University of Fribourg / Faculty of Science and Medicine / Section of Medicine/Department of OMI

Emerging Antibiotic Resistance in Gram-Negatives: Mechanisms, Epidemiology, Diagnostics

Mustafa Sadek

Antimicrobial resistance (AMR) is one of the biggest challenges facing modern medicine (both human and veterinary medicine), thus, it could bring us back to the pre-antibiotic era and face the reality that bacterial infections once easy to treat become untreatable.

This thesis work addresses several themes of the antimicrobial resistance in clinically-relevant Gram-negative bacteria including; i) different molecular epidemiological studies performed on multidrug resistance (MDR) determinants, at local and global level, including ESBL producers, carbapenemase producers, plasmid-mediated colistin and fosfomycin resistance identified among Gram-negative bacteria from various sources (animal, human, food, and environmental samples) and from different countries, ii) We also showed international spread of some given clonally-related NDM-5-producing *E. coli* isolates with reduced susceptibility/resistance to aztreonam/avibactam (ATM-AVI) with a predominance of the recently described ST167 worldwide high-risk clone, iii) the antibacterial activity of novel therapeutic choices, such as cefiderocol and ATM-AVI, has been evaluated against carbapenem resistant *Enterobacterales*, particularly, metallo-β-lactamase (MBL)-producing *E. coli* isolates, iv) This work also identified the genetic features underlying the quite novel resistance to the latest generations of antibiotics such as cefiderocol, ceftazidime/avibactam, and aztreonam/avibactam. We showed that ATM-AVI resistance among MBL-producing *E. coli* isolates have resulted from combination of different features, including modification of PBP3 protein sequence through specific amino acid insertions, and production of CMY-type enzymes, particularly CMY-42. We also reported that PER-like β-lactamases, and to a lesser extent NDM-like β-lactamases, significantly contributed to reduced susceptibility towards cefiderocol, v) Finally, a series of novel rapid diagnostic tests and selective screening media have been developed during this thesis such as SuperCAZ/AVI medium and SuperFOS medium. Those novel tests included culture-based tests such as Rapid ResaImipenem/*Acinetobacter* NP test*,* Rapid Polymyxin/*Pseudomonas* NP test and RapidResa Polymyxin *Acinetobacter* NP® test, and biochemical-based tests such as NitroSpeed-Carba NP test for ultra-rapid and simple detection of carbapenemase production in *Enterobacterales*, *P. aeruginosa* and the different classes of carbapenemases (A, B, and D).

Jury :

Prof. Dr. Szabó Csaba (President of the jury)
Prof. Dr. Nordmann Patrice (Thesis supervisor)
Dr. Poirel Laurent (Thesis co-supervisor)
Prof. Dr. Giske Christian (Co-examiner)
Prof. Dr. Hamprecht Axel (Co-examiner)