North Central London
Joint Formulary Committee

Safe prescribing of fluoroquinolones
Position Statement

Recommendations

1) Only prescribe systemic (by mouth, injection, or inhalation) fluoroquinolones **in line with Trust or NICE Antimicrobial Guidance** or **as guided by an Infection Specialist**.
2) Fluoroquinolones must only be prescribed when other antibiotics are inappropriate. Situations where other antibiotics are considered to be inappropriate are where:
   - there is **resistance** to other first-line antibiotics recommended for the infection
   - other first-line antibiotics are **contraindicated** in an individual patient
   - other first-line antibiotics have caused **side effects** requiring treatment to be stopped
   - treatment with other first-line antibiotics has **failed**
   - the only oral option following IV therapy is a fluoroquinolone
3) Where a patient has a documented penicillin allergy take a **full allergy history** to differentiate between *intolerance* and allergy. Penicillins are typically first-line treatment due to excellent efficacy and safety profiles therefore only use **alternative/second-line treatment** in those **with severe penicillin allergy (i.e. anaphylaxis)**.
4) **Do not use** fluoroquinolones in patients with known **aortic aneurysm, aortic dissection, congenital heart valve disease, pre-existing heart valve disease or history of serious side effects related to quinolone treatment** (including tendon disease/disorder) unless there are no other treatment options available
5) Fluoroquinolones are **cautioned** in the following high risk groups, other options should be considered initially and where necessary every effort should be made to **minimise course length:**
   - Elderly (≥60 years)
   - Individuals with renal impairment
   - Individuals who have had a solid organ transplantation
   - Individuals on concomitant corticosteroids
   - Presence of risk factors or conditions predisposing for:
     - Both aortic aneurysm and dissection and heart valve regurgitation (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis)
     - Aortic aneurysm and dissection (such as vascular disorders including Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome)
     - Heart valve regurgitation/ incompetence (e.g. infective endocarditis)
     - Family history of heart valve disease or aneurysm
     - Men ≥65 years old
     - Current or previous smokers
     - Use of systemically administered VEGF pathway inhibitors

Patients should be counselled to discontinue fluoroquinolone treatment and seek urgent medical attention at the **first sign** of:

- Tendon pain or inflammation (particularly in shoulder or ankle)
- Symptoms of neuropathy such as pain, burning, pins & needles, tingling, numbness or weakness
- Sudden-onset of severe and constant abdominal, chest or back pain
- Acute dyspnoea (especially when lying down flat), new onset of heart palpitations, or development of oedema of the abdomen or lower extremities
- Be alert to any mood changes, distressing thoughts, or feelings about suicide or harming themselves at any point during treatment

6) Provide patients with information about risks associated with fluoroquinolones. Consider providing the MHRA fluoroquinolone patient information leaflet to patients receiving new fluoroquinolone prescriptions (link)
7) Please continue to report suspected adverse drug reactions via the Yellow Card scheme.
8) Signpost men ≥65 years to the national Abdominal Aortic Aneurysm screening programme (a painless ultrasound scan; people who have not been screened should contact the North London service on 0333 009 6971). Never delay antibiotics for active symptomatic bacterial infections.

1. Background

There are five patient safety alerts regarding the use of systemic (by mouth, injection, or inhalation) fluoroquinolone antibiotics recently issued by the MHRA/ EMA:

- Fluoroquinolone antibiotics: must now only be prescribed when other commonly recommended antibiotics are inappropriate (link)
- Very rare reports of long-lasting and disabling tendon, joint and nervous system side-effects (link)
- Small increased risk of aortic aneurysm and dissection (link)
- Small increased risk of heart valve regurgitation (also called heart valve incompetence or insufficiency or leaking valve) (link)
- Fluoroquinolone antibiotics: suicidal thoughts and behaviour (link)

Fluoroquinolones are active against Gram-negative and Gram-positive bacteria and therefore remain valuable in certain infections, particularly in patients with penicillin allergy or where alternative antibiotics are not suitable.

Fluoroquinolones licensed in the UK:

- Ciprofloxacin
- Levofloxacin
- Ofloxacin
- Moxifloxacin

2. Severe side effects

2.1. Joint and movement disorders

Including tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies.

Tendon damage (especially to Achilles tendon but also other tendons) can occur within 48 hours of starting fluoroquinolone treatment but the damage may be delayed several months after stopping treatment.

Fluoroquinolone associated tendinopathy is a very rare side effect (<1/10,000) although this number may be higher in patients with risk factors for tendinopathy, such as those over 60 years of age, patients with renal impairment, solid organ transplant patients and individuals taking concomitant oral corticosteroids.

The combination of fluoroquinolone antibiotics and corticosteroids should be avoided wherever possible, though there are certain circumstances where it may be unavoidable (such as the treatment of infected exacerbations of bronchiectasis).

2.2. Aortic Aneurysm and dissection

Epidemiological studies suggest an increased risk of aortic aneurysm and dissection with fluoroquinolone usage, particularly in older patients. Even amongst elderly patients, aortic aneurysm and dissection is a rare side effect (<1/1000).

Patients with a history of aortic aneurysm and/or aortic dissection are considered locally to be at particularly high risk; fluoroquinolones should therefore be avoided in this group unless there are no other treatment options available.

Patients with a greater risk of aortic aneurysm or dissection than the general population include those with a family history of aneurysm disease, elderly patients, other conditions (such as Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis and connective tissue disorders, giant cell arteritis, Behcet's disease, hypertension[a] and known atherosclerosis) and use of systemically administered VEGF pathway inhibitors. The use of fluoroquinolones in these patients should be based on a careful benefit-risk assessment and consideration of other available therapeutic options.

All patients prescribed a fluoroquinolone should be advised of the rare events of aortic aneurysm and dissection, and to seek immediate medical attention in case of sudden-onset severe abdominal, chest or back pain.

Men >65 years are eligible for the national abdominal aortic aneurysm (AAA) screening programme. Whilst appropriate treatment with a fluoroquinolone should not be delayed in this cohort, it is recommended that eligible individuals who have not been screened contact the North London Screening service directly on 0333 009 6971 to obtain an abdominal ultrasound in one of their 45 screening centres.

2.3. Heart valve regurgitation

A recent retrospective, case-control, epidemiological study reported an estimated 2-fold increase in risk of mitral and aortic regurgitation in patients taking systemic fluoroquinolones compared with patients taking amoxicillin or azithromycin. Several medically confirmed cases of heart valve regurgitation affecting any heart valve have been reported in patients receiving fluoroquinolones with probable or possible causal association. A non-clinical study also reported that ciprofloxacin increases collagen degradation in heart muscle cells. These data indicate that fluoroquinolones can cause heart valve regurgitation.

Patients with heart valve disease are considered locally to be at particularly high risk; fluoroquinolones should therefore be avoided in this group unless there are no other treatment options available. Aortic and mitral valve regurgitation would be most at risk of causing pathology especially if already moderate or severe in grade.

Patients with a greater risk for heart valve regurgitation than the general population include those with congenital or pre-existing heart valve disease, connective tissue disorders (for example Marfan syndrome or Ehlers-Danlos syndrome), Turner syndrome, Behçet's disease, hypertension, rheumatoid arthritis, and infective endocarditis. The use of systemic and inhaled fluoroquinolones in these patients should be based on a careful benefit-risk assessment and after consideration of other therapeutic treatment options.

Patients should be advised to seek immediate medical attention in case of acute dyspnoea especially when lying down flat, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

[a] All patient with hypertension are known to be at greater risk of an abdominal aortic aneurysm (AAA); however, the risk is highest amongst those with untreated/uncontrolled hypertension.

2.4. Risk of psychiatric reactions

Psychiatric adverse drug reactions may occur with fluoroquinolone antibiotics, including after the first dose. If patients suffer from depression or psychosis prior to treatment with fluoroquinolone antibiotics. existing psychiatric symptoms may be exacerbated. Patients should be counselled on the potential for psychiatric reactions, which can include confusion, disorientation, anxiety, depression and suicidal thoughts or suicide attempts. For further details, see MHRA alert for Fluoroquinolone antibiotics: suicidal thoughts and behaviour (link).

2.5. Other side effects

- Gastro-intestinal including *Clostridium difficile* associated diarrhoea
- QT-prolongation
- Transaminitis (note: MHRA alert for Moxifloxacin associated risk of life-threatening liver reactions link)
- Fatigue
- Memory impairment
- Sleep disorders
- Reduced seizure threshold
- Rhegmatogenous retinal detachment
- Hypoglycaemia (note: FDA alert for quinolone associated hypoglycaemia in elderly and those with diabetes taking oral or insulin therapy link)

For further queries please contact an Infection specialist

Acknowledgement

This statement is based on a version written by Chelsea & Westminster Hospital NHS Foundation Trust. All necessary permissions have been obtained.

References

EMA. Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics. March 2019 (link)

EMA. Assessment report: Quinolone and fluoroquinolone medicinal products for systemic and inhalation use. October 2018 (link)

MHRA. Systemic and inhaled fluoroquinolones: small increased risk of aortic aneurysm and dissection; advice for prescribing in high-risk patients. November 2018 (link)

MHRA. Systemically administered VEGF pathway inhibitors: risks of aneurysm and artery dissection. July 2020 (link)

MHRA. Systemic and inhaled fluoroquinolones: small risk of heart valve regurgitation; consider other therapeutic options first in patients at risk. December 2020 (link)

MHRA. Fluoroquinolone antibiotics: suicidal thoughts and behaviour. September 2023 (link)

MHRA. Fluoroquinolone antibiotics: must now only be prescribed when other commonly recommended antibiotics are inappropriate. January 2024 (link)

Groups / Individuals who have overseen the development of this guidance:	NCL Microbiologists NCL Antimicrobial Pharmacist Group (APG)
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