Review

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Fluoroquinolone resistance: mechanisms, impact on bacteria, and role in evolutionary success

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Quinolone and fluoroquinolone antibiotics are potent, broad-spectrum agents commonly used to treat a range of infections. Resistance to these agents is multifactorial and can be via one or a combination of target-site gene mutations, increased production of multidrug-resistance (MDR) efflux pumps, modifying enzymes, and/or target-protection proteins. Fluoroquinolone-resistant clinical isolates of bacteria have emerged readily and recent data have shown that resistance to this class of antibiotics can have diverse, species-dependent impacts on host-strain fitness. Here we outline the impacts of quinolone-resistance mutations in relation to the fitness and evolutionary success of mutant strains.

The challenge of fluoroquinolone resistance

Antibiotic resistance is one of the most pressing global concerns in medicine, with highly resistant pathogens of many species proving difficult to treat. Against this backdrop there are few new drugs in development, so maintaining the utility of the currently available agents is of crucial importance. To make this possible, a thorough knowledge of the mechanisms of resistance and the fate of resistant strains is needed to understand the conditions where resistance is selected and persists. Here we give an overview of how bacteria can become resistant to fluoroquinolone antibiotics and describe some recent advances in our understanding of the ecology of resistance to these agents.

Quinolones and fluoroquinolones

The fluoroquinolones are potent, broad-spectrum antibiotics that have been used in medical practice for the treatment of severe or resistant infections since the late 1980s. As their name suggests, they are derived from the quinolone family of antibiotics; quinolones themselves are synthetic constructs, developed by modification of 1-alkyl-1,8-naphthyridin-4-one-3-carboxylic acid [1]. Fluoroquinolones differ from quinolones by the replacement of the eighth carbon atom of the backbone with a nitrogen atom and the addition of a fluorine atom at the sixth position, giving them more potent antibiotic action and a broader spectrum of activity [2]. Their spectrum of efficacy against a wide range of Gram-positive and Gram-negative pathogenic bacteria has led to widespread use worldwide, although, in an attempt to maintain their effectiveness, current UK prescribing guidelines largely recommend this class as second-line agents for use when narrow-spectrum antibiotics have failed (http://publications.nice.org.uk/antibiotic-prescribing-especially-quinolones-and-cephalosporins-ktt9/evidence-context). Even with current guidelines aiming to preserve the efficacy of these drugs, resistance to fluoroquinolones is still occurring at an increasing rate in numerous bacterial species and their usage varies around the world. Due to an absence of active surveillance, data on fluoroquinolone consumption are lacking for many countries, making comparison of consumption and rates of resistance between different parts of the world difficult. However, within Europe there are sufficient data collected by the European Centre for Disease Prevention and Control (ECDC) that allow comparison between European countries (http://www.ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/database.aspx). For instance, fluoroquinolone consumption and rates of resistance can be reviewed using Greece, France, and Sweden as examples of countries where usage and resistance rates vary. Greece is the highest user of fluoroquinolones and has the highest incidence of fluoroquinolone-resistant *Escherichia coli* isolates (Figure 1). Conversely, Sweden has the lowest consumption rate and the lowest incidence of resistance. There are now four generations of quinolone/fluoroquinolone antibiotics in clinical use (Table 1); the most commonly prescribed fluoroquinolones in current medical practice are ciprofloxacin, levofloxacin, and moxifloxacin.

Supercoiling and type II topoisomerases

Fluoroquinolones are potent inhibitors of bacterial type II topoisomerases, which are essential enzymes involved in key cellular processes including DNA replication [3–5]. In both prokaryotes and eukaryotes, DNA exists as double strands that intertwine around each other to form a double-helix structure. However, in bacteria further twisting of the double-strand structure can occur whereby torsional stresses force the double helix to cross over on itself to produce a plectonemic arrangement [6] (Figure 2). This

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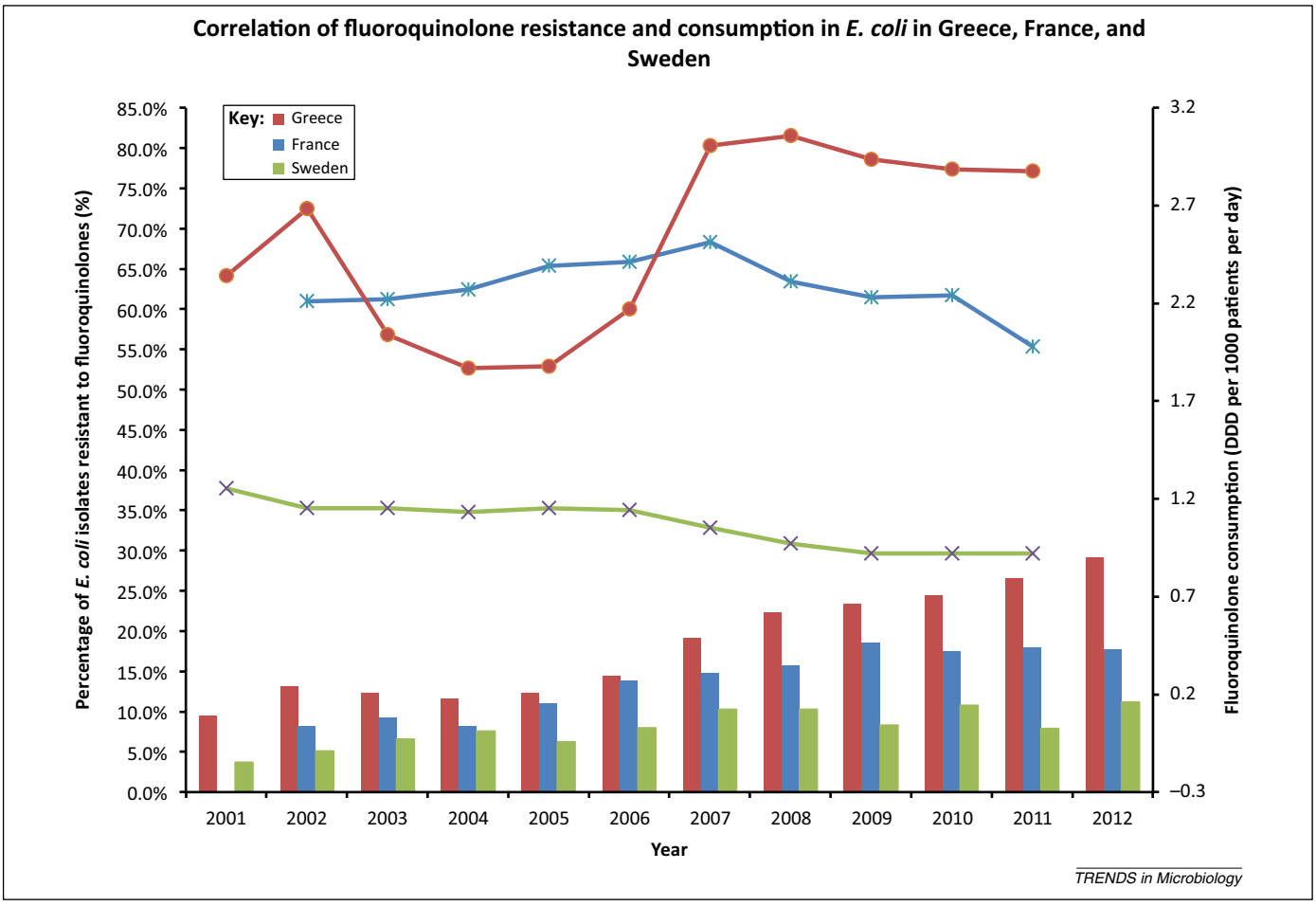

Figure 1. Correlation between fluoroquinolone (FQ) usage and resistance rates in countries with high, medium, and low use of FQs. Percentage of FQ-resistant *Escherichia coli* isolates (bars) and FQ consumption in defined daily dose (DDD) per 1000 patients per day (lines) in Greece, France, and Sweden. Greece, France, and Sweden are high, moderate, and low users of FQs respectively (relative to other European countries) and this correlates with high, moderate, and low rates of resistance in *E. coli*. Data from http://www.ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/database.aspx.

process, also known as supercoiling (Box 1), enables bacterial DNA to exist in a complicated condensed state in which the DNA can be condensed into compact supercoils allowing large amounts of DNA to be packed into the cell [7]. The degree of supercoiling of DNA is not fixed and there is continuous remodelling of DNA topology within bacteria in response to environmental stress, growth stage, and cellular processes such as transcription, DNA replication, and recombination [6–9]. Topoisomerase I and topoisomerase II enzymes work in opposition to control the level of twisting within DNA. Topoisomerase I reduces the number of negative supercoils [6]. By contrast, topoisomerase II introduces negative supercoils, which unwind over-twisted DNA into a relaxed state and can further change the DNA topology into an under-twisted plectoneme [6]. DNA gyrase and DNA topoisomerase IV are both heterotetrameric type II topoisomerase enzymes comprising two copies of each of either a GyrA and GyrB subunit or a ParC and ParE (GrlA and GrlB in *Staphylococcus aureus*) subunit, respectively. The enzymes have homologous action but with subtle differences; although both DNA gyrase and topoisomerase IV relax positively supercoiled DNA, only DNA gyrase can go on to introduce negative supercoils into relaxed DNA [9]. Topoisomerase IV has decatenating (unlinking) activity, allowing the segregation of catenated daughter chromosomes at cell division [8–10]. The careful maintenance of supercoiling is essential in key genetic processes that can control gene expression and thereby determine the phenotype of a cell [7,11–13]. Such is the importance of supercoiling that strict homeostatic control is fundamental for cell survival, because changes in the global degree of

Table 1. Fluoroquinolones licensed for clinical use and their current status

Generation	Drug	Use in clinical practice
First generation	Nalidixic acid	Generic form available
	Cinoxacin	Discontinued
Second generation	Norfloxacin	Available as Noroxin
	Ciprofloxacin	Available as Cipro and generic form
	Lomefloxacin	Discontinued
	Ofloxacin	Available as Floxin and generic form
	Levofloxacin	Available as Levaquin and generic form
Third generation	Sparfloxacin	Discontinued
	Gatifloxacin	Discontinued
	Grepafloxacin	Discontinued
Fourth generation	Trovafloxacin	Discontinued
	Moxifloxacin	Available as Avelox
	Gemifloxacin	Available as Factive

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