

CLINICAL ALERT

Rational use of the fluoroquinolones

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The systemic fluoroquinolones (FQs) have recently been reported to be associated with significant side-effects in susceptible individuals. This has prompted the Food and Drug Administration (FDA) in the USA and the European Medicines Agency (EMA) to issue warnings regarding their use. The FQs should not be used for common bacterial infections, such as urinary tract infections, travellers' diarrhoea and upper and lower respiratory tract infections, unless it is not possible to use another oral agent. There are situations, however, in which these agents are not only effective, but their benefit outweighs the risk. These include the management of conditions such as acute prostatitis, typhoid fever, prosthetic joint infections, multidrug-resistant tuberculosis, certain hospital-acquired infections and situations where the organism is susceptible to FQs, which could then be administered orally. Alternatively, the patient would have to be admitted to hospital for parenteral therapy.

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The systemic fluoroquinolones (FQs) have been used for >30 years for a variety of infectious conditions, and have been among the most widely prescribed antibiotics globally. In the USA, 32.5 million prescriptions for oral FQs were issued in 2015, representing 101 prescriptions/1 000 population, and of these, ciprofloxacin comprised 20.3 million or 63 prescriptions/1 000 population.^[1] In the hospital setting, ~3.8 million patients billed for an injectable FQ in 2011.^[2]

During this time, these drugs were lifesaving in many instances, but were also associated with significant adverse effects, including peripheral neuropathy, photosensitivity, prolonged QT interval, hypoglycaemia and tendon rupture. The Food and Drug Administration (FDA) in the USA and the European Medicines Agency (EMA) have highlighted these and other adverse effects and have suggested that, where possible, alternative agents should be used.^[3,4]

New adverse events and warnings

More recently, these warnings have been extended to include a potential risk for aortic dissection, with an increased risk from a baseline of 9/100 000 to 300/100 000, and a recommendation that the FQs should be avoided in patients at risk of an aortic aneurysm, including the elderly and those with peripheral vascular disease, uncontrolled hypertension, vasculitic syndromes and diseases such as Marfan's and Ehlers-Danlos syndromes.^[5]

The EMA has also extended a warning of potential tendon rupture to include tendinitis, myalgia, muscle weakness, arthralgia and joint swelling, and also warned of a syndrome that includes peripheral neuropathy, psychosis, anxiety, insomnia, depression, hallucinations, suicidal thoughts, confusion and impairment of vision, hearing, smell and taste.^[6,7] Older patients, those with renal dysfunction, transplant recipients and those receiving concomitant corticosteroids are at higher risk of side-effects. According to the FDA and EMA, FQs 'can be associated with prolonged (up to months or years) serious, disabling and potentially irreversible drug reactions affecting several, sometimes multiple, systems, organ classes and senses'.^[6] The overall

condition has been termed 'fluoroquinolone-associated disability syndrome' (FADS).^[7] The existence of the entire constellation of FADS relies on patient testimony and does not as yet have a recognised pathogenetic mechanism. Therefore, the actual incidence of FADS is not known. With regard to tendon rupture, tendinitis and aortic aneurysm, FQs display a high affinity for connective tissue, particularly in cartilage and bone. In an evaluation of the incidence in >11 000 patients, rates for tendinitis of 2.4/10 000 prescriptions, and for tendon rupture of 1.2/10 000 prescriptions, have been reported.^[8]

Mechanisms of harm

There are many proposed mechanisms for these adverse events, which include ischaemia, degradation of the tendon matrix and an alteration of tenocyte activity.^[9] FQs, and in particular ciprofloxacin, also enhance matrix metalloproteinase expression in tendon tissue and reduce collagen synthesis by inhibition of tenocyte proliferation.^[10,11] A very recent and important publication has shown that ciprofloxacin inhibits mitochondrial topoisomerase 2-beta, which regulates supercoiling of mitochondrial DNA. This results in accumulation of positively supercoiled DNA, which causes transcription and replication initiation failure with depletion of mitochondrial DNA copy number.^[12] This effect might be caused by oxidative damage, which FQs induce in various cell types.^[13,14] This blocks cellular proliferation and differentiation and may provide a reason for the prolonged effects seen in some patients.

Whatever the aetiology and incidence of these conditions, EMA and FDA reports have led to considerable confusion among the general public and healthcare practitioners as to when it would be appropriate to use these agents.

Is there any place for the fluoroquinolones?

Whereas it is relatively easy to decide which patients should not receive FQs, does this mean that we should abandon these agents as a class? The FQs should not be used to treat mild or moderate bacterial

infections unless other antibacterial agents commonly recommended for these infections cannot be used. Conditions that should not be treated with a FQ (or any antibiotic) include viral infections, the common cold, influenza, acute bronchitis and pharyngotonsillitis (unless <16 years of age and streptococcus is suspected, and even in that case one can wait until results of a rapid test for group A streptococcus are available, and if antibiotics are indicated, a number of other more narrow-spectrum antibiotics are as effective).^[15]

Travellers' diarrhoea

Similarly, diarrhoea not associated with fever, bloody stools or other signs of systemic sepsis (i.e. those caused by shigella, campylobacter, *Clostridium difficile*, and protozoal infections) does not benefit from any antibiotic, including metronidazole, even in the immunocompromised host. Antibiotics – FQs in particular – should be avoided in this setting, as they are ineffective and predispose to colonisation of the gut by resistant organisms.^[16] Most cases of travellers' diarrhoea are caused by enterotoxigenic *Escherichia coli* (ETEC), occur in the first week of travel, are usually mild (<6 stools/day) and do not disrupt normal activities. Most cases last 3 - 5 days and resolve without treatment. When the diarrhoea is associated with additional symptoms, as indicated above, and with interruption of normal activities, it is classed as moderate to severe and may need to be treated with an antibiotic. FQs have been the traditional agents used in this setting; however, several systematic reviews that compared antibiotics, e.g. FQs, azithromycin, and rifaximin v. placebo, showed consistent shortening of duration of diarrhoea from 3 days to 1.5 days with the use of all these antibiotics. If an antibiotic is used, it is best to avoid a FQ and preferably use azithromycin for only 1 - 3 days.^[17,18]

Salmonella infections (typhi and paratyphi)

Whereas empiric treatment is based on regional susceptibility, FQs are considered by many experts to be the drug of choice for susceptible isolates; it is still reasonable to use these agents in this setting.^[19,20] However, with regard to empiric therapy, 1 in 7 isolates of *Salmonella typhi* in SA is resistant to FQs, whereas 100% are susceptible to azithromycin, which may be an appropriate initial choice.^[21] Thereafter, antibiogram-directed therapy is vital. Other alternatives include third-generation cephalosporins; however, extended-spectrum beta-lactamase production, which renders these organisms resistant to ceftriaxone, is an increasing problem in both typhoid and paratyphoid infections. If the organism is sensitive to both ceftriaxone and FQs, patients improve more rapidly with the latter; however, the combination of ceftriaxone and azithromycin leads to more rapid resolution than ceftriaxone alone and may be an effective option.^[22] Treatment is for 2 weeks with either agent.

Lower respiratory tract infections

With regard to community-acquired pneumonia, FQs, particularly moxifloxacin or levofloxacin, have been recommended as alternatives to beta-lactams (BLs), especially in the case of severe allergy. It is recommended that they should only be used as a last resort, where no other agent is available.^[23]

With regard to acute exacerbations of chronic obstructive pulmonary disease, only patients with a C-reactive protein of >40 mg/L, those who have all three of the following symptoms, i.e. increased sputum volume, purulence and dyspnoea, or two of these features, where one is increased sputum purulence, should receive an antibiotic. When an antibiotic is deemed necessary, appropriate therapy should usually consist of a BL, inclusive of amoxicillin, cefuroxime or cefpodoxime,

a combination of a BL and a BL inhibitor or a macrolide, where pneumococcal resistance to macrolides is low. For hospitalised patients with the risk of pseudomonas or other more-resistant organisms, antipseudomonal agents, such as piperacillin-tazobactam or cefepime, may be considered. It is recommended that these patients have a sputum culture performed, and that the antibiotic choice be based, where possible, on the results.^[24]

With regard to bronchiectasis, where the patient is not considered ill enough to require hospital admission, and the cultured organism is a pseudomonas or one of the Enterobacteriaceae sensitive to ciprofloxacin but resistant to other oral antibiotics, the FQs could be considered.

Urinary tract infections and prostatitis

With regard to urinary tract infections, it is reasonable to use an oral FQ where resistance dictates that the alternative would be to admit the patient to hospital to use a parenteral agent, such as a carbapenem. It is important, however, that microscopy and culture of urine be performed to optimise therapy and that the prescription be based on sensitivities.

Acute bacterial prostatitis, as opposed to chronic prostatitis (which is usually not bacterial in origin), is due to *E. coli* in 58 - 88% of cases, *Proteus* species in 3 - 6%, other enterobacteriales, i.e. *Klebsiella*, *Enterobacter* and *Serratia* species in 3 - 11%, *Pseudomonas aeruginosa* in 3 - 7% and occasionally *Staphylococcus aureus* and streptococcal or enterococcal infection.^[25-27] Although there are no comparative trials evaluating optimal antimicrobial therapy, FQs are a reasonable choice, provided that the organism is sensitive and that the alternative would be the need to admit the patient to hospital for parenteral therapy. Ciprofloxacin attains a ~2-fold higher concentration in the prostate than in the plasma, and levofloxacin a ~3-fold higher concentration. More recently, high-dose oral fosfomycin has been recommended as an effective outpatient therapy. An oral regimen of 3 g daily for 1 week, followed by 3 g every second day for a total treatment duration of 6 - 12 weeks or 3 g every second or third day for 6 weeks, appears to be effective.^[28-30] This has recently been confirmed to be extremely effective in a prospective observational study of 44 patients, where the majority of organisms were FQ resistant. Cure was achieved in 82% at end of treatment (EOT) and in 80% and 73% at 3 and 6 months, respectively. Microbiological eradication was achieved in 86% and 77% at EOT and 6 months, respectively.^[31] The longer course was reserved for patients with prostatic calcification.

Other agents that penetrate prostatic fluid and would be effective if the organism is sensitive are the macrolides, trimethoprim-sulfamethoxazole (TMP/SMX) and doxycycline.^[27,32] If the organism is resistant to these agents, admission is required for intravenous therapy with antibiotics, such as ertapenem, tigecycline or ceftriaxone, the latter particularly in the case of *Neisseria gonorrhoeae*. Community-acquired enterococcal infections can be treated with amoxicillin, and staphylococcal infections with oral cloxacillin or intravenous (IV) ceftazidime (1 g IV every 8 hours). If there are risk factors, or a history of methicillin-resistant *S. aureus*, vancomycin or linezolid may be administered.

Prosthetic joint infections and osteomyelitis

The FQs are useful in the management of prosthetic joint infection (PJIs) if the offending organism is susceptible. Management is primarily surgical and a 2-stage arthroplasty is most commonly employed. Antibiotic therapy is most frequently administered for 6 weeks, initially for 2 weeks with parenteral therapy and thereafter for 4 weeks with oral therapy.^[33] Oral ciprofloxacin is often effective against many

Gram-negative pathogens and has also been used successfully with rifampicin for staphylococcal infections in an IV to oral switch if the organism is susceptible.^[34] However, other oral anti-staphylococcal agents that might be effective are TMP/SMX and clindamycin. Oral linezolid has limited use, given the toxicity that occurs after 14 days of therapy.

A very recent study showed that oral therapies, including the FQs, were effective in treating osteomyelitis.^[35] Depending on susceptibility, a FQ would be acceptable if it decreased the duration of IV therapy and allowed earlier discharge of patients. Patients would have to be observed closely for adverse events, given the long duration of use.

Intensive care unit-acquired infections

Intensive care unit (ICU) use of the FQs has been limited because of the potential for this class of drugs to cause collateral damage, i.e. enhance the emergence of resistance in organisms for which the antibiotic was not originally intended.^[36] However, FQs are used as carbapenem-sparing agents for extended-spectrum beta-lactamase producers if they are sensitive, and along with TMP/SMX are also valuable for the treatment of organisms such as *Stenotrophomonas maltophilia* and *Burkholderia cepacia*.^[37,38]

Meningococcal prophylaxis

Meningococcal infections are potentially fatal and easily transmissible. Prophylaxis is warranted for close contacts and for exposed healthcare workers. A single dose of ciprofloxacin 500 mg was the recommended protocol; however, as it is not known if duration of therapy is necessarily the determinant of toxicity, and because ciprofloxacin resistance has been reported, it may be wise to use an alternative regimen. This consists of rifampicin 600 mg twice daily for 2 days or a single dose of ceftriaxone IV.^[39-41] This regimen might not always be practical if all the children in a classroom need prophylaxis. Paediatric doses differ from those for adults.

Mycobacterial infections

Another indication for FQ use is the management of *Mycobacterium avium intracellulare* infections; however, FQs have generally been relegated to second-line therapy, as outcomes are inferior to macrolide-based regimens, specifically clarithromycin or azithromycin, along with ethambutol, and rifamycins (rifampicin, rifabutin), with or without aminoglycosides in more severe infections.^[42,43]

The new World Health Organization guidelines for the management of multidrug-resistant *Mycobacterium tuberculosis* include levofloxacin/moxifloxacin, linezolid and bedaquiline in their category A agents, i.e. those that should be used first.^[44] Thereafter, the recommendation is to use agents in categories B or C if those in the preceding category cannot be used. It is unlikely that this recommendation would be withdrawn, given the potential toxicities of the other agents and the high mortality of patients with the disease.

Fluoroquinolone use in situations of beta-lactam allergy

When considering an alternative agent to BL, it should be recognised that BL allergy is exceedingly rare and, where an allergy to penicillin exists, there is little cross-reactivity between the second- and third-generation cephalosporins. Unless the patient has developed a severe reaction inclusive of urticaria or anaphylaxis (type I reaction), or severe non-IgE-mediated reactions, such as Stevens-Johnson syndrome/toxic epidermal necrolysis, drug-induced hypersensitivity syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), renal failure, cytopenias, serum sickness or

any other life-threatening reaction, the first- and second-generation cephalosporins can be considered safe.^[45] It is, however, probably necessary to perform allergy testing more frequently than is currently done, as most patients who believe they are allergic to BL are probably not.^[46]

Conclusions

The overall aim is to reduce the use of FQs, probably also as topical agents, as there is emerging evidence that they may also be harmful when used in this manner.^[47] However, as mentioned above, there is a role for these agents in certain circumstances, both in the community and in hospital. It is nevertheless important to be aware that prescription of FQs may have significant unwanted consequences and it is therefore important to consider carefully the circumstances where use would be rational.

A summary of recommendations is given in Box 1.

Box 1. Summary of recommendations

- Systemic FQs should not be used for common bacterial infections, where other agents are likely to be just as effective.
- Prescribe systemic FQs only if alternative agents are unavailable, or if the organism has been shown to be resistant to first- or second-line agents or there has been microbiological or clinical failure.
- Prescribe systemic FQs only for BL allergy if the patient has previously developed a life-threatening reaction with BL use and has been proven to be truly allergic.
- Consider prescribing oral FQs only where hospitalisation for intravenous antibiotics would be the only suitable alternative.
- Document use, and the justification for use, whenever a systemic FQ is prescribed.
- Inform all patients of the risks and benefits of the FQ prior to prescription.

FQs = fluoroquinolones; BL = beta-lactam.

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