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Exploring the role of KPC variants in cross-resistance to last-line antibiotics

03. Bacterial susceptibility & resistance

03b. Resistance surveillance & epidemiology: Healthcare-associated bacteria

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Background

Klebsiella pneumoniae carbapenemase (KPC) variants, specifically KPC-2 and KPC-3, have emerged globally as prevalent resistance mechanisms in *K. pneumoniae*. These β-lactamases confer resistance to most β-lactams, including carbapenems, while remaining susceptible to newer β-lactam/β-lactamase inhibitors such as ceftazidime-avibactam (CZA). However, numerous KPC variants have since evolved resistance to CZA, harboring mutations, insertions, or deletions in key regions, particularly in the Omega loop, the 237–243 loop, and the 266–275 loop. Understanding these mutations is crucial for addressing cross-resistance to last-line antibiotics like cefiderocol (FDC) and ceftipime/zidebactam (FPZ).

Methods

A total of fifteen clinical isolates of KPC-producing Klebsiella spp. collected from various regions in Argentina (2020–2023) were analyzed, including 15 KPC variants. Antimicrobial susceptibility testing determined the MICs for CZA, carbapenem, FDC, FPZ, and other antibiotics. Whole-genome sequencing (WGS) was performed to identify mutations contributing to resistance. Synergy between CZA and FDC was assessed.

Results

Resistance to CZA was confirmed in 12 of the 15 KPC variants tested. Cross-resistance to FDC was observed in eight isolates. In five strains, including one FDC susceptible spontaneous resistant subpopulations were noted (Fig.1). Notably, six FDC-resistant strains carried mutations in the 266–275 loop. Cross-resistance to FPZ was observed in five KPC variants, predominantly those with mutations in the 266–275 loop, though many omega loop and 237–243 loop mutants remained susceptible to FPZ (Fig.1). Synergy between CZA and FDC was observed in four strains, with an additive effect in the remaining isolates. WGS analysis of FDC resistant subpopulations revealed additional mutations in *ompC*, *rpoC*, *dksA*, *cirA*, among others.

Conclusions

Our study demonstrates that KPC variants, particularly those with mutations in the omega and 266–275 loops, exhibit high levels of resistance to both CZA and FDC, with cross-resistance to FPZ observed to a lesser extent. The emergence of cross-resistance in strains not previously exposed to these antibiotics is concerning and underscores the need for continuous surveillance. The detection of mutations in the *bla*_{KPC}, *cirA*, and others novel genes, highlight the importance of understanding the molecular mechanisms behind these resistance patterns to develop effective therapeutic approaches.

Table 1. KPC variants strains, molecular and phenotypic characteristics

| Strain ID | KPC variant | <i>bla</i> KPC specific region | Mutation detected | Minimum Inhibitory Concentration (mg/L) | | | | | | Hetero resistance to FDC | |
|-----------|-------------|--------------------------------|--------------------------------|---|--------|------|-----|-----|-------|--------------------------|-----|
| | | | | CZA | FDC | FEP | ZID | FPZ | IMP | | MEM |
| KPNMA212 | KPC-14 | Loop 237–243 | del_242-243_GT | 64 | 0.75 | >64 | >64 | 1 | 0.75 | 0.125 | NO |
| KPNMA227 | KPC-96 | | Y241N | 8 | 0.5 | >512 | >64 | 1 | 0.5 | 2 | YES |
| KPNMA214 | KPC-161 | loop 266–275 | Ins 269-279_DDKHSEAVIAA | 24 | 6 | >512 | >64 | >16 | 16 | 8 | NO |
| KPNMA215 | KPC-162 | | Ins 263-269_TRAPNKD | 24 | 4 | >512 | >64 | >16 | 3 | 1 | YES |
| KPNMA216 | KPC-163 | | Ins 258-263_KDDKHS | 24 | 8 | >512 | >64 | >16 | 48 | 32 | YES |
| KPNMA217 | KPC-164 | | Ins 274-276_EAV | 24 | 4 | >512 | >64 | 4 | 8 | 1 | YES |
| KPNMA221 | KPC-44 | | Ins 261_AVYTRAPNKDDKHSE | 48 | 12 | 512 | >64 | 4 | 12 | 4 | NO |
| KPNMA225 | KPC-80 | | ins_267_PNK | 48 | 0.19 | >512 | >64 | 2 | 4 | 1 | NO |
| KPNMA228 | KPC-97 | Ins 276_VNSEA | 64 | 24 | 32 | >64 | 2 | 16 | 2 | NO | |
| KPNMA213 | KPC-160 | Omega-loop | Del 165,166_EL | 2 | 0.38 | >64 | 1 | 1 | 0.75 | 0.75 | NO |
| KPNMA218 | KPC-165 | | N169S | 0.5 | <0.016 | 512 | >64 | 4 | 0.25 | 0.064 | NO |
| KPNMA219 | KPC-25 | | ins_165_EL | 0.5 | <0.016 | 512 | >64 | >16 | 0.5 | 0.023 | NO |
| KPNMA220 | KPC-33 | | D179Y | 32 | 12 | 64 | >64 | 2 | 0.5 | 4 | NO |
| KPNMA222 | KPC-57 | D179V | 64 | 6 | >512 | >64 | 2 | 3 | 0.75 | YES | |
| KPNMA224 | KPC-73 | Combinations of | del_168-169_EL, ins_269_KDDKHS | 48 | 0.75 | 512 | >64 | 16 | 0.125 | 2 | NO |

Keyword 1

Antimicrobial resistance (AMR)

Keyword 2

Emerging infections

Conflicts of interest

Do any of the authors have conflicts of interest related to the studies presented in this abstract?

No