



## Platinum Opinion

# Time to Adapt Our Practice? The European Commission Has Restricted the Use of Fluoroquinolones since March 2019

Gernot Bonkat<sup>a,†,\*</sup>, Adrian Pilatz<sup>b,‡</sup>, Florian Wagenlehner<sup>b,§</sup>

<sup>a</sup> alta uro AG, Merian Iselin Klinik, Centre of Biomechanics & Calorimetry, University of Basel, Basel, Switzerland; <sup>b</sup> Clinic for Urology, Paediatric Urology and Andrology, Justus-Liebig University, Giessen, Germany

On March 11, 2019—relatively unnoticed by the public and medical professionals—the European Commission (EC) implemented stringent regulatory conditions regarding the use of fluoroquinolones in urology. Fluoroquinolones (eg. ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin) are the antimicrobial drugs most frequently used in urology and this legally binding decision is applicable in all EU countries. National authorities have been urged to enforce this ruling and to take all appropriate measures to promote the correct use of this class of antibiotics.

The review of fluoroquinolones was initiated in February 2017 at the request of the German medicines authority. On October 5, 2018, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) recommended restricting the use of fluoroquinolones and removing a number of medical products from the market because of the possibility of persistent adverse effects. The PRAC decision was informed by a review of all evidence identified on the long-lasting, disabling, and potentially irreversible adverse drug reactions associated with fluoroquinolones, including the benefit-to-risk balance for their indications. The PRAC review also included a public hearing during which patient experiences of fluoroquinolones were presented. The indications for the use of fluoroquinolones, as defined by the PRAC review, are outlined in [Table 1](#). The final PRAC recommendation was sent to the Committee for Medicinal Products for Human

Use, which supported the conclusions of the PRAC review. Therefore, on November 15, 2018, the EMA finalised its review on the serious, disabling, and potentially permanent side effects associated with administration of quinolone and fluoroquinolone antibiotics given by mouth, injection, or inhalation. This ultimately led to the legally binding decision taken by the EC in March 2019 to limit the use of these antibiotics ([Table 1](#)).

The EC ruling has a major impact on urological practice and raises three key questions for urologists.

- (1) Is the limitation justified by the frequency of complications and side effects?

Fluoroquinolone use has been associated with serious side effects that include: diarrhoea; vomiting; negative effects on tendons, joints, muscles, and nerves; retinal detachment; aortic aneurysm; and a variety of central nervous system disturbances (insomnia, restlessness, fatigue, seizures, convulsions, and psychosis). More rarely, reactions such as haemolytic uraemic syndrome and Stevens Johnson syndrome have been reported. A meta-analysis showed that fluoroquinolones are associated with more central nervous system and gastrointestinal adverse events in comparison to other types of antimicrobials. The US Food and Drug Administration has recently recognised a fluoroquinolone-associated disability (FQAD) syndrome in otherwise healthy people. These patients have taken

\* Corresponding author. alta uro AG, Merian Iselin Klinik, Centre of Biomechanics & Calorimetry, University of Basel, Basel, Switzerland. Tel. +41 61 2263000.

E-mail address: [bonkat@alta-uro.com](mailto:bonkat@alta-uro.com) (G. Bonkat).

† Chairman of the European Association of Urology guidelines panel on urogenital infections.

‡ Associate of the European Association of Urology guidelines panel on urogenital infections.

§ Chairman of the European Association of Urology section for infections in urology.



**Table 1 – European Commission classification of indications for the use of fluoroquinolones****Category 1: Indication should be maintained**

- Complicated urinary tract infections/pyelonephritis, prostatitis, epididymo-orchitis, urethritis, urogenital tuberculosis, and infection in immunocompromised patients

**Category 2: Indications to be restricted**

- Uncomplicated cystitis (ie, uncomplicated acute cystitis, recurrent cystitis in women)

**Category 3: Deletion of indications**

- Prevention of exacerbations in women with recurring urinary tract infections (ie, prophylaxis for recurrent urinary infection, long-term prophylaxis for recurrent urinary infections, prophylaxis for frequently repeating infections of the urinary tract, and prophylaxis for systemic urinary tract infections)
- Prevention of infection in surgical procedures (ie, prophylaxis after surgeries or interventions in the urogenital system, prophylaxis for recurrent urinary infections following transurethral surgery or transrectal prostate biopsy)
- Sepsis

**Category 4: Rewording of indications according to current medical knowledge**

- Infections of the kidney, urinary tract, and genitals
- Urinary tract infection
- Prevention of infection in surgical procedures
- Prophylaxis for systemic urinary tract infections
- Prevention of systemic urinary tract infections

fluoroquinolones for minor conditions and developed disabling side effects, some of which are permanent. However, despite the seriousness of these events, the overall number of patients affected remains low. In the USA, 178 cases with persistent disabilities were reported between 1997 and 2015. This represents approximately ten cases per year and one case per 3 000 000 prescriptions [1]. In Canada, there have been 115 cases involving persistent disabilities reported over a period between 1986 (early marketing of fluoroquinolones) and 2017. This represents approximately four cases per year and one case per 1 000 000 prescriptions. From a statistical point of view, application of a legislative instrument aimed at restricting the use of fluoroquinolones will lead to a lower number of adverse events reports. However, this legal approach has left medical professionals, and in particular urologists, to deal with the consequences of a shift in prescribing indications without consultation or clear guidance on alternative treatment options.

- (2) What do these regulations mean for practicing urologists in the context of the EAU urological infections guidelines [2]?

In the treatment of complicated urinary tract infections/pyelonephritis, urethritis, bacterial prostatitis, and epididymo-orchitis, fluoroquinolones can still be used as before as the benefits outweigh the side-effect profile. No changes in the EAU guidelines are necessary.

For uncomplicated cystitis, despite lower resistance rates in certain countries, fluoroquinolones are not considered a first-line treatment option owing to adverse effects including negative ecological effects and selection for resistance. For this reason, the EAU guidelines have not recommended fluoroquinolone antibiotic therapy for uncomplicated cystitis for several years. Again, no changes in the EAU guidelines are necessary.

For patients with urosepsis there is no longer any indication for fluoroquinolone use because of the high resistance of causative pathogens to fluoroquinolones in urosepsis. The EAU guidelines do not recommend

fluoroquinolones for empiric therapy in patients with urosepsis; therefore, no changes in the EAU guidelines are necessary.

For (female) patients with recurrent urinary tract infections, the indication for fluoroquinolones has been restricted by the EC. This is in line with the recommendations of the EAU guidelines proposing nitrofurantoin, fosfomycin, or trimethoprim in cases in which nonantimicrobial measures have been unsuccessful. No changes in the EAU guidelines are necessary.

For perioperative antibiotic prophylaxis, the EC has banned fluoroquinolones. This means that fluoroquinolones can no longer be used as prophylaxis for ureterorenoscopy, percutaneous nephrolithotomy, transurethral resection of the prostate, transurethral resection of the bladder, or transrectal prostate biopsy. The EAU guidelines do not recommend fluoroquinolones for perioperative prophylaxis because of the lack of evidence for their benefit over other antibiotics, with the exception of transrectal prostate biopsy. Despite increasing resistance rates, fluoroquinolones are still the antibiotic prophylaxis most widely used for transrectal prostate biopsy. This is because of their favourable pharmacokinetics and the fact their value in this setting is supported by high-level scientific evidence. However, this must now change because of the EC ruling, despite the fact the most recent meta-analyses have revealed that 24-h duration is sufficient for prophylaxis [3,4]. Consequently, the recommendations of the EAU urological infections guidelines for antibiotic prophylaxis before transrectal biopsy must be amended to reflect the EC ruling.

- (3) Do we have proven alternatives for antibiotic prophylaxis before transrectal prostate biopsy?

Several meta-analyses have shown significantly lower infection rates after transrectal prostate biopsy when using antimicrobial prophylaxis when compared to placebo/control, with fluoroquinolones being the most commonly used [3,4]. However, owing to increasing fluoroquinolone resistance and the resulting septic complications, new

studies have been undertaken to assess the effectiveness of alternative antibiotic regimens; for example, comparing fosfomycin to standard fluoroquinolone therapy. Two meta-analyses that also included nonrandomised controlled trials showed an advantage for fosfomycin (relative risk 0.20, 95% confidence interval [CI] 0.13–0.30; odds ratio 0.25, 95% CI 0.11–0.58, respectively) [5,6]. Of note, the randomised controlled trials included were performed in countries with high fluoroquinolone resistance [7,8].

Considering the increase in fluoroquinolone resistance among faecal isolates, use of a rectal swab with subsequent bacterial culture for prebiopsy screening could offer individual targeted antimicrobial therapy. A 2016 systematic review and meta-analysis on this topic included nine studies with 4571 patients [9]. All the studies included except for one were cohort studies and included a combination of retrospective and prospective data. The authors calculated a sepsis rate of 2.21% (95% CI 1.71–2.87%) in the standard prophylaxis group compared to 0.48% (95% CI 0.26–0.88%) in the targeted prophylaxis group ( $p < 0.001$ ).

Finally, a switch to transperineal biopsy offers the possibility of avoiding contamination by rectal flora; therefore, in theory the risk of infectious complications should be lower when using the transperineal biopsy technique. However, there are only a limited number of randomised studies comparing transrectal and transperineal biopsies. A systematic review that identified 165 articles in which infection complications were recorded in 162 577 patients showed a higher rate of hospitalisation (1.1% vs 0.9%) and sepsis (0.8% vs 0.1%) for the transrectal compared to the transperineal route. However, the studies included were markedly heterogeneous, with significant regional differences in complication rates [10].

## Conclusions

The EC classification of indications for the use of fluoroquinolones into the four categories is not surprising and is mostly in line with current recommendations in the EAU guidelines. An amendment of the recommendations in the EAU guidelines only applies to antibiotic prophylaxis for transrectal prostate biopsy. Fluoroquinolones may no longer be used for this indication. Possible alternatives are, for example, the use of fosfomycin or a targeted therapy approach based on rectal swab cultures, as well as the change to transperineal prostate biopsy. The 2020 EAU

urological infections guidelines will be updated to reflect the restriction on fluoroquinolone prophylaxis before transrectal prostate biopsy.

Finally, urologists must be aware of the practical implications of the EC ruling when prescribing fluoroquinolones. Guidelines for the correct use of antibiotics must be followed and urologists must consider the serious side effects associated with fluoroquinolones and participate in shared medical decision-making with patients who have an elevated risk of complications.

**Conflicts of interest:** The authors have nothing to disclose.

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