



## Symposium 15.3

### Carbapenem resistance

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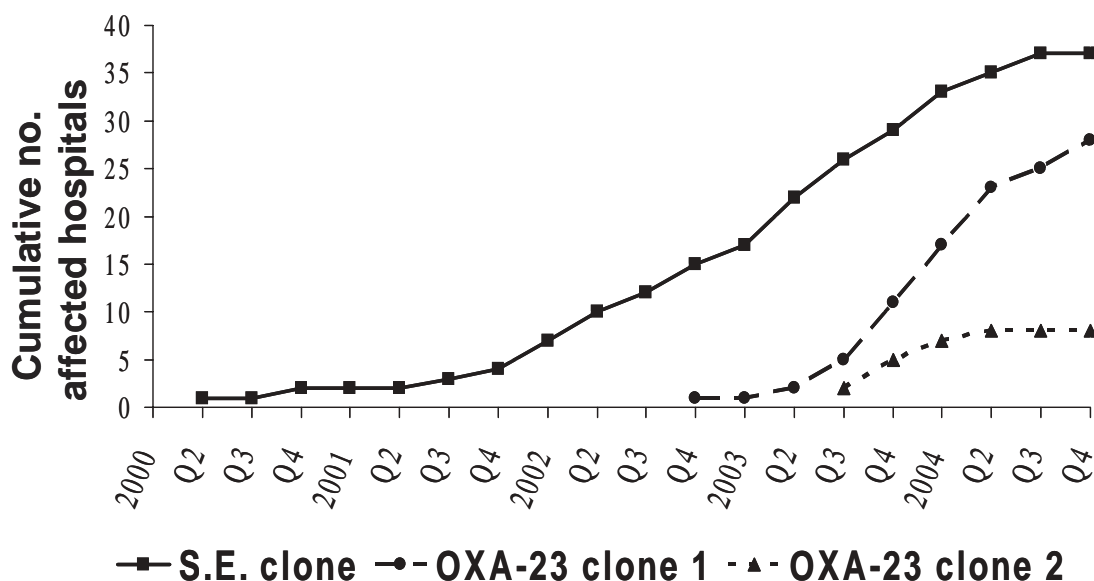
Twenty years after introduction, imipenem remains active against >98% of Enterobacteriaceae in surveys, and many 'resistant' isolates are cases where the disc had deteriorated. Inherent resistance occurs in species with chromosomal metallo-carbapenemases e.g. *Stenotrophomonas maltophilia* and some *Chryseobacterium* (*Flavobacterium*) species - also in gram-positive cocci with  $\beta$ -lactam-resistant PBPs. Acquired resistance has mostly been a concern in *Pseudomonas aeruginosa*, where it arises via mutational loss of the 'carbapenem-specific' porin, OprD, a trait sometimes selected during therapy. OprD loss reduces meropenem susceptibility too, but frank resistance requires additional mutations that up-regulate efflux (1). This may reduce the selection risk, since it is harder to select two mutations than one.

Now, though, four further types of resistance are causing concern: (i) OXA carbapenemases, (ii) acquired metallo- $\beta$ -lactamases, (iii) KPC non-metallo-carbapenemases and (iv) combinations of impermeability with ESBL or AmpC.

#### OXA carbapenems in *Acinetobacter* spp.

Carbapenem-resistant *Acinetobacter baumannii* have been reported since the 1980s but, until c. Year 2000, cases were few and scattered; moreover the mechanism(s) remained unclear. Subsequently, resistance has increased and has been shown to mostly involve OXA (class D) carbapenemases (2). These divide into four clusters based on sequence homology: OXA-23-like, -40(-24) like, -51 (-69)-like and -58. *bla*<sub>OXA-51-like</sub> is ubiquitous in *A. baumannii*. Usually it is silent, but can be expressed, with contingent resistance, through upstream migration of insertion *ISAba1*, and imipenem susceptibility varies according to whether this rearrangement has occurred. One strain with resistance via this mechanism - the 'SE' clone - is widespread SE England (Figure); another has been imported from Iraq. Since *ISAba1* is common in *Acinetobacter*, and is also involved in the *ampC* activation, it is remarkable that carbapenem resistance by this mechanism did not emerge more rapidly and widely.

**Figure:** Rise of carbapenem-resistant *A. baumannii* clones in England



The other OXA carbapenemases are not ubiquitous in *Acinetobacter* and may be plasmid mediated, though chromosomal insertion of their genes is common. *Acinetobacter* clones with OXA-23 enzyme have spread in the UK, China, Colombia and Korea; one with OXA-40 has disseminated in northern Spain and another in Chicago; in the UK 'OXA-23 clone 1' has affected over 30 hospitals (Figure). Strains with OXA-58 are scattered widely but have not been associated with such extensive multi-hospital spread. Many *acinetobacters* with OXA carbapenemases are pan-resistant, except to the polymyxins and, perhaps, tigecycline.

### Acquired metallo-β-lactamases

The first acquired metallo-β-lactamase, IMP-1, was reported from a *P. aeruginosa* isolate collected Japan in 1988. Subsequently, 22 more IMP variants have been described along with 14 VIM variants and single representatives of the GIM, SIM, and SPM families (<http://www.lahey.org/studies>). Isolates - mostly *P. aeruginosa* and *Acinetobacter* spp. but also Enterobacteriaceae - with VIM and IMP enzymes have been found worldwide; SPM-1 is carried by a widespread *P. aeruginosa* clone in Brazil; GIM and SIM are known only from small clusters of *P. aeruginosa* and *Acinetobacter* spp., in Germany and South Korea, (3) respectively. These enzymes can be plasmid-mediated, but widespread transfer among strains has not yet occurred. Rather, most reported problems have involved clonal spread of producers among patients, sometimes causing outbreaks that have persisted for years at more the one site.

Metallo-β-lactamases hydrolyse carbapenems rapidly but, in Enterobacteriaceae, only confer carbapenem resistance if coupled with porin loss (they may confer resistance alone in non-fermenters). This has two implications: (i) there is potential for hidden spread, with host strains appearing susceptible, and, (ii) cephalosporins - to which these enzymes do confer obvious resistance - may be stronger selectors than carbapenems.

### KPC carbapenemases

Molecular class A carbapenemases of the NMC/IMI and SME clusters have been reported in Enterobacteriaceae since the 1980s but remain extremely rare (2). Recently, however, a further Class A group, KPC, has become prominent, with four variants recognised. These have been largely found in nosocomial *Klebsiella* and *Enterobacter* spp in the NE USA, with major clonal outbreaks in New York (4), sometimes with significant mortality in vulnerable patients. Ertapenem resistance may be more obvious than that to other carbapenems, and can be a marker in settings where producers are prevalent; however, ertapenem is also the most vulnerable carbapenem to combinations of ESBL and impermeability, below, and a pattern of ertapenem resistant, imipenem susceptible is **NOT** diagnostic of KPC).

### Combinations of ESBL or AmpC with impermeability

Although carbapenems are relatively stable to AmpC and ESBL enzymes, these can confer resistance in a sufficiently impermeable background, created by porin loss. Reports of imipenem and meropenem resistance arising by this mechanism in Enterobacteriaceae date back to the 1980s but, until recently, the mechanism was uncommon (2). This is now changing and the UK reference laboratory has received over 200 representatives in the past 2 years, mostly non-clonal *K. pneumoniae* and *Enterobacter* spp. (5).

**Table:** Geometric mean carbapenem MICs for *Klebsiella* and *Enterobacter* spp. with combinations of ESBL or AmpC together with impermeability (from 5)

Antibiotic	<i>Klebsiella</i>		<i>Enterobacter</i>	
	Ertapenem <sup>low level</sup> (MIC 4-16 mg/L; n=57)	Ertapenem <sup>high level</sup> (MIC >16 mg/L; n=38)	Ertapenem <sup>low level</sup> (MIC 4-16mg/L; n=46)	Ertapenem <sup>high level</sup> (MIC >16 mg/L; n=30)
Ertapenem	9.4	>16.0	5.4	>16.0
Meropenem	1.6	8.1	0.8	5.7
Imipenem	0.7	2.5	1.4	7.5

This rise in referral probably reflects a wider base of ESBL and AmpC producers in which the mechanism can evolve, along with more testing of carbapenems. Resistance to ertapenem (MIC >2 mg/L) is consistent, with

MICs often >16 mg/L; that to imipenem and meropenem is variable, is restricted to the more-ertapenem-resistant representatives, whereas the remainder show reduced susceptibility (Table). This mode of resistance is occasionally selected during carbapenem therapy, perhaps particularly with ertapenem, where there are several recent reports. The resistance is often unstable, probably because the porin loss impedes nutrition as well as antibiotic uptake; this may limit the problem.

## Conclusions

Carbapenem resistance remains rare outside *P. aeruginosa* and those gram-positive cocci with resistant PBPs, but it is increasing. For several of the accumulating resistant types  $\frac{3}{4}$ *A. baumannii* with OXA carbapenemases, *Acinetobacter* spp. and *P. aeruginosa* with metallo-carbapenemases, and *K. pneumoniae* with KPC enzymes- the major problem is clonal spread suggesting that the best answers lie in improved infection control. The exception is the resistance that arises owing to combinations of an ESBL or AmpC plus impermeability; here the problem may be limited by strain instability, but it would be reckless to assume so.

- (1) Livermore DM. Of *Pseudomonas*, porins, pumps and carbapenems. *J Antimicrob Chemother* 2001; **47**:247-250.
- (2) Livermore DM, Woodford N. The b-lactamase threat in Enterobacteriaceae, *Pseudomonas* and *Acinetobacter*. *Trends Microbiol* 2006; **14**: 413-420.
- (3) Walsh TR. The emergence and implications of metallo-b-lactamases in Gram-negative bacteria. *Clin Microbiol Infect* 2005; **11 Suppl** 6:2-9.
- (4) Paterson DL. Resistance in gram-negative bacteria: Enterobacteriaceae. *Am J Infect Control* 2006; **34(5 Suppl 1)**:S20-S28.
- (5) Woodford N, Dallow JWT, Hill RLR *et al*. Ertapenem resistance among *Klebsiella* and *Enterobacter* submitted in the United Kingdom to a reference laboratory. *Int J Antimicrob Agents* 2006; in press.