Genomic co-occurrence of blaNDM-5 and yersiniabactin-associated loci in cefiderocol-resistant Enterobacterales

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INTRODUCTION

Resistance to cefiderocol (CFDC) among Gram-negative bacteria is multifactorial and may involve beta-lactamase activity, metallo-beta-lactamase production, alterations in siderophore uptake pathways, changes in permeability, efflux, and/or target-related mechanisms.

CFDC is a siderophore-conjugated cephalosporin with a catechol residue that allows iron binding and facilitates entry through bacterial iron acquisition systems. Therefore, the expression and functionality of iron uptake receptors may influence CFDC activity. Several siderophore systems, including enterobactin, aerobactin, yersiniabactin and salmoc helin, may be relevant under iron-limited conditions, although their contribution to CFDC susceptibility depends on bacterial species, receptor integrity, gene expression and co-existing resistance mechanisms.

OBJECTIVES

To describe whole-genome sequencing findings in CFDC-resistant NDM-producing Enterobacterales, focusing on the co-occurrence of blaNDM-5 and genes involved in siderophore/iron acquisition pathways, and to discuss their potential contribution to the observed CFDC-resistant phenotype.

MATERIALS AND METHODS

Five CFDC-resistant NDM-producing Enterobacterales isolates (CFDC MIC range: 4-16 mg/L) were analyzed by whole-genome sequencing. The isolates carried blaNDM-5, and genes associated with the yersiniabactin system, including irp1 and fyuA, were identified in all cases.

In addition, other siderophore-associated genes were detected in some isolates.

RESULTS

All five CFDC-resistant NDM-producing isolates carried blaNDM-5 and the yersiniabactin-associated genes irp1 and fyuA. Additional siderophore-related genes were variably present across isolates, suggesting heterogeneity in iron acquisition repertoires.

The consistent co-occurrence of blaNDM-5 with yersiniabactin-associated loci is biologically plausible in the context of reduced CFDC activity.

CONCLUSIONS

These preliminary WGS data show a consistent co-occurrence of blaNDM-5 and yersiniabactin-associated genes among CFDC-resistant Enterobacterales isolates. The findings support the hypothesis that siderophore/iron uptake pathways may contribute to CFDC resistance in NDM-5 producers, but functional studies and comparative genomic analyses are required to establish causality.