously characterized as susceptible to those antibiotics. On the other hand, all CRKp were truly susceptible to AZA, and no tolerance/persistence was detected. 48/53 isolates harbored $bla_{\text{KPC-2}}$, 1/52 harbored $bla_{\text{KPC-33}}$ (resistant to CZA), and 3/53 harbored $bla_{\text{KPC-2}}$ and $bla_{\text{NDM-1}}$. One isolate (NA109) was not

tolerant/persistent to any of the antibiotics evaluated, did not present any carbapenemase-encoding genes, and the carbapenem resistance was due to *ompK35* and *ompK36* mutations, associated with ESBL (CTX-M-14) production. **Conclusion:** Resistance to FDC and newer BL/BLI, such as MEV and I/R, was detected among CRKp, and tolerance/persistence to FDC, MEV, and I/R was detected in all CRKp isolates previously categorized as susceptible to these antibiotics.

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