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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 cilastatin (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 (Girlich *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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