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Carbapenem-resistance in gram-negative bacteria

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Carbapenems have a well-deserved reputation as potent broad-spectrum β-lactams that evade most b-lactamases, including AmpC and extended-spectrum types. As was recognised from the 1980s, *P. aeruginosa* can easily mutate resistant via loss of its 'carbapenem-specific' OprD porin; otherwise, though, resistance remained rare in gram-negative bacteria until the turn of the century.

Soon afterwards there was a rapid accumulation of resistance in *A. baumannii*, reflecting either *IS*Aba1-mediated up-regulation of the chromosomal OXA-51-like carbapenemase, which is inherent to the species, or the acquisition of additional OXA-carbapenemase genes, principally $bla_{\text{OXA-23}}$ and $bla_{\text{OXA-40}}$. These mechanisms rapidly became widespread, largely my clonal spread between units and hospitals.

Although occasional carbapenem-resistant Enterobacteriaceae were encountered in the 1990s, they began to accumulate significantly only from the middle of the last decade. Sometimes – particularly for ertapenem – resistance involves just the combination of an ESBL or AmpC enzyme together with mutational porin loss, which is often unstable. More often, however, resistance involves the acquisition of plasmid-mediated carbapenemases. These are include members of molecular classes A (principally KPC), B (IMP, VIM and NDM) and D (OXA-48), with different enzymes predominant in different parts of the globe – KPC in China, Greece, Israel, Italy and the Americas, NDM in India and Pakistan and OXA-48 in the Middle East, France and Germany. *K. pneumoniae* is the commonest host for all these enzymes and one lineage, *K. pneumoniae* ST258, has carried KPC enzymes across continents. The other carbapenemases are largely spread among Enterobacteriaceae by promiscuous plasmids, disseminating among strains and links to particular clones are weaker or absent.

Regardless of species, most carbapenemase producers are broadly resistant, with colistin, tigecycline and fosfomycin often the only antibiotics to retain in-vitro activity. The diversity of important carbapenemase types challenges the development of stable β-lactams or inhibitors Avibactam and MK-7655, now under development, inhibit KPC enzymes but not the Class B (metallo) carbapenemases, whereas diacarboxylic acids (e.g. ME1071) have the converse profile; RPX7009, a boronate, inhibits only KPC types.

Because of this paucity of current and future options it is vital that public health initiative are deployed to prevent the spread of carbapenemase producers. Their potential was illustrated in Israel, where government-mandated surveillance, isolation and cohorting policies achieved a 75% reduction in infections due to KPC-positive *K. pneumoniae*, mostly belonging to the ST258 clone. It remains however to be seen whether this achievement can be replicated in other less centrally-controlled healthcare systems and countries, or in cases where the problem is plasmid spread rather than clonal dissemination.