



**Molecular Epidemiology and Mechanisms of Antibiotic
Resistance in Clinical Isolates of *Pseudomonas aeruginosa*
from Qatar**

av

Mazen Abulhassan Mustafa Sid Ahmed

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Opponent: Professor Christian Giske
Karolinska Institutet
Stockholm, Sweden

Örebro universitet
Institutionen för naturetenskap och teknik
Fakultetsgatan 1
701 82 ÖREBRO

ABSTRACT

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Inappropriate and excessive use of antibiotics promotes antimicrobial resistance (AMR), particularly in Gram-negative bacteria (GNB). There is a noticeable increase in nosocomial infections caused by multidrug-resistant (MDR) *Pseudomonas aeruginosa*, which is associated with significant morbidity, mortality, and an increase in cost management. Although this is a global problem, there is a lack of sufficient data on regional differences that can contribute towards effective AMR management. This thesis presents a study of MDR-*P. aeruginosa* at five different hospitals in Qatar conducted prospectively between October 2014 - September 2017. The aim was to study the epidemiology, microbiological and clinical characteristics of MDR-*P. aeruginosa* infections as well as investigate the activity of new antibiotic combinations against these bacteria. The prevalence of MDR-*P. aeruginosa* isolates in the first year was 8.1% (205/2533), isolated from different clinical specimens, but the majority were from respiratory infections (44.9%, n=92). Most cases were exposed to antibiotics during the 90 days prior to isolation (85.4%, n=177), and the resistance to cefepime, ciprofloxacin, piperacillin/tazobactam, meropenem was >90%. To compare pre- and post-Antimicrobial Stewardship Program, there was a significant reduction in antibiotic consumption by 30.4% of total inpatient antibiotic prescriptions ($p=0.008$) and the prevalence of MDR-*P. aeruginosa* significantly declined from 9% to 5.4% ($p=0.019$). The *in vitro* investigation of ceftazidime/avibactam (CZA) and ceftolozane/tazobactam (C/T) against MDR-*P. aeruginosa* isolates, showed promising results with susceptibility of 68.8% (n=141/205) and 62.9% (n=129/205), respectively, which was higher than other antipseudomonal agents except colistin. Seventy-five isolates that were sequenced belonged to 29 different sequence types, with ST235 being predominant at 21.3% (16/75). Among the 42 isolates that were resistant to CZA and/or C/T, the most prevalent genes were *bla*_{OXA-488} and *bla*_{VEB-9} detected in 45.2% (19/42) of isolates. Spearman's analysis showed that resistance to CZA and C/T were positively correlated with the presence of *bla*_{OXA-10}, *bla*_{PDC-2a}, *bla*_{VIM-2}, and *bla*_{VEB-9}, respectively. The study highlights potential key mechanisms that could explain the resistance of MDR-*P. aeruginosa* to the new antibiotic combinations.

Keywords: Antibiotics, C/T, CZA, MDR, *Pseudomonas aeruginosa*, ST235, VEB, VIM

Mazen Abulhassan Mustafa Sid Ahmed, School of Science and Technology
Örebro University, SE-701 82 Örebro, Sweden, mazen.sid-ahmed@oru.se