Comprehensive characterization of emerging carbapenem-resistant *Klebsiella pneumoniae* clinical isolates at a public hospital in Lima - Peru

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**Introduction**

- In contrast with other countries in Latin America, Peru had been notoriously spared by the global dissemination of carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp), until recently.
- Isolated cases of KPC-producing *K. pneumoniae* have been reported since 2013 in Lima.
- In 2015 , the first outbreak of NDM- producing *K. pneumoniae* was described in Peru.
- By 2017, a rapid emergence of CR-Kp took place in Hospital Cayetano Heredia (HCH), a tertiary care hospital in Lima. Here, we provide a description of the clinical, microbiological and molecular characteristics of the CR-Kp isolates recovered during this emergence.

**Objectives**

- Determine the clinical and microbiological characteristics of the emerging CR-Kp isolates recovered at HCH until December 2017.
- Determine the prevalence of co-resistance to routine and last-line antibiotics among the CR-Kp strains.
- Characterize the molecular mechanisms of carbapenem resistance, comparing them over time.

**Methods**

- Retrospective study of the emerging cases of CR-Kp infections diagnosed at a tertiary hospital in Lima - Peru, from July 2015 to December 2017.
- Demographic and clinical data were obtained by chart review.
- Archived CR-Kp isolates were recovered and tested:
  - Antibiotic susceptibility testing by disc diffusion, E-test (mipenem and ceftazidime/avibactam) and broth dilution (colistin), using CLSI breakpoints.
  - DNA extraction (Qiagen), whole genome sequencing (Illumina MiSeq) and de novo sequence assembling (Velvet), for identification of antibiotic resistance genes, using publically available tools (*Kleborate, Resfinder, NCBI*).

**Results**

**Epidemiological characteristics**

- The first case of CR-Kp in HCH dated from July 2015. Since then, a total of 69 CR-Kp clinical isolates, from 59 patients had been recovered until December 2017.
- A significant increase in the number of cases was observed during calendar year 2017 (Fig. 1) and affected mostly ICU patients (Fig. 2).

**Clinical characteristics**

- Among all 59 patients, 68% were male, the average age was 58 and the average Charlson score was 1.
- Urinary, and respiratory sources of infection or colonization were the most common one, followed by blood stream infections (Fig. 3).
- Among the 48 hospitalized patients, 15 died, resulting in a 38% all-cause in-hospital mortality. Among patients with bacteraemia, in-hospital mortality was 50% (4/8 died).

**Microbiological and molecular characteristics**

- Recovery of stored CR-Kp isolates was achieved in 40 cases and whole genome sequencing was performed in 30 of these isolates.
- Genes of carbapenemases were detected in 29 out of the 30 tested isolates: 14 (47%) were blaNDM, 12 (40%) were blaKPC, and 3 (10%) were blaIMP-1 (Table 1 and Fig. 5).
- blaKPC-isolates were more prevalent during years 2015-2016 and blaNDM-isolates were more prevalent during year 2017 (p<0.0001).
- Antibiotic susceptibility testing revealed that amikacin and colistin were the most active antimicrobials, with the rest of antimicrobials having extremely high rates of resistance (Fig. 6).
- Colistin resistance was found in 3 isolates (5%), none of these isolates carried gene mcr-1.

**Discussion**

- In 2017, the number of incident CR-Kp cases at HCH was more than six times higher than the number of cases observed on previous years. This sudden increase in numbers coincide with the appearance of blaNDM-producing CR-Kp isolates at this institution.
- Further investigation is needed to determine if this finding reflects the introduction of one or more clones of blaNDM-*K. pneumoniae* that may be better adapted for dissemination than the initial blaKPC-*K. pneumoniae* clones, or a coincidental change in the hospital setting that facilitated dissemination of these strains.
- As described in previous studies, a high in-hospital mortality was observed (38%), especially among patients with CR-kp bacteraemia (50%). A more in-depth analysis is planned to evaluate clinical and molecular risk factors for increased mortality.
- Amikacin remains the only active antimicrobial within the routinely tested antibiotics, highlighting the need to add other antimicrobials, such as colistin, to the routine testing panel. This is also necessary for continuous monitoring of emergence of colistin resistance among CR-Kp.

**Conclusions**

- The described emergence of CR-Kp infections at HCH represents the largest outbreak reported in Peru to date.
- The different mechanisms of carbapenem resistance found suggest a polyclonal expansion, with some predominance for blaNDM-*Klebsiella pneumoniae* clones.
- The finding of 3 cases of CR-Kp with colistin resistance at our institution is worrisome, and warrants immediate efforts to improve the surveillance and infection control strategies at our institution and in Peru.

**References**

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