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Antimicrobials: Epidemiology of MDR-Gram-negatives

Characterisation of carbapenem resistance mechanisms among Turkish *Escherichia coli* and *Klebsiella pneumoniae* clinical isolates: the silent dissemination of NDM-1

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Objectives: Spread of carbapenemase-producing *Enterobacteriaceae* isolates is a global problem. Various studies from Turkey have identified OXA-48 and IMP as the dominant genes in Turkey. At the Acibadem Labmed Clinical Laboratories which receives clinical specimens from various cities in Turkey, we aimed to investigate the mechanisms responsible for carbapenem resistance in *Escherichia coli* and *Klebsiella pneumoniae*.
Methods: Between September 2011-November 2013, for *E. coli* and *K. pneumoniae* clinical isolates submitted from six major Turkish cities (Istanbul, Ankara, Bursa, Adana, Eskisehir, Kocaeli), antimicrobial susceptibility testing was performed using Vitek 2 system (bioMérieux, France) at Acibadem Labmed Clinical Laboratories, Istanbul. *Escherichia coli* (n=29) and *Klebsiella pneumoniae* (n=119) isolates showing non-susceptibility to carbapenems were further tested to confirm carbapenem resistance. These isolates (n=148) were subjected to disk diffusion test according to EUCAST methodology and screened with the suggested disk diffusion zone diameter cut-offs (ertapenem <25 mm, imipenem <23 mm, meropenem <27 mm). For the phenotypic characterization of carbapenem resistance, meropenem disks supplemented with different beta-lactamase inhibitors were used and synergy was sought by the increase in zone diameter in supplemented meropenem disks as compared to disk with meropenem alone. Also a multiplex PCR for the investigation of IMP, VIM, NDM-1, KPC and OXA-48 genes was performed for all isolates.
Results: The initial screening revealed 17 *K. pneumoniae* isolates with zone diameters above the screening cut-offs and multiplex PCR was found negative for all genes tested, thus these isolates were regarded as carbapenem susceptible. For the remaining isolates (n=131), multiplex PCR revealed OXA-48 gene in 100 (76.3%) isolates (*E. coli:* n=27; *K. pneumoniae:* n=73), VIM gene in two *K. pneumoniae* isolates, and NDM-1 gene in 11 (8.4%) isolates (*E. coli*: n=3, *K. pneumoniae*: n=8). Interestingly, six isolates (3 *E. coli*, 3 *K. pneumoniae*) were found to harbour both OXA-48 and NDM-1 genes. Also isolates from the same patient, *E. coli* from urine and *K. pneumoniae* from tracheal aspirate, were found positive for NDM-1. IMP and KPC genes were not detected among the study isolates. No synergy was observed with the beta-lactamase inhibitors in 110 isolates and OXA-48 was found in 88 of these isolates, in the remaining 22 isolates which were negative in PCR for all tested genes, the mechanism responsible for carbapenem resistance was regarded as extended-spectrum beta-lactamase production plus porin loss.
Conclusion: On the contrary to previous studies from Turkey which dominantly reported OXA-48 and IMP genes, we have found another distribution profile for carbapenemase genes, OXA-48 followed by NDM-1. To our knowledge, NDM-1 was reported from Turkey once from a non-Turkish citizen. We have found NDM-1 in Turkish patients from seven different institutions situated in Istanbul which indicates the requirement for strict infection control measures to stop further dissemination of NDM-1.