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Diversity of OXA-235-like encoding plasmids in Acinetobacter baumannii clinical isolates

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Background: Carbapenem resistance in *Acinetobacter baumannii* is most frequently conferred by the presence of OXA-type carbapenemases. These can be both chromosomally and plasmid-encoded and are often associated with insertion elements, particularly IS*Aba1*. The aim of the present study was to characterize OXA-235-like encoding plasmids and the genetic environment of $bla_{\text{OXA-235-like}}$ subclass among *A. baumannii* clinical isolates from multiple geographical regions.

Material/methods: Total DNA was prepared from five clinical *A. baumannii* isolates from the United States and Mexico recovered in the years 2005 and 2007 using the MagAttract HMW DNA Kit (Qiagen, Germany). Sequencing libraries were prepared using the Nextera XT library prep kit for a 250bp paired-end sequencing run. Whole genome sequencing was performed on MiSeq (Illumina, USA). SPAdes and Velvet were used for the *de novo* assembly. Plasmid assembly and predicted gaps were confirmed and filled by PCR-based gap closure using plasmid DNA prepared with the PureYield Plasmid Midiprep System (Promega, USA).

Results: A diversity of $bla_{\text{OXA-235-like}}$-encoding plasmids was identified in the *A. baumannii* isolates. Two isolates harboring $bla_{\text{OXA-235}}$- and one harboring $bla_{\text{OXA-237}}$-encoding plasmids showed a plasmid scaffold similar to that of the $bla_{\text{OXA-237}}$-encoding pORAB01-3 plasmid identified in an *A. baumannii* isolate from the US. These plasmids carried a replicase of the GR2 type and a TonB-dependent receptor involved in iron uptake. This feature may contribute to bacterial survival in bloodstream infections. Additional, these plasmids were found to carry components of a toxin-antitoxin (TA) system,

ensuring plasmid stability and maintenance during bacterial cell division. One isolate harboring *bla*$_{OXA-236}$-carrying plasmid also showed a plasmid scaffold carrying a replicase described only in the *bla*$_{OXA-24}$-carrying pMMA2 plasmid identified in an *A. baumannii* isolate from Spain. In another isolate, *bla*$_{OXA-235}$ was identified on a completely different plasmid scaffold, including a replicase gene of GR3 type, similar to the pABLAC1 plasmid from an *A. baumannii* isolate from the US. In all five *bla*$_{OXA-235-like}$-carrying plasmids analyzed the carbapenemase gene was bracketed by two inverted copies of IS*Aba1*.

Conclusions: The present study describes the diversity of plasmids involved in the dissemination of the OXA-235-like carbapenemase, a class D β-lactamase in *A. baumannii* with as yet unknown prevalence. Our results demonstrate that OXA-235-like was found on three different plasmid types, discernable by the replicase genes. Three of these plasmids presented a similar genetic environment for OXA-235-like including the TonB-dependent receptor and components of a TA system. Similar OXA-235-like encoding plasmids were found in unrelated *A. baumannii* isolates from different countries. This evidence suggests that these plasmids may support a worldwide spread of the OXA-235-like carbapenemase.