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Carbapenems: do they have a future?

The pivotal role of glycopeptides in the control of meticillin-resistant *Staphylococcus aureus* is well known and the notoriety of this organism has ensured that new antibacterial treatments have been developed. Far less publicized is the crisis in the treatment of Gram-negative infections, especially those that are hospital-acquired. In many cases, particularly because of the emergence and spread of extended-spectrum β-lactamases (ESBLs) in the *Enterobacteriaceae* and the increased isolation of non-fermenting bacteria, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, the remaining standard treatment option has been a group of penem antibiotics with a carbon atom in the side ring rather than the traditional sulphur. These are the carbapenems.

In the UK, there are three main carbapenems, imipenem, meropenem and ertapenem, and a new addition, doripenem. Imipenem is a broad-spectrum antibiotic, derived from a compound isolated from the soil bacterium *Streptomyces cattleya* (Kahan et al., 1983), which has to be co-administered with cilastatin to prevent its degradation by the kidney. Meropenem is also a broad-spectrum β-lactam, and has a therapeutic advantage over imipenem because it can be used to treat central nervous system infections. The addition of a methyl group in the 1-position of the carbapenem moiety in meropenem makes it structurally different from imipenem (Wiseman et al., 1995) and this modification enhances the *in vivo* stability of meropenem, compared to imipenem, and it does not need to be co-administered with cilastin (Edwards, 1995). Both compounds are used as empiric therapy for a wide range of severe Gram-negative infections. Ertapenem has a more limited spectrum and has largely been recommended for the treatment of community-acquired infections, especially those caused by bacteria carrying an ESBL. It can partially inhibit non-fermenting bacteria and thus would select those strains that have a pre-disposition to carbapenem resistance (Amyes et al., 2007). This reason questions its use in the treatment of hospital-acquired infections as it may preferentially select non-fermenting bacteria. Doripenem has a profile similar to that of imipenem and meropenem and does not overcome the majority of currently prevalent mechanisms of resistance to the carbapenems.

**Mechanism of resistance**

Unfortunately, resistance has emerged in many bacteria treated with carbapenems. The most common mechanisms of resistance are the acquisition of carbapenem-hydrolysing β-lactamases of Ambler class D enzymes (oxacillinases) (CDO) (Poirel & Nordmann, 2002), β-lactamases belonging to class B (metallo-enzymes) (MBLs) (Walsh et al., 2005) and a few class A β-lactamases such as the KPC enzymes in *Klebsiella* species. Often these β-lactamases do not act alone and are often accompanied by mutations in genes encoding penicillin-binding proteins and alteration in outer-membrane permeability; for example, the loss of porins CarO and Omp33–36 in *A. baumannii* (Gehrlein et al., 1991).

In *A. baumannii*, the spread of carbapenem resistance largely results from the clonal dissemination of a resistant strain where a crucial combination of a mobile carbapenem resistance gene (often encoding the class D β-lactamases OXA-23 or OXA-58) has entered a congenial host (Brown & Amyes, 2006). The spread of these resistant bacteria is due as much to cross-infection as to antibiotic usage. These genes have migrated to the congenial host because they are closely linked to insertion sequences, which have promoted their mobility (Turton et al., 2006; Poirel & Nordmann, 2006). A further complication is that all *A. baumannii* possess an inherent class D β-lactamase, collectively known as OXA-51-like, which can provide weak hydrolytic activity on the carbapenems, though currently only rarely produces clinical resistance.

There are five groups of acquired MBLs (IMP-like, VIM-like, SIM-1, SPM-1 and GIM-1 enzymes). These have largely been found in non-fermenting bacteria; for instance the first three have been identified in *A. baumannii* (Peleg et al., 2008). They are less common in other Gram-negative bacteria. Recent concern has focussed on the emergence of resistance in the *Enterobacteriaceae*, particularly with the emergence of the NDM-1 β-lactamase in *Klebsiella* species. Coupled with the emergence of the KPC class A serine β-lactamases, this augurs badly for the carbapenems (Kumarasamy et al., 2010). Unlike *A. baumannii*, the development and spread of resistance in *Klebsiella* species is less well defined and currently much rarer; the emergence of the mobile β-lactamase genes is still in its infancy and the crucial combination of this gene in a suitable host does not yet appear to have occurred. Thus the mobile genes are still migrating and this would be aided by imprudent therapy.

The importation of carbapenem-hydrolysing β-lactamases is not the only threat in *Klebsiella* species. ESBL-producing *Klebsiella pneumoniae* strains are now very common and the carbapenems are often the preferred course for treatment; in particular, ertapenem, a once daily parenteral 1-β-methyl carbapenem antibiotic, licensed in 2002 for the treatment of intra-abdominal and gynaecological infections and community-acquired pneumonia (Livermore et al., 2003). It is considered a first-line antibiotic for complicated community-acquired infections and, as such, is often prescribed for the treatment of ESBL-producing coliform infections (Livermore et al., 2003). It has been shown that the use of ertapenem in *K. pneumoniae* can select for the loss of the major outer-membrane protein OmpK36, resulting in reduced accumulation of ertapenem in the bacterial cell and subsequently reduced susceptibility (Gitlich et al., 2009). Studies in *K. pneumoniae* have shown that the loss of OmpK36 and the presence of non-carbapenemase β-lactamases, such as...
the ESBL CTX-M-15, are sufficient to exert resistance to ertapenem whilst causing a concomitant reduction in susceptibility to meropenem and imipenem (Doumith et al., 2009; Jacoby et al., 2004). The potential for cross-resistance is particularly worrying because if ertapenem is administered to a patient prior to other carbapenem treatment for a recurring infection, porin-deficient mutants may be inadvertently selected for, resulting in reduced susceptibility to the other carbapenems, which potentially can result in therapy failure.

Carbapenems, especially the broad-spectrum variants, are an extremely important part of our ability to control severe Gram-negative infections, particularly those caused by multidrug-resistant bacteria. However, resistance is emerging in the form of new β-lactamases able to migrate to clinically important strains and confer high levels of clinical resistance, a situation similar to that seen with the ESBLs two decades ago. The situation is more complicated; some species of bacteria (A. baumannii, K. pneumoniae, etc.) already possess β-lactamases that can, under certain conditions particularly with the assistance of reduced permeability, reduce the susceptibility of the bacterium to all carbapenems. The alternative to carbapenem therapy is the re-emergence of the polymyxins, such as colistin methanesulphate, which are considered a last resort salvage therapy (Li et al., 2006). The ESBLs caused the decline of the cephalosporins; there are now sufficient β-lactamases to do the same to the carbapenems. Prudent therapy with carbapenems should prolong their efficacy and this should not be compromised by empiric therapy with less-active drugs. The alternative would be an increased reliance on colistin and that would appear a poor substitute if we allow the carbapenems to join the large group of excellent antibiotics that we once had to treat severe Gram-negative infections.

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