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Inappropriate and excessive antibiotic use has contributed to the rapid increase in antimicrobial resistance (AMR), particularly in Gram-negative bacteria (GNB), and they are now becoming resistant to all available antimicrobial agents. There is a noticeable increase in nosocomial infections caused by multidrug-resistant (MDR) *Pseudomonas aeruginosa*, which is associated with significant morbidity, mortality, and increases in cost management. Recently, the World Health Organization (WHO) has published its foremost list of MDR “priority pathogens” which included carbapenem-resistant *P. aeruginosa* as a second most frequent. In response to this urgent call, WHO encourages an effectual approach to prevent the spread of AMR in addition to the development of new antibiotics. Although the problem is global, there is a lack of sufficient data about the status of AMR in GNB in Qatar.

This study focuses on the molecular epidemiology, microbiological and clinical characteristics, as well as resistance mechanisms associated with MDR-*P. aeruginosa* infections, encompassing five different hospitals in Qatar. In addition, investigations into the activity of novel antibiotic combinations against MDR-*P. aeruginosa* was done. Although there was a low prevalence of MDR-*P. aeruginosa*, the associated risk factors that contribute to AMR include prior antimicrobial therapy, invasive medical devices, and previous colonization with *P. aeruginosa*. This study also highlighted a significant reduction in the prevalence of MDR-*P. aeruginosa* which was associated with a sustained reduction in antimicrobials consumption in Qatar due to the implementation of Antimicrobial Stewardship Program. The MDR-*P. aeruginosa* isolates demonstrated high *in vitro* susceptibility to ceftazidime/avibactam (CZA) and ceftolozane/tazobactam (C/T), that paved the way for the introduction of these new antibiotic combinations into clinical practice in Qatar. There was a remarkable predominance of epidemic clones of ST235 and ST357 in Qatar, which exhibit multiclass resistance, in particular to class B metallo- $\beta$ -lactamase (e.g. *bla*<sub>VIM-2</sub>) and class A (e.g. *bla*<sub>VEB-9</sub>) which were associated with the resistance to CZA and C/T. The study is the largest from the Qatar which examined the epidemiology, microbiological and clinical characteristics of multidrug-resistant *P. aeruginosa* as well as explored the underlying molecular and genomic mechanisms of resistance particularly for novel antibiotics such as CZA and C/T.

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Doctoral Dissertation

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