Metallo-β-Lactamases & Other Carbapenemases

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Old carbapenemases, posing little threat

Carbapenems are famously stable to AmpC β-lactamases and extended-spectrum-β-lactamases. A few infrequent pathogens -*S. maltophilia*, some *Aeromonas* spp. and Flavobacteria, also *Legionella gormannii*- have chromosomal metallo-carbapenemases of molecular class B, but these do not present major problems in most settings. In addition, a few Enterobacteriaceae isolates with carbapenemases belonging to molecular class A were found at around the time imipenem entered use.[1] These included two *S. marcescens* with SME-1 enzyme in the UK in 1982 and several *Enterobacter cloacae* with IMI-1 in California in 1986. These enzymes, or variants of them, have been found again on a few occasions, with SME-types from *S. marcescens* in the USA and NMC-A (a relative of IMI-1) from *E. cloacae* in France. Producers have not spread; nevertheless the isolation of each enzyme family in two continents implies some low-prevalence dissemination.

Another long-known acquired metallo-carbapenemase is CcrA (CfiA). Its gene occurs in c. 1-3% of *B. fragilis* isolates, but fewer produce the enzyme since expression demands appropriate migration of an insertion sequence. CcrA was known before imipenem was introduced, and producers have shown little subsequent increase.

VIM and IMP metallo-β-lactamases- a growing problem

Much more important than SME, IMI, NMC and CcrA was the Japanese discovery, in 1988, of a *P. aeruginosa* isolate with a transferable metallo-β-lactamase, later dubbed IMP-1.[2] Over the next few years this enzyme was found repeatedly in Japan, mostly in *P. aeruginosa* and *S. marcescens.* Since 1997, it has also been reported from *K. pneumoniae* in Singapore and *Acinetobacter* spp. in the UK. Moreover, 11 further IMP variants have been described worldwide, mostly from isolates of *P. aeruginosa* and *Acinetobacter* spp., but also -more rarely- from Enterobacteriaceae.[1] Some types -e.g. IMP-3 and -6 are point mutants of IMP-1, others, e.g. IMP-2, have over 40 amino-acid substitutions. A second family of acquired metallo-β-lactamases, the VIM types- has also become prominent with four representatives, described. VIM-1 was discovered in *P. aeruginosa* in Italy in 1996; subsequently, VIM-2 -now the predominant variant- was found repeatedly in Europe and the Far East; VIM-3 and -4 are minor variants of VIM-2 and -1, respectively. VIM enzymes mostly occur in *P. aeruginosa*, also *P. putida*- and, very rarely, *Enterobacteriaceae*. The association with *P. putida* is interesting because the organism is rarely pathogenic.[3] Perhaps -speculatively- *P. putida* is a conduit whereby VIM enzymes reach *P. aeruginosa* from unspecified environmental organisms.

Amino acid sequence diversity is up to 10% in the VIM family, 15% in the IMP family, and 70% between VIM and IMP. Enzymes of both the families nevertheless are similar.[1] Both are integron-associated, sometimes within plasmids. Both hydrolyse all *β*-lactams except monobactams, and evade all *β*-lactam inhibitors. Sequence variation in the IMP family has some effect on kinetics; e.g. the Ser196Gly substitution in IMP-3 and -6 reduced efficiency. Some blaIMP/VIM gene positive isolates appear susceptible to carbapenems *in vitro*, perhaps because resistance demands impermeably as well as the enzyme, or because carbapenemase expression is weak in some strains.

One further acquired metallo-*β*-lactamase -SPM-1- is described, from a *P. aeruginosa* isolate collected in Brazil.[4] It had 35.5% homology with IMP-1 and was plasmid determined and transferable; no evidence of integron association was found.

OXA carbapenemases- mostly in Acinetobacter

The metallo-*β*-lactamases receive most attention, but OXA (class D) carbapenemases are also important among *Acinetobacter* spp. The OXA family is large and diverse and its carbapenemase members form two related clusters, with further un-sequenced variants belonging to neither.[1] Members of one cluster, including OXA-24, -25, -26 and -40, are epidemiologically linked to Spain and Portugal, where they have been isolated at multiple sites. These share 98-99% amino-acid homology, but only 60% homology with OXA-23 and -27, which form the other cluster. The latter enzymes have been recorded from *Acinetobacter* spp. on single occasions, over 15 years, in Brazil, Scotland and Singapore - also once in *Proteus mirabilis* in France. OXA carbapenemases hydrolyse carbapenems very slowly in vitro, and the high MICs seen for some Acinetobacter hosts (>64 mg/L) may reflect secondary mechanisms. More generally, although it is clear that carbapenem resistance is accumulating in *A. baumannii* in the USA and UK but the relative prevalence of different mechanisms remains unclear. Non-*β*-lactamase mechanisms may be more important than either metallo-*β*-lactamases or OXA carbapenemases in some centres and countries.

KPC- Class A enzymes that may spread

The last acquired carbapenemases to mention are the KPC types, which belong to class A.[5] Three variants are known, distinguished by one or two amino-acid substitutions. KPC-1 was found in North Carolina, KPC-2 in Baltimore and KPC-3 in New York. They have only 45% homology with SME and NMC/IMI enzymes and, unlike them, can be encoded by self-transmissible plasmids. It is disturbing that these enzymes were found in rapid succession in a species notorious for its ability to spread among patients and to act as a vector for plasmids, also that the New York isolates were highly multi-resistant, and caused an outbreak with several deaths.[6] Nevertheless, no evidence of further spread has come in the past year.

Conclusion

Carbapenems have retained antibacterial activity to a remarkable degree, with less than 0.001% of Enterobacteriaceae resistant in the USA. Nevertheless, increasing numbers of carbapenemases are reported, predominantly from non-fermenters and -in the case of metallo-enzymes- predominantly from East Asia.

Carbapenemase-producing Acinetobacter and *P. aeruginosa* have caused major outbreaks in a few centres. In view of the poor correlation between gene carriage and carbapenem resistance, it is also plausible that carbapenemases have disseminated far more widely than is realised, or could do so. Control is difficult, as most carbapenemase producers (except SME-1-positve *Serratia*) are multi-resistant. Aztreonam is stable to the metallo-β-lactamases but many IMP and VIM producers are resistant, owing to other mechanisms. There is some interest in metallo-β-lactamases inhibitors, but none is in advanced development; moreover it remains possible that the greater threat will come from quite different enzymes, such as the OXA carbapenemases or, more plausibly, the KPC types.

References

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