Title: mcr gene family evolution and structural mechanisms of colistin resistance: from mcr-1 to emerging variants

Author names: Muhammad Shahid Mehmood, Uthpala Kavindi Rupasinghe Koggala Marakkalage , Tabish Arif , Fariha Javaid , Muhammad Ali Abid , Muntha Shahid , Anwar Parvez , Muhammad Nabeel Saddique

Abstract: The mcr gene family, responsible for plasmid-mediated resistance to colistin, poses a growing threat to public health by reducing the efficacy of colistin, a critical last-resort antibiotic for multidrug-resistant Gram-negative bacteria. The mcr-1 gene, discovered in 2015, marked a significant shift in understanding colistin resistance, and subsequent mcr variants (mcr-2 to mcr-10) have emerged globally. These genes alter lipid A in bacterial cell membranes, decreasing colistin's binding and efficacy. The mcr genes are typically located on mobile plasmids, facilitating horizontal gene transfer across bacterial species. Our review examines the evolution, genetic mechanisms, and structural characteristics of the mcr gene family, discussing their spread across human, animal, and environmental contexts. In this review, we highlight the clinical implications of mcr-mediated resistance, noting the co-occurrence of mcr with other antimicrobial resistance determinants, which complicates treatment options. Additionally, it explores detection methods, global epidemiology, and potential strategies to combat mcr resistance, including the development of inhibitors and CRISPR-based gene editing. Our review concludes that combating mcr-mediated colistin resistance requires global surveillance, coordination across sectors, and continued research to stop its spread and impact.

Keywords: Mcr gene family; Antimicrobial resistance (AMR); Colistin resistance; Horizontal gene transfer; Lipid A modification; Plasmid-mediated resistance.

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