Carbapenem resistance in *Enterobacteriaceae,* an ongoing story

Hôpital de Bicêtre, Faculté de Médecine Paris-Sud, INSERM U914: Emerging Resistance to Antibiotics, Le Kremlin-Bicêtre, France

The *Enterobacteriaceae* are among the most important causes of serious nosocomial and community-onset bacterial infections in humans, and resistance to antimicrobial agents in these species has become an increasingly relevant problem for healthcare providers. Carbapenems have the most consistent in vitro activity against multidrug-resistant *Enterobacteriaceae,* however carbapenem-resistant *Enterobacteriaceae* (CRE) are emerging as an important challenge in health-care settings. Carbapenem resistance in *Enterobacteriaceae* is mainly related to acquired carbapenem-hydrolyzing ß-lactamases (carbapenemases). They have the ability to hydrolyze penicillins, cephalosporins, monobactams, and carbapenems. Bacteria producing these ß-lactamases may cause serious infections in which the carbapenemase activity renders many ß-lactams ineffective. These ß-lactamases can be either carbapenem-hydrolysing penicillinases (Ambler class A). metallo ß-lactamases (Ambler class B), and expanded-spectrum oxacillinases, (Ambler class D).

The class A carbapenemase group includes members of the SME, IMI, NMC, GES, and KPC families. Of these, the KPC carbapenemases initially reported from the USA and now worldwide, are the most prevalent class A carbapenemases. The metallo-beta-lactamases belong to the IMP, VIM, SPM, GIM, and SIM families and have been detected primarily in *Pseudomonas aeruginosa*; however, there are increasing numbers of reports worldwide of this group of ß-lactamases in the *Enterobacteriaceae*. The Ambler class D OXA-48 ß-lactamase has so far been reported only in enterobacterial species. Recent evidence identified this OXA-48-mediated carbapenem-resistance in *Enterobacteriaceae* not only as widespread in Turkey but also in Belgium, UK, France, Lebanon and Egypt. The carbapenem resistance phenotype

conferred by this enzyme is variable ranging from susceptibility to full resistance and therefore very difficult to detect in clinical microbiology, thus suggesting that the spread of this novel and powerful resistance determinant could be more important.

Carbapenemases spread easily on plasmids and cause nosocomial infections and outbreaks with excess mortality. Carbapenem-hydrolysing ß-lactamases confer decreased susceptibility or resistance to virtually all β-lactams. Carbapenems (imipenem, meropenem, ertapenem) may thus become inefficient for treating enterobacterial infections with carbapenemase-producing bacteria, which are in addition resistant to many other non β-lactam molecules, leaving very few therapeutic options available.

Carbapenem-resistance continues to increase worldwide in enterobacterial species, mostly in *K. pneumoniae*. The resistance trend is related to spread of known ß-lactamases and increasing-identification of novel carbapenem-resistance determinants.