Emerging carbapenem resistance in *Acinetobacter baumanni*

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Acinetobacter spp. are non-motile Gram-negative coccobacilli. Over 30 genomic species have been identified to date, the most common and significant clinically being *A. baumannii*. It is involved in 1–2% of pneumonia (mostly nosocomial) in immunocompromised patients. Outbreaks of *A. baumannii* have been reported worldwide, mainly in patients who are hospitalised in intensive care units (ICUs). Many of these outbreaks involve multidrug-resistant (MDR) isolates for which very few (if any) antibiotic molecules retain significant antibacterial activity.

Acinetobacter spp. possess a remarkable ability to accumulate resistance mechanisms, in particular to β-lactams (penicillins, cephalosporins and carbapenems), tetracyclines, aminoglycosides, and fluoroquinolones. The emergence of carbapenem resistance is the most crucial issue since carbapenems are the antibiotic molecules of last resort for treating multidrug resistant bacterial infections. Resistance to β-lactams is related mostly to the expression of β-lactamases, whereas alteration of outer-membrane permeability, modification of penicillin-binding proteins and increased activity of efflux pumps play a secondary role.

A. baumannii produces naturally an AmpC-type cephalosporinase, which upon over-expression leads to resistance to expanded-spectrum cephalosporins but not to carbapenems. Resistance to carbapenems in *A. baumannii* may be result of the over-expression of a naturally occurring oxacillinases (OXA-51-like variants) that have a low level of carbapenemase activity. In addition to those naturally occurring β- lactamases, several acquired ß-lactamases have been identified as a source of carbapenem resistance in *A.*

baumannii. They belong either to class D oxacillinases (carbapenem-hydrolysing oxacillinases [CHDLs]) or class B (metallo-β-lactamases [MBLs]). Three CHDLs (OXA-23, OXA-40 and OXA-58) have been identified frequently in carbapenem-resistant *A. baumannii* isolates. They confer low-level resistance to carbapenems (and often do not confer resistance to meropenem) without significant activity against expanded-spectrum cephalosporins. CHDLs in *A. baumannii* are now increasingly identified worldwide. Interestingly, the natural reservoir of one of the group of CHDL genes, the $bla_{\text{OXA-23}}$ gene, has been identified as being the *A. radioresistens*, an *Acinetobacter* species rarely identified in humans.

MBLs are powerful carbapenemases. MBLs reported in *A. baumannii* belong to three groups: the IMP-like, VIM-like and SIM-1 enzymes. While VIM-like enzymes have been mostly isolated in Europe, IMP variants mostly from Asia, and SIM-1 has been reported only in *A. baumannii* in South Korea where this determinant might be widespread.

Carbapenemase (CHDL or MBL)-producing strains exhibit resistance to almost all currently available antibiotics. In vitro studies reveal that tigecycline and colistin are the only antibacterial agents that remain activity against these strains. However tigecycline- and colistin-resistant *A. baumannii* isolates have already been reported.

Carbapenem resistance in *A. baumannii* continues to increase but our therapeutic options remain woefully inadequate - a dilemma that will not improve in the foreseeable future.