Although K. pneumoniae isolates of strain type ST 258 are dominant worldwide, multiple clonal types are also reported as the result of transfer of blaKPC genes among strains. Currently it appears that virtually all the blaKPC genes are carried on transposons, often related to Tn4401, which likely accounts for the widespread transmission of KPC genes among different plasmids and different species.

Although healthcare facilities in which these strains have become endemic have successfully lowered the incidence of KPC-producing pathogens through strict infection control measures, they have not been able to eradicate the organisms from the health centers (3). In the future we can expect that KPC-producing isolates will continue to spread throughout the Asia-Pacific area, Africa and the rest of Europe. As more carbapenems are used to combat ESBL-producing infections, we can only expect further expansion of carbapenemase-hydrolyzing enzymes among multidrug-resistant Gram-negative pathogens.

Reference

The first acquired carbapenemase to be recognised in gram-negative bacteria was IMP-1, a metallo-type, found in Pseudomonas aeruginosa in Japan in 1989, followed by the class A types, IMI-1/NMC-A and SME-1 in Enterobacter cloacae and Serratia marcescens, respectively. The earliest producers of IMI-1, NMC-A and SME-1 date from before imipenem was first marketed but, despite this, they remain extremely rare enzymes, with no significant spread. IMP-1 did slow a little more early success, continuing to be reported in the Japan (principally) and elsewhere in the Far East through the 1990s, principally in P. aeruginosa but also in Enterobacteriaceae. A second metallo-carbapenemase, VIM (Verona Integron Metallo-)-1, and its relatives began to be seen in Europe in 1997, with later reports from Asia, also first in P. aeruginosa, then Enterobacteriaceae (1). Thus, by the turn of the century, the main (any very slowly) emerging threat to carbapenems seemed to come from metallo-carbapenemases. This changed with the recognition of KPC types and their rapid spread, first in the USA, then globally (2). This had a marked effect on antibiotic development, with inhibitors such as NXL104 and MK7655 selected based, inter alia, on their ability to inhibit KPC enzymes and despite a lack of inhibitory activity against metallo-types (3). Nevertheless, it is strongly arguable that the importance of KPC carbapenemases is now being over-emphasised relative to metallo- and OXA- type carbapenemases, and this view is underscored by the recent and rapid spread of NDM type carbapenemases and, more insidiously, OXA-48.

Current distribution of IMP, VIM and NDM and other metallo-carbapenemases

IMP and VIM enzymes initially were seen largely in P. aeruginosa but have increasingly been recorded in Enterobacteriaceae, principally Klebsiella and Enterobacter spp. Although there...
are multiple variants in each family, with sufficient amino-acid divergence to suggest that there have been multiple genetic escapes from their (unknown) source species, their ability to confer resistance is extremely similar (4). Both VIM And IMP types are usually integron associated. IMP types are internationally scattered, nowhere common, whereas Klebsiella pneumoniae with VIM enzymes, principally VIM-2, have become prevalent in Greece. By the mid 2000s they accounted for c. 40% of K. pneumoniae from bacteraemia in the country and were recorded from 25/40 survey hospitals (5). Multiple Enterobacteriaceae with VIM carbapenemases coded by IncN plasmids are scattered in northern Italy too, representing fewer than 1% of clinical isolates but carried by 6% of care home residents (6;7).

A further important metallo carbapenemase, NDM-1 (New Delhi Metallo), was found much more recently and had much publicity in the Summer of 2010. The original producers -a urinary K. pneumoniae and a faecal Escherichia coli- isolated in Jan 2008 from a patient in London. The UK accounted for c. 40% of K. pneumoniae from bacteraemia in the country and were recorded from 25/40 survey hospitals (5). Multiple Enterobacteriaceae with VIM carbapenemases coded by IncN plasmids are scattered in northern Italy too, representing fewer than 1% of clinical isolates but carried by 6% of care home residents (6;7).

Further acquired metallo carbapenemases occur. One, SPM-1 (Sao Paolo Metallo), is widespread in Pseudomonas aeruginosa in Brazil (13), substantially owing to the dissemination of a single producer clone; others, e.g. the AIM, GIM and SIM types are known from tiny numbers of isolates, mostly non-fermenters (12).

Metallo carbapenemases hydrolyse and confer resistance to all β-lactams except aztreonam, which is often (usually in the case of strains with NDM-1) inactivated by coproduced ESBLs or AmpC enzymes (14). Most producers are multi-resistant to other drugs. Those with NDM enzymes generally have 23S rRNA methylases conferring resistance to aminoglycosides, including ACHN-490, an analogue that retains activity against many strains with other carbapenemases (15).

OXA carbapenemases

OXA carbapenemases are the dominant source of carbapenem resistance in Acinetobacter spp., where Acinetobacter baumannii, the main pathogen: (i) has a chromosomal OXA-51-like carbapenemase that may be up-regulated by insertion sequences, and (ii) has a propensity to acquire further carbapenem-inactivating enzymes, principally OXA-23, -40 and -58 (16).

There is a single report of OXA-23 having reached Enterobacteriaceae, with this enzyme seen in 10 non-replicate Proteus mirabilis collected at a hospital in France (17), but with no further spread. Far more important is a further member of the large OXA family, OXA-48. This is evolutionarily remote from the OXA carbapenemases of Acinetobacter, with little in common beside a few sequence motifs seen in all members of the large and rather ramshackle OXA family. OXA-48 was first reported in K. pneumoniae from Turkey in 2001 (18). The encoding gene probably originated in Shewemella spp. (19). OXA-48 is now widespread in Turkey, with producer Klebsiella spp. causing large nosocomial outbreaks (20). Since around 2007, isolates, mostly K. pneumoniae with OXA-48 have repeatedly been found in the Middle East, N. Africa, W. Europe, with reports also from India and Argentina, and with many of the strains sharing related blaoxa-48 encoding plasmids (19). There have been several single-hospital outbreaks in the UK and France, as well as ‘imported’ cases with a history of hospitalisation in Turkey or elsewhere in the Middle East.
Advancing solutions to evolving resistance

A further important metallo carbapenemase, NDM-1 (New Delhi Metallo), was found much more recently and had much publicity in the Summer of 2010. The original producers - a urinary *K. pneumoniae* and a faecal *Escherichia coli* isolated in 2008 from a patient in Sweden, transferred a day earlier from New Delhi in India (8). During the 2008-9, the UK recorded 29 cases of infection by bacteria with the enzyme, including *K. pneumoniae*, *E. coli*, *Enterobacter* spp., *Citrobacter* spp., *M. morganii* and *Acinetobacter* spp. Seventeen of the patients had travelled to India or Pakistan and 14 had been hospitalised there, whether as ‘medical tourists’ or following accident and illness whilst travelling (9). This linkage led to snapshot surveys being undertaken on the Indian subcontinent, which found widespread dissemination (9). Denominators are weak, but a recent study in a major Mumbai hospital found 49/57 carbapenem-resistant Enterobacteriaceae had NDM enzyme, with these accounting for 5-7% of all Enterobacteriaceae at the hospital, according to the infection site (10). During 2010 around 36 further cases were seen in the UK, many again linked to the India subcontinent, whilst more cases with similar Asian links have been reported for the USA, Europe, East Asia and Australasia (11;12). Strikingly, not all of those colonised or infected individuals had been hospitalised: some were simply travellers to India, just as some clinical cases within the country no record of prior hospitalisation (9). This links to recent evidence reported via a UK TV station, that bacteria with NDM-1 enzyme widely present in open sewers and stagnant water in New Delhi (http://www.channel4.com/news/drug-resistant-superbug-threatens-uk-hospitals; last accessed 22 Dec 2010). Such data imply a wide circulation and, in view of: (i) population flows to and from the subcontinent (ii) the size of the population (iii) the speed of medical development and (iv) the growth of medical tourism, there is every reason to be fearful that bacteria with NDM-1 enzyme will continue to be exported internationally.

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Unlike the other acquired carbapenemases, OXA-48, is a narrow-spectrum enzyme, conferring resistance to carbapenems, anti-gram-negative penicillins and penicillin-β-lactamase inhibitor combinations, but not oxyimino cephalosporins (18). Many producers are however resistant to these drugs owing to co-production of ESBLs or plasmid AmpC enzymes.

Countering the problem
The diversity of emerging carbapenemases challenges (i) the laboratory, which must detect producers, not all of them clearly resistant; (ii) the clinician, who must identify treatment – commonly colistin, fosfomycin or tigecycline- for the patient and (iii) the pharmaceutical developer, who must find agents that evade hydrolysis by, or inhibit, enzymes belonging to three quite different molecular classes. Critically, the metallo (class B) enzymes use a different molecular mechanism to the KPC and OXA types, which both have a serine at their active site, and do not, like the serine types, form a covalent adduct with their substrates. This makes it much harder to trap enzyme molecules in an inactivated form (3). Perhaps the best chance of overcoming all these enzymes lies in combining a monobactam (stable to metallo types) with an inhibitor, such as NXL-104, that inhibits serine type carbapenemases as well as the ESBL and AmpC enzymes that commonly accompany metallo carbapenemases, conferring resistance to unprotected monobactams (14). In this context, we found aztreonam+NXL104 active, at 4+4 mg/L against all carbapenemase producing Enterobacteriaceae tested, and would urge its development (14).

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