Fluoroquinolones: The Main Mechanisms Of Resistances In *Escherichia Coli* And *Pseudomonas Aeruginosa*.

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INTRODUCTION:

Fluoroquinolones (FQs) are made with an addition of a fluorine molecule to quinolones, their main function was treating urinary diseases, respiratory infections or gonorrhea. There are 4 generations of FQs. **Mechanism of action:** FQs inhibit microbial DNA synthesis, interacting with DNA gyrase (Topoisomerase II) which allows the relaxation of chromatin affecting the negative supercoiling, essential for the access of the main enzymes for replication, so that when it is blocked the replication does not take place. They inhibit also topoisomerase IV, which separates the replicated chromosomes during the cell cycle. They form a physical barrier to the movement of the replication fork, affecting the maintenance of supercoiling.

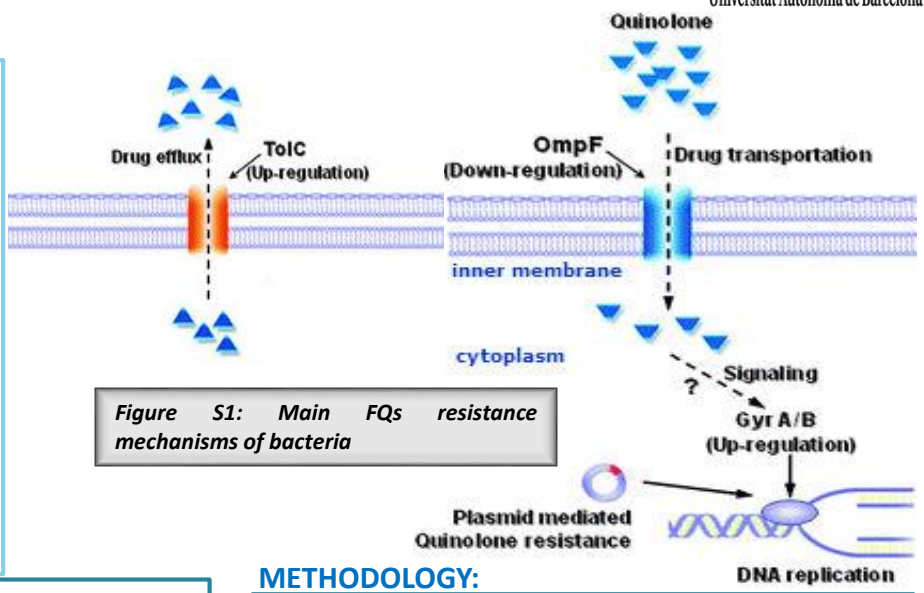


Figure S1: Main FQs resistance mechanisms of bacteria

AIMS:

-Review the **mechanisms** in which resistances are being produced in *P.aeruginosa* and *E.coli*.
-Localize the sites where **mutations** are given.

METHODOLOGY:

Publications between May 2006 and February 2015. The searches were restricted to **pubmed** and **scifinder**.
Key words: Fluoroquinolones; *Escherichia coli*; *Pseudomonas aeruginosa;* Resistance; efflux pump;QRDR

ESCHERICHIA COLI

EFFLUX PUMPS: AcrA-AcrB-TolC and YhiU-YhiV-TolC belonging to RND superfamily, and MdfA-Cmr pump belonging to MFS superfamily.

1. AcrA-AcrB-TolC is related with a resistance when there is a overexpression of sdiA (involved in regulation cell division) and marA (activator modulating of acrA, acrB and tolC.). The **early resistant stage** of FQs is caused by **efflux pumps**, and the high level stage is mediated by QRDRs of gyrA, gyrB, parC and parE.
2. **Porins** are involved in resistance: a decreased expression in **OmpF** protein (porin complex in the outer membrane) that takes part in the pump, increases MIC of FQ, it is regulated by MarA, affecting at AcrA-AcrB gene expression.
Moreover, if the expression of ***OmpX*** is increased contributes to resistance also, because OmpX downregulates OmpF porin.

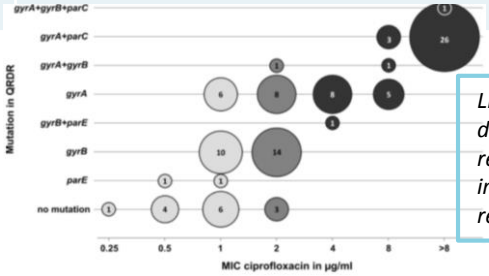
QRDRs in DNA gyrase and Topoisomerase IV: GyrA and ParC subunits are involved in resistance. The mutations are located to the amino terminus that has the active site (formed by a tyrosine covalently linked to the broken DNA strand during enzyme action).
It's known that **low level resistances** of FQs are due to a single mutation in **gyrA**. However, a second step mutation in gyrA and additional mutations in **parC or parE** can develop in a **high-level** resistance.
The 2nd generation of FQs the mutations develop even faster than in the third.

PSEUDOMONAS AERUGINOSA

EFFLUX PUMPS involved:MexAB-OprM,MexXY-OprM,MexCD-OprJ and MexEF-OprN.

Moreover the regulator genes involving the main pumps are : *mexT*, *mexS* and *mvaT*, when they are inactivated, overexpress MexEF-OprN operon, which is the main pump that causes FQs resistance. It has been reported that MexEF-OprN pump alleviates oxidative stress induced by the drugs. Also, SOS response triggered by FQs increases the number of mutations in QRDRs and so the resistance levels.

The presence of SNPs within QRDRs of gyrA, gyrB, parC, and parE is related with phenotypic resistance to FQ in *P. aeruginosa*. The majority of mutations occurred in amino acid positions 466 to 468. *In **figure S2**: Bruchann, Dösch et al, characterised the antibiotic resistance profiles from cystic fibrosis strains pyrosequencing, sequencing with sanger and making a PCR from all QRDRs. It was reported that mutations in QRDR of gyrA or gyrB increased MIC of ciprofloxacin 8-to 16-fold.*



Light, medium, and dark shaded circles represent sensitive intermediate, and resistant isolates.

CONCLUSIONS:

QRDRS in DNA gyrase | Mutations in topoisomerase IV | ddnpA and alarmones

FUTURE PERSPECTIVES:

Synergistic and antagonistioc activity of the pumps.

Avoiding the activation of the SOS responses.

OTHER MECHANISMS: -A putative deacetylase (**dnpA**) is involved in persistence, related with non-dividing cells,when overexpressed in wt cells increases the number of persister cells, resistant to antibiotics. **ppGpp** (alarmone) high levels,released in harsh environments in bacteria, in higher levels restores the FQ sensibility, because produces less persister cells→ **SOS response**.

REFERENCES:

Figure S1- *Adapted from* ***L.Hui,Pan.J Liu.X,Gao.J,W .H,Wang.C,*** *et al. 2012.*Alterations of protein complexes and pathways in genetic information flow and response to stimulus contribute to *Escherichia coli* resistance to balofloxacin.Mol.BioSyst. **8**, 2303-2311. ***Figure S2..Bruchmann, S.,Döstch,A.,Nouri,B.,Chaberny,I., Häussler,S.*** *et al. 2013. Quantitative contributions of target alteration and decreased drug accumulation to pseudomonas aeruginosa fluoroquinolone resistance.A. Agents and Chemotherapy.57:1361-1368.*