Editorial

Emerging Amikacin Resistance in IMP-Type Carbapenem-Resistant Enterobacterales: A New Concern in Japan

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The global spread of carbapenem-resistant Enterobacterales (CRE) remains one of the most pressing challenges in contemporary infectious diseases and clinical microbiology. While the molecular epidemiology of CRE differs substantially across geographic regions, Japan has long exhibited a characteristic resistance profile dominated by IMP-type metallo-β-lactamase (MBL)-producing Enterobacterales, particularly those harboring $bla_{\text{IMP-6}}$ on pKPI-6–related plasmids. Unlike many carbapenemase-producing strains reported in Europe, the United States, and other parts of Asia, these Japanese IMP-type CRE isolates frequently retain susceptibility to amikacin (AMK), despite carrying aminoglycoside resistance-associated genes such as *aac(6′)-Ib*.

In this issue of Laboratory Medicine International, Yokoyama et al. provide important insights into this unique microbiological phenomenon through a detailed molecular analysis of carbapenem-resistant *Escherichia coli* isolates collected during a 13-year surveillance period in Osaka, Japan. Their study highlights the emergence of two multidrug-resistant *E. coli* strains that acquired clinically relevant resistance to AMK in addition to carbapenem and fluoroquinolone resistance. Importantly, the authors demonstrate that resistance was associated not simply with the presence of the commonly detected *aac(6′)-Ib* (L119S) variant, but rather with acquisition of additional aminoglycoside acetyltransferase genes, including *aac(6′)-Iae* and *aac(6′)-Ib-cr*.

This observation is clinically meaningful for several reasons. First, AMK has often remained one of the limited therapeutic options against IMP-type CRE infections in Japan. The relative preservation of AMK susceptibility among IMP-6-producing Enterobacterales has influenced empirical treatment strategies and infection control perspectives in Japanese clinical settings. The present study suggests that this situation may change over time. The acquisition of supplementary resistance determinants capable of conferring higher AMK minimum inhibitory concentrations (MICs) could gradually reduce one of the few remaining antimicrobial vulnerabilities of these organisms.

Second, the study illustrates how subtle genetic differences may significantly alter antimicrobial susceptibility profiles. The *aac(6′)-Ib* (L119S) variant itself appeared to confer only modest increases in AMK MICs, remaining below clinical resistance breakpoints. In contrast, acquisition of *aac(6′)-Iae* or *aac(6′)-Ib-cr* was associated with substantially elevated AMK resistance. These findings emphasize that the mere presence of aminoglycoside resistance genes may not fully predict phenotypic resistance and that detailed molecular characterization remains essential for understanding resistance evolution.

The identification of *aac(6′)-Iae* in *E. coli* is also noteworthy. This gene has been reported predominantly in *Pseudomonas aeruginosa* and appears to be relatively uncommon in Enterobacterales. Its detection on an IncC plasmid raises concern regarding horizontal transfer of resistance determinants across bacterial species. Such interspecies dissemination represents a critical mechanism driving the diversification of antimicrobial resistance in healthcare environments.

Another important aspect of this report is the continued predominance of ST131 among carbapenem-resistant E. coli isolates. ST131 is already recognized globally as a highly successful multidrug-resistant lineage associated with fluoroquinolone resistance and extended-spectrum β-lactamase production. The coexistence of ST131 with IMP-type carbapenemases and additional aminoglycoside resistance determinants may further enhance its clinical impact. Moreover, the detection of ST648 carrying distinct resistance determinants suggests that international dissemination and diversification of resistant lineages are ongoing processes that may increasingly influence the Japanese epidemiological landscape.

From a laboratory medicine perspective, this study also underscores the importance of integrating phenotypic susceptibility testing with genomic surveillance. Carbapenemase-producing organisms do not necessarily exhibit uniform resistance profiles, and small genetic variations may substantially alter therapeutic options. Continuous molecular monitoring is therefore essential not only for epidemiological surveillance but also for guiding antimicrobial stewardship and informing infection control measures.

Several limitations should be acknowledged. The study was conducted at a single institution, and only two AMK-resistant isolates were identified. Nevertheless, the detailed genomic and functional analyses provide valuable mechanistic insights and generate important hypotheses regarding the future evolution of IMP-type CRE in Japan.

In summary, the work by Yokoyama et al. highlights a potentially important shift in the resistance characteristics of IMP-type carbapenem-resistant E. coli. Although AMK susceptibility remains relatively preserved in many Japanese IMP-producing CRE isolates, acquisition of additional aminoglycoside resistance determinants may compromise this advantage. Their findings serve as a timely reminder that antimicrobial resistance is continuously evolving and that resistance phenotypes previously considered characteristic of regional strains may change through ongoing genetic diversification. Continued genomic surveillance and careful interpretation of susceptibility profiles will therefore remain indispensable in the management of CRE infections.

References

1) Yamagishi T, Matsui M, Sekizuka T, et al. A prolonged multispecies outbreak of IMP-6 carbapenemase-producing Enterobacterales due to horizontal transmission of the IncN plasmid. Sci Rep. 2020; 10(1): 4139.