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► To cite this version:

Alexis Maillard, Pauline Jeanmougin, Elisabeth Bouvet, Sylvie Lariven, Josselin Le Bel, et al.. Fluoroquinolones in primary care, a first step for patient empowerment towards antimicrobial stewardship?. *Clinical Microbiology and Infection*, In press, 10.1016/j.cmi.2023.06.011 . hal-04176492

HAL Id: hal-04176492

<https://hal.science/hal-04176492v1>

Submitted on 3 Aug 2023

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Title: Fluoroquinolones in primary care, a first step for patient empowerment towards antimicrobial stewardship?

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Word-count: 1305 words

TEXT

In France, patients have claimed to have suffered serious adverse effects after receiving oral fluoroquinolones. Recently, lawsuits have been filed against physicians because patients believe they were given fluoroquinolones unnecessarily without being properly informed about potential side effects. These patients claim that "six million people" have been exposed to fluoroquinolones in France over four years (almost 10% of the French population) [1]. Indeed, fluoroquinolones remain the fourth most commonly prescribed antibiotics worldwide [2], especially in primary care where misuse for minor infections or off-label use is high according to the European Medicines Agency (EMA) [3]. Reducing the use of fluoroquinolones in these settings must be a priority, and this patient alert could be an opportunity to understand how we can improve antibiotic prescribing in primary care. Primary care physicians may find the process harsh, but could it not be the first step towards patient empowerment in antimicrobial stewardship?

Fluoroquinolones are formidable antibiotics with a broad antibacterial spectrum, high intracellular penetration and diffusion, excellent bioavailability and bactericidal activity. This high potency comes with significant drawbacks, that are too often overlooked in daily practice. Fluoroquinolones are associated with a risk of adverse effects including acute tendinopathy, aneurysm, arrhythmias and neurotoxicity [4], most commonly in elderly patients, who are most exposed to these antibiotics [3]. As broad-spectrum antibiotics, fluoroquinolones also have a strong impact on the human microbiota, which is a major driver of the acquisition of antimicrobial resistance [5]. In 2018, the EMA issued restrictions on the use of fluoroquinolones owing to their serious and potentially permanent side effects. However, as other broad-spectrum antibiotics, fluoroquinolones are essential for difficult-to-treat or severe infections, especially osteoarticular infections, or those involving resistant pathogens such as

3GC-resistant *Enterobacterales* or *Pseudomonas aeruginosa*. Such a potent, but not harmless, antibacterial weapon should be reserved for situations where there are no viable alternatives.

One way to improve antibiotic prescribing in primary care is to use Computerized Decision Support Systems (CDSS) that are designed for this setting. ‘*Antibiocliv*’ is a CDSS for antibiotic prescribing in primary care that has been widely used by French general practitioners (GPs) for over a decade. In March 2023, 49,607 GPs were registered in the system, representing more than half of the French GP population. In France, community acquired urinary tract infections (UTIs) account for most of the infections for which fluoroquinolones are prescribed in primary care (**Figure S1**). As described previously [6], ‘*Antibiocliv*’ can provide individualized, patient-specific recommendations for antibiotic prescription in UTIs, based on clinical characteristics and urine culture results. The CDSS provides a single top choice of antibiotic for first-line treatment, but physicians can decide to check for possible alternatives offered by the CDSS, depending on susceptibility testing, and eventually select one. [3]. We analyzed UTI requests submitted to the CDSS between 2017 and 2022 (**Figure S2**). Over 422,868 analyzed requests for UTIs, 182,495 were for cystitis, for which the CDSS does not offer fluoroquinolones, either as empiric or documented therapy. A total of 79,968 requests were for documented febrile UTIs in adult patients (acute prostatitis or pyelonephritis). The antibiotic regimen selected by the physician was available for 40,168 (50%) UTIs due to *Escherichia coli* (**Figure S2**). A total of 35,751 (89%) were susceptible to fluoroquinolones. Despite a possible oral alternative to fluoroquinolones for 34,276 (96%), fluoroquinolones were selected by GPs in 21,757 cases (61%), showing that misuse of antibiotics by CDSS users is still possible if the system is not restrictive (**Table S1, Figure S3**). Overall, when a fluoroquinolone was initiated for pyelonephritis (n = 6,251), an oral alternative molecule was possible in 96% of cases, including amoxicillin (68%), amoxicillin-clavulanate (75%), cotrimoxazole (83%), and cefixime (94%)

(**Table S2**). When a fluoroquinolone was initiated for an acute prostatitis ($n = 15,506$), cotrimoxazole was an oral alternative in 93% of cases (**Table S3**). Thus, even if the CDSS guides towards effective and safer narrow spectrum antibiotics fitting with susceptibility testing in febrile UTI, primary care physicians continue to largely select fluoroquinolones. How can we further improve fluoroquinolone prescribing and, more generally, antibiotic stewardship in primary care?

There appear to be two main ways to further improve practice (**Figure**). The most obvious and important is to strengthen existing interventions targeting physicians, by restricting the access to fluoroquinolones in the primary care sector. Guidelines should be modified to limit the use of fluoroquinolones to infections for which there are no oral alternatives, especially in documented UTIs, to stop trivializing these molecules. Although fluoroquinolones appear as a very convenient and useful oral option for empirical therapy, an oral alternative can be used in almost all cases after documentation. The integration of interoperable CDSS into physicians' prescribing software could allow the use of patients' clinical characteristics and comedications, to provide individualized antibiotic prescriptions. This could offer the opportunity to implement alerts and reminders, as well as educational and training messages based on the physician's prescribing habits (e.g. possible side effects and impact on antimicrobial resistance). A promising tool to limit broad-spectrum prescribing (including fluoroquinolones) is the selective reporting of antibiotic susceptibility test results: susceptibility test results are only reported back to the physician for few antibiotics that should be used first-line for a given infection, while other results remain available at the practitioners' request [7]. In addition, one of the main barriers to the de-escalation of antibiotic therapy after microbiological documentation is the lack of routine reassessment of patients, especially for those who improve. We could imagine that the reassessment of probabilistic fluoroquinolone prescribing could be made mandatory in

most situations to continue fluoroquinolones beyond 48 to 72 hours for UTIs, by using clear indications related to antibiotic prescription (e.g. “broad-spectrum” pictograms) or by involving primary care pharmacists in antimicrobial stewardship with audit and feedback. Although such a measure may be difficult to implement in primary care, it could encourage systematic reassessment and better use of antimicrobials.

Second, the recent complaints about fluoroquinolone misuse in France could be an opportunity to promote better use of antimicrobials by empowering patients. This may be uncomfortable for physicians, but patients may question prescriptions after reading information on the internet or in the media. This is an opportunity to challenge our practice and improve the therapeutic alliance with patients. With the rise of antimicrobial resistance, patients need to take ownership of the issue: not only should they be informed about the risks of taking antibiotics in general, but they should also be more aware that not all antibiotics are the same. The first step in empowerment is to give patients a sufficient understanding of what guides clinical decisions. Documents, educational brochures, websites and apps should be developed to provide practical and public-oriented information on antibiotic stewardship and antimicrobial resistance [8]. These tools could be promoted through public campaigns and by primary care physicians. For example, patients could be made more aware that a narrow-spectrum antibiotic (e.g. amoxicillin) is as effective as, and safer, than a broad-spectrum antibiotic (e.g. levofloxacin). An option could be to add the words “broad-spectrum” or pictograms after prescribing some antibiotics, such as fluoroquinolones. In addition to passive educational tools, which have been the focus of most previous studies [9], patients could be provided with innovative interventions such as individual dashboards about their own exposure to broad-spectrum antibiotics in the recent years. Such a dashboard could help them take real ownership of antimicrobial stewardship. The more patients know about their exposure to broad-spectrum antibiotics,

including fluoroquinolones, and their side effects, the more they will be able to adequately question antibiotic prescriptions. If patient demand has been shown to increase the rate of unnecessary antibiotic prescribing in primary care [10], we can bet that it could also reduce the rate of broad-spectrum antibiotic prescribing when unnecessary. We believe that for antibiotic stewardship, patient empowerment could be a huge step towards better practices in primary care. Perhaps it is time to stop relying on physicians alone to rationalize antimicrobial prescribing.

FUNDING

‘Antibiocllic’ is a non-profit organization. The steering committee members are volunteers and funding is obtained through competitive calls for tenders from universities, the French health authorities or learned societies. No specific funding was obtained for this study.

TRANSPARENCY DECLARATION

None to declare.

AUTHOR CONTRIBUTIONS

A.M., T.D., and J.LB. conceptualized the study. T.D. extracted data and A.M. performed statistical analyses. A.M. and T.D. designed the figure. A.M., T.D., and J.LB. wrote the first draft of this manuscript. All authors critically revised and approved the final manuscript. T.D. and J.LB. are the guarantors of the study, had full access to all the data, and took responsibility for the integrity of the data and the accuracy of the data analysis.

AKNOWLEDGEMENT

We thank all the users for their positive feedback and their participation in the CDSS development. We thank Gunther Groenewege for his help in ergonomics design. We thank the ANTIBIOCLIC+ study group (alphabetical order): Emilie Ferrat, Jean Gaschignard, Nathan Moreau, Raphaël Lepeule, Philippe Lesprit, Louise Rossignol, and Cécile Souty. We also thank the Paris Diderot University, the SPILF, the CNGE, the CMG, the Regional Health Authorities of Ile-de-France (ARS Ile-de-France), as well as the Health Insurance Agency of Ile-de-France (DRSM Ile-de-France) for their active collaboration.

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