

## Acquired resistance to broad spectrum $\beta$ -lactams and plasmid-mediated resistance to polymyxins

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Antimicrobial resistance is a growing concern. The emergence of multi-resistant Gram negative bacilli lead to the necessity of novel antimicrobial drugs. This work contributes to the analysis of new resistance mechanisms toward carbapenems and polymyxins that are last resort treatments of multidrug-resistant Gram-negative rods.

This work describes two new carbapenemase genes encoding for metallo- $\beta$ -lactamases isolated from environmental bacterial isolates which expression in *Escherichia coli* conferred resistance to almost all  $\beta$ -lactams. Then, the efficacy of new therapy strategies to treat carbapenem-resistant Gram negative bacilli have been evaluated including (i) the study of the activity of dual carbapenem associations in the treatment of carbapenemase-producing Enterobacteriaceae, (ii) the activity of the new molecule cefiderocol against carbapenemase producers and (iii) the report of the resistance mechanism against ceftolozane/tazobactam of a *Pseudomonas aeruginosa* isolate.

Then, different plasmid-mediated colistin resistant genes (*mcr*-like genes) focusing in particular on the *mcr-1* gene have been characterized. The genetic features of the *mcr-1* gene, its origin (*Moraxella* spp.) and its mechanism of acquisition by transposition have been identified. Finally, different epidemiological studies performed during this thesis showed that the reservoir of the different *mcr*-like genes is likely to have an animal origin.

This work contributed to the knowledge of carbapenem and polymyxin resistance in multi-drug resistant Gram-negative bacteria and evaluated new therapeutic solutions in order to treat infections caused by these latter.

### Jury:

Prof. Patrice Nordmann (thesis supervisor)  
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