FLUOROQUINOLONE
ANTIBIOTICS

BEST PRACTICES FOR THE USE OF FLUOROQUINOLONES: GUIDELINE FOR HEALTHCARE PROFESSIONALS

LET'S USE THEM WISELY
ANTIBIOS
LET'S PRESERVE THEIR EFFICACY

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1 INTRODUCTION

The fluoroquinolones (FQs) are in a class of antibiotics that are active against various bacterial infections caused by both gram-negative and gram-positive bacteria as well as mycobacteria (Tuberculosis).

The extensive use in practice of FQs had the consequence of a harmful effect in terms of the epidemiological impact given their selection pressure with the emergence of resistances which are problematic today.

The European Medicines Agency (EMA) reassessed these antibiotics in 2019, due to the risk of serious side effects, which are lasting (for several months or years), disabling, and potentially irreversible, affecting the musculoskeletal system and the nervous system.

However, data from a study by the EMA[1] suggets that fluoroquinolones continue to be prescribed outside of the recommended use.

Given the threat related to bacterial resistances and the aspect of pharmacovigilance, it is imperative to ensure compliance with the rules of "proper use" of fluoroquinolones in accordance with current recommendations.

KEY MESSAGE:

The prescription of fluoroquinolones must only be done in the absence of alternatives and within the validated indications, for documented bacterial infections or empirically for severe infections in hospitalised patients, this is to avoid:

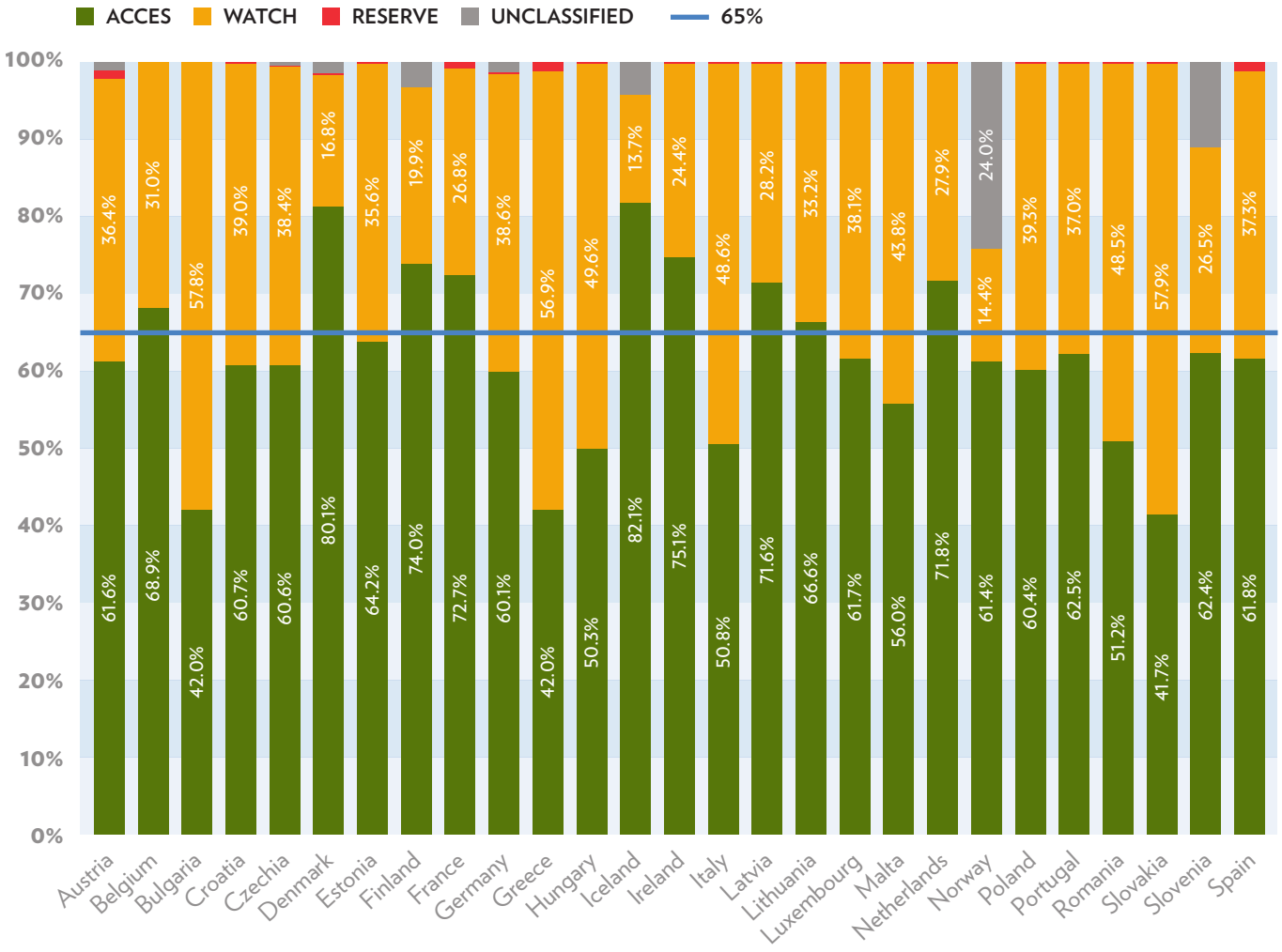
- ⚠ **the risk of selecting resistant bacteria and infections with *C. difficile* in cases of repeated use of fluoroquinolones.**
- ⚠ **disabling, lasting, and potentially irreversible side effects.**

2 CLASSIFICATION AWaRe

The classification AWaRe[2] of the World Health Organization (WHO) divides most antibiotics into three groups, some antibiotics being not yet classified:

- **Access :** antibiotics whose accessibility is essential, intended to be used as first-line and second line therapy ;
- **Watch :** mainly broad-spectrum antibiotics intended for use for specific indications (higher potential to induce the development of a resistance or unfavorable risk/benefit ratio) ;
- **Reserve :** last-resort antibiotics, to be used if the other antibiotics are not effective anymore.

According to the WHO, antibiotics in the Access group should account for at least 60% of total national consumption in 2023, while the recommended target by the EU Council is at least 65% by 2030. In Luxembourg, 60.8% of the antibiotics dispensed (total consumption) are antibiotics from the Access group in 2022 (figure 8 extracted from the ESAC-Net 2022 annual epidemiological report[3]).



Agents included in these analyses: antibacterials for systemic use (J01), oral neomycin (A07AA01), oral streptomycin (A07AA04), oral polymyxin B (A07AA05), oral kanamycin (A07AA08), oral vancomycin (A07AA09), oral colistin (A07AA10), rifaximin (A07AA11), fidaxomicin (A07AA12), oral rifamycin (A07AA13), rifampicin (J04AB02), IV rifamycin (J04AB03), rifabutin (J0AB04), oral metronidazole (P01AB01), oral tinidazole (P01AB03) and secnidazole (P01AB07)

3 GOOD PRACTICES FOR PRESCRIBING FLUOROQUINOLONES

The WHO AWaRe tool specifies which antibiotics to use for infections, from the most common to the most severe, which should always be available in the healthcare system, those that must be used sparingly, and those that should only be used as a last resort.

Fluoroquinolones administered systemically or by inhalation are categorized in the "WATCH" group as they have a higher potential to induce the development of resistance and may have an unfavourable risk/ benefit ratio.

As a result, FQs should only be prescribed for approved indications and after a thorough evaluation of the benefits and risks for each patient.

GENERAL RULES FOR A GOOD USE:

- Avoid prescribing a fluoroquinolone in situations where other antibiotics can be used;
- Do NOT prescribe fluoroquinolones repeatedly to the same patient and take into consideration the history of treatment with fluoroquinolones, considering any previous prescription of a fluoroquinolone in the past 6 months regardless of the indication (an important factor for isolating resistant strains);
- Choose the most active FQ against the isolated or presumed bacterium responsible for the infection; choose the FQ that has the most appropriate pharmacokinetics for the site of the infection;
- Adhere to the recommended prescribed dosage of the FQ.

FLUOROQUINOLONES SHOULD NOT BE USED:

- To treat viral infections (such as pharyngitis, acute bronchitis);
- To treat benign ENT infections (streptococcal tonsillitis, otitis, sinusitis) even bacterial but most often self-resolving;
- To treat mild to moderate bacterial infections (including uncomplicated cystitis, acute exacerbation of chronic bronchitis, and chronic obstructive pulmonary disease (COPD). In case of failure of first-line treatment, microbiological documentation is essential and the antibiogram will guide the choice of the antibiotic;
- To treat non-bacterial infections such as chronic non-bacterial prostatitis;
- In prevention of traveller's diarrehoa or recurrent urinary infections unless advised by a nephrologist;
- To treat gastroenteritis that does not require antibiotic treatment on an outpatient facility;
- To treat patients who have already experienced serious side effects with a fluoroquinolone or a quinolone.

FLUOROQUINOLONES CAN MAINLY BE PRESCRIBED IN THE FOLLOWING SITUATIONS:

Empirical treatment in adults:

→ Pyelonephritis in case of allergy to β-lactams;

→ Prostatitis;

→ Alternatives in case of immediate type I allergy to β-lactams.

Targeted treatment (specific cases or second-line) with bacteriological documentation:

→ Pyelonephritis;

→ Prostatitis;

→ Osteoarticular infections (in combination);

→ Legionnaires' disease;

→ Oral treatment for *P. aeruginosa*;

→ Alternatives in case of immediate type I allergy to β-lactams.

In children:
Only on specialist advice.

*As a reminder, the recommendations from the Scientific Council are available **at the end of the brochure** for urinary[4] and respiratory[5] infections (in hospital settings).*

Precautions
Fluoroquinolones should be used with particular caution in elderly individuals, in patients with kidney disease, and those who have undergone organ transplants, as these patients are at a higher risk of tendon injury. Since the use of a corticosteroid with a fluoroquinolone also increases this risk, the combined use of these medications should be avoided.

4 SIDE EFFECTS RELATED TO THE USE OF FLUOROQUINOLONES: INFORMATION FOR HEALTHCARE PROFESSIONALS

Fluoroquinolones can cause serious side effects, requiring clear information to patients.

Photosensibilisation :

To avoid photosensitivity reactions (skin burns), protection from the sun is necessary during treatment and for up to 48 hours after its discontinuation.

⚠ Tendinopathies:

The risk of developing a tendon injury is rare but can have serious consequences, such as a rupture of the Achilles tendon. This risk is increased in elderly patients and those on corticosteroids. Tendinopathies can occur quickly after the initiation of treatment (2 days) but can also arise up to 42 days after starting the treatment. These effects can also be observed after a single dose.

An urgent consultation is necessary in case of tendon pain or inflammation to consider the immediate cessation of fluoroquinolones.

The occurrence of a tendinopathy requires stopping treatment. The patient will no longer be able to use this class of antibiotics.

The care management may include resting the tendon, appropriate support, the use of heel inserts, and may require consultation with a specialist.
Symptoms generally disappear 1 to 2 months after stopping treatment, but prolonged impairments have been reported in the literature.

⚠ Peripheral neuropathies:

Symptoms of burning, paresthesia's, pain particularly in the hands and feet. These symptoms may appear quickly after the initiation of treatment with fluoroquinolones. Seek medical attention immediately at the first symptoms to prevent a possible progression to irreversible damage.

⚠ Cardiac Effects:

→ In patients known to be at risk, it is important to remember that precautions for use or even contraindications are required for fluoroquinolones that have the potential to prolong the QT interval:
- Moxifloxacin has a high potential for prolonging the QT interval;
- Levofloxacin, norfloxacin, ofloxacin, and ciprofloxacin have the potential to prolong the average QT interval.

→ The drugs responsible for Torsade's de Pointes (TdP) block specific channels in cardiac cells, thereby inhibiting or reducing the expulsion of potassium which is responsible for the relaxation phase of the heart. The torsadogenic potential of a drug increases with the dose, and the risk increases in the case of combining multiple torsadogenic drugs[6] (among others: amiodarone, sotalol, ...).

→ The risk factors predisposing to TdP are: hypokalemia, hypomagnesemia, history of myocardial infarction, heart failure, sinus bradycardia, atrioventricular block (AVB), congenital long QT.

→ It is important to encourage patients to consult a doctor immediately if they experience signs suggesting a cardiac arrhythmia.

⚠ Aneurysms and aortic dissections:

→ The FQs used systemically (orally, parenterally) or inhaled may increase the risk of aneurysm and aortic dissection, particularly in elderly people.

→ In patients at risk of aneurysm and aortic dissection, FQs must only be used after a careful assessment of the benefit/risk ratio and after considering therapeutic alternatives.

→ The predisposing factors for developing an aneurysm and an aortic dissection include a family history of aneurysm, pre-existing aneurysm or aortic dissection, Marfan syndrome, Ehlers-Danlos vascular syndrome, Takayasu arteritis, giant cell arteritis (or Horton's disease), Behçet's disease, hypertension, and atherosclerosis.

→ Patients should be informed about the risk of aneurysm and aortic dissection. They should be warned about the necessity of immediate care by a doctor in an emergency unit in case of sudden and severe abdominal, chest, or back pain.

⚠ Impact on the bacterial flora:

→ The impact of FQs on the anaerobic gut flora is low; they induce a limited decrease in Gram-positive aerobic bacteria and a significant decrease in aerobic Gram-negative bacteria.

→ FQs treatments select resistant mutants from the intestinal microbiota *(E. coli)* and the rhino-pharyngeal area (alpha-hemolytic streptococci), regardless of the doses used.

→ The use of FQs has also been associated with the selection of strains of *C. difficile* that are highly resistant to FQs, particularly those of the hypervirulent ribotype 027 clone.

⚠ Other Risks:

→ Convulsions: FQs should not be used in case of pre-existing central nervous system (CNS) disorders.

→ Neuropsychic manifestations (e.g., insomnia, agitation, hallucinations, delirium), in rare cases, even a single dose can lead to suicidal thoughts

→ Hypersensitivity reactions (rare) that can lead to an anaphylactic reaction or severe bullous skin reactions.

→ Worsening of myasthenia.

→ Hepatic effects:
- If the elevation of transaminases is relatively common, more severe cytolytic or cholestatic injuries have been reported, particularly with moxifloxacin.
- Patients should be informed to contact their doctor in case of signs of fulminant hepatitis such as rapid asthenia associated with jaundice, dark urine, and a tendency to bleed.

→ Blood sugar disorders (hypo-, hyperglycemia) in patients receiving hypoglycemic therapy.

→ Reactions of hemolysis in cases of glucose-6-phosphate dehydrogenase (G6PD) deficiency.

→ Or even vision disorders; a doctor must be consulted immediately if vision deteriorates, in case of hearing, smelling, and taste disorders.

More information on safety, notification of side effects, and the available molecules on the Luxembourg market can be found in the DHPC document[7] sent to healthcare professionals in June 2023.

5 SIDE EFFECTS RELATED TO THE USE OF FLUOROQUINOLONES: INFORMATION TO PROVIDE TO PATIENTS

Fluoroquinolone antibiotics can cause serious side effects affecting, among other, the nervous and cardiac systems, tendons, muscles, and joints. Your doctor should only prescribe these medications for their approved uses.

These very rare but serious side effects include inflamed or ruptured tendons, muscle pain or weakness, joint pain or swelling, difficulty walking, tingling, burning, fatigue, depression, memory problems, sleep issues, vision or hearing problems, as well as alterations in taste and smell. Tendon swelling and injury can occur within 2 days of starting the treatment but can also happen several months after stopping the treatment.

You must not take any fluoroquinolone-based medication if you have previously experienced a serious side effect with a fluoroquinolone.

If you are aged over 60, if you have a history of kidney problems, or if you have had an organ transplant, or if you are taking a corticosteroid (medications such as prednisolone or hydrocortisone), you have a higher risk of developing tendon damage with a fluoroquinolone.

→ **The appearance of sudden and intense abdominal, chest, or back pain requires immediate attendance to a hospital emergency unit.**

→ **If you experience the following side effects, stop the treatment and contact your doctor immediately,** who will decide if you can continue the treatment or if you need another type of antibiotic:

- Pain or swelling of the tendons, especially in the ankle or calf;
- Unusual pain and/or weakness in the arms or legs;
- Feeling of irregular or rapid heartbeat;
- Difficulty breathing, whether or not associated with swelling of the legs;
- Neuropsychic manifestations (convulsions, hallucinations, agitation, insomnia);
- Intense fatigue, jaundice, tendency to bleed;
- Decreased vision or the appearance of any other eye disorder;
- Redness, irritation or itching of the skin, especially following exposure to the sun or artificial UV radiation (tanning lamp, solarium, etc.).

If you have any questions or concerns about your medications, please talk to your doctor or pharmacist.

6 SOURCES:

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https://www.cbip.be/fr/chapters/1?frag=9990169#qt

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