Pan-aminoglycoside resistance: the emergence of 16S rRNA methyltransferases in the UK

Emma Taylor*, Katie Hopkins2, Shiranee Sriskandan1, Neil Woodford3

1Imperial College London; Department of Medicine
2Public Health England
3Public Health England; Antimicrobial Resistance and Healthcare Associated Infections (Amrhai) Reference Unit; Antimicrobial Resistance & Healthcare Associated Infections Unit

Background: 16S rRNA methyltransferases (16S RMTases) are an emerging resistance mechanism, and cause high-level resistance (MICs ≥256 mg/L) to all clinically-relevant aminoglycosides in Gram-negative bacteria. The aim of this study was to identify the prevalence of 16S RMTase genes (armA, rmtA-H and npmA) in isolates from the Antimicrobial Resistance and Healthcare Associated Infections (AMRHAi) Reference Unit’s collection at Public Health England (PHE). These isolates were sent to AMRHAi as they displayed unusual resistance profiles, especially carbapenem resistance.

Material/methods: Acinetobacter baumannii (n=550) and Enterobacteriaceae (n=817) isolates from 2004-2015 displaying pan-aminoglycoside resistance (amikacin, gentamicin and tobramycin MICs of ≥64, ≥32 and ≥32 mg/L, respectively) were screened for armA, rmtA-H and npmA by PCR. Whole-genome sequencing (WGS) data, available for 449 Enterobacteriaceae, were analysed to identify 16S RMTase genes and sequence types (STs).

Results: Five hundred and twenty-seven (95.8%) A. baumannii and 755 (92.4%) Enterobacteriaceae were positive for 16S RMTase genes (Figure). armA, rmtB, rmtC, rmtE, rmtF and various two gene combinations were identified; no rmtA, rmtD, rmtG, rmtH or npmA genes were detected. The vast majority (94.5%, 1211/1282) of 16S RMTase-positive isolates also produced a carbapenemase where blaOXA-23 + blaOXA-51 (n=490), blaOXA-23-like (n=5), blaOXA-40 + blaOXA-51 (n = 4), blaNDM + blaOXA-23 + blaOXA-51 (n=3) and blaOXA-51-like (n=2) were found in A. baumannii and blaNDM (n=527), blaOXA-48-like (n=112).
**Conclusions:** 16S RMTase activity has been identified as the major mechanism conferring pan-aminoglycoside resistance in this group of Gram-negative organisms displaying unusual resistance phenotypes, predominantly carbapenem resistance. This combination of carbapenemase and 16S RMTase genes poses a serious threat to the treatment of mult drug-resistant Gram-negative isolates with already limited treatment options should this combination become more widespread. 16S RMTase genes appear to be spreading through co-selection with carbapenemase genes, which is supported by their carriage in high-risk clones known to be carbapenemase producers such as A. baumannii international clone II, E. coli ST410 and K. pneumoniae ST14.