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Editorial

Epidemiology and carbapenem resistance mechanisms in *Pseudomonas aeruginosa*: Role of high-risk clones in multidrug resistance☆

Epidemiología y mecanismos de resistencia a carbapenemas en *Pseudomonas aeruginosa*: papel de los clones de alto riesgo en la multirresistencia

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Pseudomonas aeruginosa, a microorganism that is ubiquitous in nature and highly versatile, is one of the main pathogens involved in opportunistic human infections.[1] *P. aeruginosa* is one of the most common causes of infection in hospitalised patients. It particularly affects patients admitted to intensive care units (ICUs) with pneumonia associated with mechanical ventilation or with infection in extensive burns. Both processes are associated with a high rate of mortality. In addition, *P. aeruginosa* is the main cause of chronic respiratory infection (with high morbidity and mortality) in patients with cystic fibrosis, bronchiectasis or chronic obstructive pulmonary disease.

The growing prevalence of nosocomial infections due to strains of *P. aeruginosa* that are multi-drug resistant (MDR, i.e. resistant to 3 or more classes of antibiotics), extensively drug-resistant (XDR, i.e. resistant to all but 1 or 2 classes of antibiotics), or sometimes even pan-drug resistant (PDR, i.e. resistant to all available antibiotics)[2] enormously compromises the selection of effective treatments, and therefore is associated with high rates of morbidity and mortality.[3] This growing prevalence of MDR/XDR strains results from the conjunction of the extraordinary capacity of *P. aeruginosa* to develop resistance to almost all available antimicrobials through selection of chromosomal mutations on the one hand, and the increasingly common production of exogenous resistance determinants, which are generally located in integrons encoded in transferable genetic elements (plasmids or transposons), on the other.[4] Notable among these determinants due to their clinical significance are genes for β-lactamases with a greater hydrolytic spectrum (carbapenemases and extended-spectrum β-lactamases [ESBLs]), which are commonly associated with determinants of aminoglycoside resistance. Amplification due to intrahospital dissemination giving rise to epidemic/endemic situations involving certain MDR/XDR strains undoubtedly plays a key role in the growing scope of this problem, although evidence of the existence of epidemic MDR/XDR strains widely disseminated at an international level, called high-risk clones, mainly ST111, ST175 and ST235, is even more alarming.[5–8]

In this issue of *Enfermedades Infecciosas y Microbiología Clínica*, Estepa et al.[9] analyse the molecular epidemiology and mechanisms of carbapenem resistance of *P. aeruginosa* strains from Hospital San Pedro in Logroño, La Rioja, Spain. Specifically, the study includes 85 isolates from clinical samples obtained between 2008 and 2011 from 60 patients. The molecular epidemiology study through pulsed-field gel electrophoresis showed relatively high clonal diversity (35 different patterns). Even so, despite the apparent clonal diversity, a significant association is documented between resistance to carbapenems and resistance to other antibiotics; in fact, 100% of the isolates met the MDR criterion, since the vast majority of them were resistant to fluoroquinolones and aminoglycosides as well as carbapenems. These data obtained for the carbapenem-resistant *P. aeruginosa* strains, which have relatively high clonal diversity but are associated with multi-drug resistant profiles, are consistent with the results of a Spanish multicentre study carried out in 2003.[10]

Undoubtedly, one of the key matters to take into account with respect to carbapenem resistance in *P. aeruginosa*, both from an epidemiological standpoint and from a therapeutic standpoint, is whether this is mediated by transferable carbapenemases or by chromosomal mutations in the OprD porin gene. Fortunately, all strains were negative for carbapenemase production, and in all cases resistance resulted from OprD mutation, either through the creation of premature termination codons, insertions, deletions or through interruption of the gene due to insertion sequences. This is positive news, on the one hand because the risk of (horizontal) spread of the resistance mechanism is much lower, and on the other hand because, as production of carbapenemases, particularly metallo-β-lactamases (MBLs), is not involved, the new combinations of β-lactams plus inhibitors of β-lactamase, ceftolozane–tazobactam and ceftazidime–avibactam could show activity in these strains. The low prevalence of carbapenemase-producing *P. aeruginosa* strains is consistent with the national data; while it is a problem that is on the rise, the latest multicentre studies still place its prevalence at 1–2%.[11,12] Even so, significant epidemic outbreaks, both of MBL-producing strains

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(VIM-2) and of class A carbapenemases (GES-5), have already been reported at some hospitals.[5,7] Contrary to that documented for β-lactams, aminoglycoside resistance in the study by Estepa et al. was mainly due to the presence of class 1 integrons carrying genes for exogenous aminoglycoside-modifying enzymes, particularly *aadB*.

Despite the relatively high clonal diversity, the multilocus sequence typing (MLST) analysis, performed on the 41 integron-carrying strains, revealed the presence of only 4 clones, the most abundant by far being S175 (35 of the 41 isolated). Again, these data are consistent with those documented at a national level: the majority (77%) of the XDR strains (15%) documented in the REIPI (Spanish Network for Research in Infectious Diseases) multi-centre study on bacteraemia due to *P. aeruginosa* belonged to ST175.[13] In fact, the two most common markers of resistance in the study by Estepa et al. — the Q142X mutation in OprD and the presence of the *aadB* gene — are key components of the resistome of the clone ST175.[14,15] Although not specifically addressed in this study, the clone ST175 has several mutations in QRDR regions. This would explain quite a bit of the documented association between resistance to carbapenems and fluoroquinolones. By contrast, the study by Estepa et al. found no association with hyperproduction of AmpC. This differed from the data from the multi-centre study which show that the clone ST175 tends to contain mutations determining hyperproduction of AmpC, particularly G154R in AmpR.

To sum up, studies such as the one conducted by Estepa et al. are required in order to ascertain the status and outlook of the epidemiology and mechanisms of resistance of *P. aeruginosa*. This has important implications both for establishing infection control measures and for determining the prospects of the new therapeutic options against *P. aeruginosa*, including ceftolozane–tazobactam and ceftazidime–avibactam, which are already available, and the multiple combinations of β-lactams plus β-lactamase inhibitors, which are currently being developed.

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