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The use of fluoroquinolones in children: recent advances

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Fluoroquinolones are an important group of antibiotics that are used widely in the treatment of various infectious diseases in adults as a result of their excellent spectrum of activity, significant tissue penetration and convenient routes of administration. Their use in children, however, has been limited until recently as a result of possible fluoroquinolone-induced joint toxicity. Nevertheless, this group of antibiotics is rapidly gaining consideration for use in children as new agents are emerging with a wide antimicrobial range of action and minimal toxicity, even in young children. This review presents the pharmacokinetics, clinical indications and possible toxicity of fluoroquinolones in children, as well as the newer agents and their safety profile in pediatrics.

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Fluoroquinolones (FQs) are licensed and indicated widely for use in adults, owing to their broad-spectrum antibacterial activity, extensive tissue and intracellular penetration, and their suitability for oral administration [1]. Their antimicrobial profile includes *Pseudomonas aeruginosa*, Gram-positive microorganisms and intracellular pathogens [1]. Their pharmacokinetic and pharmacodynamic effects are significant as they are absorbed from the gastrointestinal tract and have a high penetration ability in most tissues with good intracellular diffusion [2]. FQs are therefore efficacious in the prevention and therapy of various bacterial infections in adults, predominantly those of the respiratory system, urinary tract, skin and soft tissue, bones and joints, eyes and ears [1]. These antibiotics do not cause significant adverse reactions in adults and most of them are derived from the gastrointestinal system and only rarely from the CNS [1].

The above-mentioned characteristics could have led to numerous indications and wide use of FQs in pediatrics but unfortunately they did not [3–5]. Their use in children is limited as a result of possible FQ-induced joint/cartilage toxicity observed mainly in juvenile animal models [6]. Recently, however, they were used successfully in immunocompromised children, in cystic fibrosis (CF) and also in those suffering from multidrug-resistant Gram-negative infections (including neonatal infections and multidrug-resistant enteric infections caused by *Salmonella* and *Shigella* spp.) [6]. The FQs were efficacious and well tolerated in the treatment of complicated cases of acute otitis media, while no associated arthropathy was evident [6].

Taking into account the potential benefits and risks of FQs in pediatric patients, different experts [3,4,7,8] and the American Academy of Pediatrics (AAP) [9] have recommended prescribing quinolones as a second-line antibiotic and restricting their use to a few specific situations, including *P. aeruginosa* infections in patients with CF, prophylaxis and treatment of bacterial infections in immunocompromised patients, life-threatening multiresistant bacterial infections in newborns and infants and *Salmonella* or *Shigella* gastrointestinal tract infections.

Most recent studies evaluating the use of FQs in children are in line with the AAP recommendations and conclude that, with the exception of CF and life-endangering infections, the use of FQs in pediatrics should be limited to Gram-negative neonatal meningitis, *Salmonella* and *Shigella* spp. infections, chronic suppurative otitis media and some

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cases of complicated acute otitis media [6,10]. The same studies also conclude that the uncontrolled use of FQs in children, particularly in those with community-acquired lower respiratory infections, could accelerate the emergence of pneumococcal resistance [6].

Pharmacokinetics

The pharmacokinetics of FQs in children have not yet been investigated extensively. The studies so far have proven that the systemic elimination of quinolones is faster in children than in adults, hence larger doses are required in the pediatric population. They are absorbed well from the gastrointestinal system, however, their bioavailability ranges from 10 to 30% for norfloxacin to 80–90% for ofloxacin. All of the FQs, with the exception of norfloxacin, have high tissue penetration and intracellular concentration. They are excreted mainly from the kidneys without any prior metabolism or through the biliary system [11–13].

A recent study investigated the pharmacokinetics of gatifloxacin after a single dose in infants and children from 6 months to 16 years of age [14]. Gatifloxacin is an 8-methoxy FQ effective against a wide range of bacterial pathogens, including antibiotic-resistant *Streptococcus pneumoniae* [14]. This is consistent with its overall increased potency against Gram-positive organisms compared with earlier FQs, ciprofloxacin, ofloxacin and levofloxacin (which is probably the most widely used new quinolone in the adult population) [14,15]. The pharmacokinetics of gatifloxacin in adults is characterized by rapid and complete absorption, with an average bioavailability of 96%. It distributes extensively into body tissues and is eliminated almost exclusively in the urine with renal clearance exceeding glomerular filtration. Its relatively long half-life in adults (7 h) affords once-daily dosing [16]. There are, however, issues regarding glucose homeostasis and gatifloxacin that are being investigated currently [17].

The pharmacokinetics of gatifloxacin and its activity against a broad spectrum of pediatric pathogens support its development for infants and children. Gatifloxacin was safe as a single dose in infants and children. Low intersubject variability in concentrations in plasma was noted in this population. No important age- or formulation-related differences in gatifloxacin pharmacokinetics were noted, suggesting similar dose requirements among all pediatric populations. Gatifloxacin at a dose of 10 mg/kg every 24 h with a maximum dose of 400 mg, which is the adult dose, will achieve therapeutic exposures in children and infants. A total of 60% of this will be excreted unchanged from the kidneys within 24 h (TABLE 1) [14].

Potential clinical indications of FQs in children

See BOX 1.

Cystic fibrosis

The most significant experience from the use of FQs is derived from CF patients. *S. pneumoniae* in addition to nonencapsulated *Haemophilus influenzae* and respiratory viruses have been considered to predispose patients to acute and chronic airway infections, as well as *P. aeruginosa* and *Staphylococcus aureus*, which are mainly responsible for clinical exacerbations [18]. The combination of an anti-*Pseudomonas* β-lactam antibiotics and an aminoglycoside has been proven to control the clinical exacerbations effectively, although there is not always a very precise relation between clinical and bacteriological improvement. The major disadvantage of the above-mentioned therapeutic scheme is the emergence of resistant strains and the parenteral route of administration.

FQs, especially ciprofloxacin, enable the oral administration of therapy in CF patients. A considerable number of studies have investigated the effectiveness of ciprofloxacin in children with CF, while the experience with ofloxacin and perfloxacin is still limited [18–20]. All of the studies document a clinical improvement of these patients comparable with classic intravenous therapy, although the percentage of relative suppression of *Pseudomonas* was lower. The administration of FQs in children with CF, even for long periods (e.g., 3–6 months) was well tolerated without an increase in the side-effect profile. The emergence of resistant strains was relatively rare and transient, without clinical significance [18–20].

Box 1. Possible indications of use of fluoroquinolones in children.

Pneumonic exacerbations due to *Pseudomonas aeruginosa* in children with cystic fibrosis

Infections due to multiresistant Gram-negative bacteria:

- Complicated urinary tract infections
- Chronic otitis media
- Acute or chronic osteomyelitis
- Meningitis

Gastroenteritis due to multiresistant microorganisms (*Salmonella*, *Shigella*)

Typhoid fever

Infections from multiresistant mycobacteria

Chemoprophylaxis or therapy for anthrax

CNS infections

FQs have considerable penetration to the cerebrospinal fluid and have been administered effectively for the management of CNS infections in adults, such as meningitis from Gram-negative microorganisms. These antibiotics are considered very effective against Gram-negative Enterobacteriaceae, owing to their significant CNS penetration, high concentration in the cerebral tissue and their considerable intracellular concentration. FQs have been administered successfully in *Enterobacter, Salmonella* and *Escherichia coli K1* meningitis. It has been suggested that their administration reduces the risk of cerebral abscess in neonates and immunocompromised patients [21,22].

Table 1. Recommended doses of fluoroquinolones in children.

Medication	Route of administration	Dose (mg/kg)	Number of doses/day	Maximum daily dose (mg)
Ciprofloxacin	Orally	15–20	2	1500
	Intravenously	10–15	2	800
Ofloxacin*	Orally	7.5	2	800
	Intravenously	5	2	600
Norfloxacin†	Orally	10–15	2	800
Gatifloxacin§	Orally	10	1	400
	Intravenously	10	1	400

*Ofloxacin has been given to children with cystic fibrosis.
†Norfloxacin has been tried in children with urinary tract infections.
§Gatifloxacin has been prescribed in children with acute otitis media.

Gatifloxacin and moxifloxacin are currently investigated extensively, as they appear to be effective against *S. pneumoniae*, even the penicillin-resistant strains [14]. These antibiotics are currently being studied for the management of meningitis from resistant *S. pneumoniae*, which is an extremely dangerous condition with limited therapeutic options [14].

Orally administered ciprofloxacin has been used successfully as chemoprophylaxis following exposure to a patient with manifested invasive meningococcal disease. Although the number of studies so far is limited, it has been advocated that a single dose of ciprofloxacin can produce eradication percentages of up to 90%, which are comparable with rifampicin or ceftriaxone [22].

Complicated urinary tract infections

Complicated urinary tract infections are encountered when there is an incomplete excretion of urine and are mainly attributed to Gram-negative Enterobacteriaceae and *P. aeruginosa*. Lately, there has been an increase in the number of urinary tract infections due to multiresistant Gram-negative microorganisms [23]. FQs are a very good choice for the management of urinary tract infections caused by multiresistant strains that have not responded to conventional antibiotics and can be administered orally, which can shorten or even avoid hospitalization. Norfoxacin has been safe and effective in the management of complicated urinary tract infections in children [23–25].

Bone & joint infections

FQs can reach high concentrations in bones and joints and have significant action against *Staphylococcus* and *Streptococcus*, which are the most common pathogens in children in this context. Quinolones appear to be effective against *Pseudomonas*, Salmonella and other Gram-negative microorganisms that rarely cause skeletal infections [26]. In the case of osteomyelitis from *P. aeruginosa* in children that puncture their feet with a sharp instrument, oral ciprofloxacin for 14 days has been proven to be effective, although surgical debridement of the wound is still necessary [4,26].

Infections of the gastrointestinal system

Gastrointestinal infections cause significant mortality and morbidity in infants and children worldwide, especially in developing countries. The incidence of resistant strains of *Shigella*, *Salmonella*, *Campylobacter*, *Vibrio cholerae* and *Escherichia coli* has increased in recent years [6]. FQs are effective against these microorganisms and are superior to other antimicrobial agents because they are absorbed well and their concentration in feces remains constant, irrespective of diarrhea; they produce high and stable concentrations in the intestine and can, therefore, be administered for a short period of time; they produce high concentrations in the biliary tract and can, therefore, prevent the chronic carriage of *Salmonella*; and they have significant tissue penetration. Ciprofloxacin has been administered successfully in a large number of children with intestinal infections in the developing world and has been proven to be safe and effective [6,27].

FQs are considered by many to be the first line of treatment against typhoid fever. The duration of therapy is short (5–7 days) and it can be administered orally [28,29]. A recent study has demonstrated that a single dose of ciprofloxacin is effective in the management of *V. cholera* diarrhea in children [30].

The use of FQs for the management of gastrointestinal infections should be rationalized because the overuse or the administration of subtherapeutic doses for financial reasons can precipitate the emergence of resistance [28,31]. Recently, there have been increasing reports of resistant strains of *Salmonella*, *Shigella* and *Campylobacter*, especially from developing countries [28,31].

Neutropenia in pediatric oncology patients

Oncology patients develop neutropenia during chemotherapy and are therefore at an increased risk of severe, most commonly bacterial, infections. If these patients become pyrexial while neutropenic, they are admitted to hospital and are managed with intravenous therapy predominantly against Gram-negative microorganisms. Gram-positive microorganisms are the second largest group of pathogens that can

cause severe infections in these patients [32]. Ciprofloxacin has been evaluated successfully as monotherapy in selected low-risk febrile neutropenic patients. These patients were administered ciprofloxacin orally following a single intravenous dose of a β-lactam agent. The disadvantages of ciprofloxacin monotherapy are their relatively inadequate action against Gram-positive microorganisms and that this cohort of patients frequently develops mucositis and enteritis, and therefore cannot receive any medication orally.

Oral FQs as prophylaxis could reduce the incidence of Gram-negative bacteremia in patients with long-standing neutropenia. The major disadvantage of this prophylactic use would be the emergence of resistance [32,33]. Outpatient therapy with either oral ciprofloxacin or intravenous ceftriaxone for fever and neutropenia is currently considered effective and safe in pediatric patients with solid tumors and stage I/II non-Hodgkin lymphoma (low-risk patients) [32].

Chronic otitis media

Chronic otitis media is defined as the otorrhea through a perforated tympanic membrane or a grommet that lasts for 6 weeks or more and can cause auricular or intracranial sequelae. The most frequent causative agent is *P. aeruginosa.* These cases are dealt with through the systemic use of antibiotics and topical agents. Ciprofloxacin appears to be active against *P. aeruginosa* and can be administered orally [34–36].

Mycobacterial infections

Ciprofloxacin, as an adjunct therapy, has been used successfully in the management of atypical mycobacterial infections. It can also be administered along with other antimicrobial agents for the management of *Mycobacterium tuberculosis* when there is resistance to first-line medications [37]. Moreover, moxifloxacin is active against *M. tuberculosis* and other mycobacteria [38].

FQ toxicity

Toxicity in animals

All of the quinolones cause transformations in the immature cartilage of joints that carry weight in all of the animal species that have been studied. This toxicity manifests only in juvenile animals, with the exception of perfloxacin, which can affect mature dogs. The toxicity is detected clinically through symptoms of acute arthritis, pain, swelling and gait disturbances. The lesions appear as pathological findings in the magnetic resonance of the affected joints. These lesions are constant and do not regress even after the discontinuation of therapy.

The mechanism that is responsible for these cartilage lesions is not known. It has been hypothesized that these lesions are caused by regression of DNA synthesis in cartilage cells by inactivation of DNA gyrase, by an oxidative effect on cartilage cells, by a discontinuation of mitochondrial integrity or by the clearance of magnesium from cartilage cells surface, which disrupts the function of surface integrins that are responsible for the cellular integrity of the cartilage [6,36,39].

Joint complications in children

Currently, there has been no irrefutable proof that quinolones can cause arthropathy in children [6]. Arthralgia and joint swelling have been documented in certain case series [6]. There are certain case series that report arthralgia and fluid collection in the joint following FQ use. Perfloxacin was administered in most cases. Long-term complications have not been documented, except for one case where other possible reasons have not been evaluated. In these studies, magnetic resonance findings, which detected characteristic lesions in animal models, were not evaluated. Ultrasound examination of large joints, such as the hip and knee, can detect the presence of fluid and can evaluate the quality of the cartilage. Ultrasound examination can be utilized in the follow-up of patients who are receiving quinolones, when performed before and after the initiation of therapy [6,40].

Ciprofloxacin use in children has been thoroughly evaluated recently [41]. Recent data from Bayer's ciprofloxacin clinical trials database found that the incidence of arthralgia in children did not differ between the ciprofloxacin and nonquinolone antimicrobial control groups. The incidence of arthralgia was not higher than expected for the underlying condition, which was CF in most cases. It has been suggested that 4% of children and 7–8% of adolescents with CF have arthralgia. These patients' arthralgia is a manifestation of hypertrophic pneumonic osteoarthropathy. In those patients that underwent magnetic resonance, ultrasound or histological examination, no significant joint deformities were encountered. The optimum adult height does not appear to be influenced either. There has only been one report of increased incidence of joint swelling in adolescents who received perfloxacin, however, that report documented a complete resolution following discontinuation of treatment [6,40,41].

Tendon disorders

Similar histological disorders to the ones appearing on cartilages have also been described on tendons. These lesions are believed to be due to a similar toxic action on tendon cells. The majority of patients who have experienced FQ-induced tendinopathy were older than 60 years of age and most of them were prescribed perfloxacin. Corticosteroid use accelerates this tendinopathy. Most commonly, the Achilles tendon is affected and the tendinopathy may lead to the complete rupture of the tendon [42].

Other adverse effects of FQs

The most frequent adverse effects of FQs are gastrointestinal disturbances, such as nausea, vomiting, abdominal pain and diarrhea. Mild effects on the CNS, such as headache, agitation, insomnia and, rarely, seizures, are not uncommon, as well as skin rashes, allergies and photosensitivity [13]. A small percentage of patients (1–4%) develops neutropenia, eosinophilia and a rise of the transaminases. All of these effects are transient and reversible [13].

Severe disorders that can be attributed to FQ use are nephrotoxicity, anaphylactic reactions, hemolysis, cardiotoxicity and hepatotoxicity. Seizures and raised intracranial pressure have been described and neonates with meningitis should be monitored closely for these effects [13,43,44].

Teratogenesis was not encountered in a prospective study of women receiving FQs during pregnancy. It should be noted that some of the quinolones were retained from clinical use because of severe side effects, such as hemolysis and renal failure (temafloxacin), phototoxicity (sparfloxacin), severe hepatic insufficiency (trovafloxacin) and sudden deaths due to QT prolongation (grepafloxacin) [13,44,45].

Emergence of resistance to FQs

FQs act by binding to the topoisomerases of microorganisms that are necessary for DNA replication. Quinolones target two of the four topoisomerases: topoisomerase II (which is also called DNA gyrase) and topoisomerase IV. DNA gyrase has four subunits, two of which are encoded by the genes *Gyr*A and *Gyr*B. Topoisomerase IV has a similar structure and two of its subunits are encoded by the genes *Par*C and *Par*E. Resistance to quinolones is evolving owing to mutations in the above-mentioned genes. In the case of resistant Gram-negative bacteria, the mutation most commonly affects *Gyr*A. Resistance to one FQ suggests resistance to all quinolones. In the case of Gram-positive microorganisms, resistance evolves from mutations affecting *Par*C and, less commonly, *Gyr*A, although other mutations may coexist. The incidence of resistance increases with proportion to the number of mutations and resistance to one FQ does not suggest resistance to all. Where Gram-positive microorganisms are concerned, resistance *in vitro* should be investigated for each FQ separately. Resistance to Gram-positive microorganisms evolves from sequential mutations, however, resistant clones can spread quickly in the community and over a considerable geographical region. Resistance can also develop by a mechanism of efflux pump to all bacteria [46,47].

FQ use should follow strict criteria as overuse can easily lead to the emergence and spread of resistant strains. Although resistance is more common in a hospital setting, one should not overlook the fact that wide use of these antibiotics can lead to resistant strains in the community. In several countries, there have been reports of resistant Gram-negative enterobacteroids, while in other areas, resistant strains of *Salmonella typhi*, *Shigella* and *Campylobacter* have evolved. Newer quinolones, such as gatifloxacin and moxifloxacin, are active against resistant *S. pneumoniae* and they are therefore recommended for use in community pneumonia in adults who have received antibiotics recently or have a chronic illness. Nevertheless, reports of *S. pneumoniae* resistant to these agents have already emerged. It is, therefore, important to avoid the wide use of these agents as a first line of treatment in children with a common infection, such as acute otitis media [6,20,46–48].

Expert commentary

FQs are a group of antibiotic agents with a wide antimicrobial range and high efficacy against several infections in childhood. These antibiotics are safe for use in children and do not cause significant side effects. FQ-induced arthropathy, which has been encountered in juvenile animal models, has not been observed in humans. The episodes of arthralgia, with or without fluid collection, that have been documented following the use of FQs are transient and do not lead to permanent damage.

Quinolones possess remarkable antibacterial and pharmacodynamic properties and are therefore useful therapeutic options in the management of various pediatric infections. Nevertheless, owing to the probability of arthropathy but mostly owing to the increased danger of emergence of resistance, these agents should not be considered as a first-line therapy for common infections when other therapeutic options exist.

The use of FQs in children, however, should not be avoided in special cases when other effective management is unavailable or other treatment options that could be given orally do not exist. Quinolones are used nowadays to treat the pneumonic exacerbations of *P. aeruginosa* in children with CF. Other possible indications of use in pediatrics are presented in BOX 1.

Five-year view

It is speculated that, over the next 5 years, FQs will be used increasingly in pediatrics as in adult medicine, mainly owing to the launch of newer agents that are more active against Gram-positive microorganisms, while retaining excellent action against Gram-negative pathogens. These antibiotics are derived from the older FQs with the addition of a methoxy-unit in C8. 8-methoxy FQs, such as gatifloxacin, moxifloxacin, gemifloxacin and others, are more active against DNA gyrase of Gram-positive microorganisms. Newer quinolones induce a better action against staphylococci, even the methicillin-resistant strains (methicillin-resistant *S. aureus* [MRSA]), streptococci, including resistant *S. pneumoniae*, *Mycoplasma* and *Chlamydia* [49,50].

Penicillin-resistant *S. pneumoniae* is a significant health problem worldwide. Clinical failures have been reported with the use of β-lactam agents in the management of meningitis and acute otitis media due to resistant strains. The improved action of newer quinolones against *S. pneumoniae*, with medium-to-complete resistance to penicillin and third-generation cephalosporins, constitutes a significant advantage of these antibiotics, which may be an option for the management of meningitis and acute otitis media in childhood. The pharmacodynamic properties of these agents have been studied in animal models and in adults; they have been found to achieve satisfactory concentrations in the cerebrospinal fluid and they can be administered once daily. Experimental studies in animal models with bacterial meningitis have demonstrated that their bacteriocidal action is equivalent to, if not more potent than, β-lactam agents and carbapenems, which are currently widely used in this context [36].

Gatifloxacin has been studied in depth with regards to the management of acute otitis media and, when it is administered once daily (10 mg/kg orally for 10 days), it is safe and effective, even in recurrent and complicated cases. However, the anticipated wide use of FQs for the management of otitis media over the next few years should be avoided as it could easily lead to the emergence of resistance. Young children become colonized with *S. pneumoniae* in their nasopharynx and they can

easily spread resistant strains in childcare facilities. Newer quinolones should only be used in children with otitis media when no other therapeutic options are available [50].

The effect of FQ therapy on the growth and development of infants constitutes another issue that has begun to be evaluated. Reports so far are encouraging. No osteoarticular problems or joint deformities were observed and no significant adverse effects were noted from the use of FQs in neonates. Quinolones therefore appear to provide a therapeutic option therapy for newborns with sepsis due to multiresistant organisms and it is speculated that they will be used increasingly in this context over the next few years [51,52].

Key issues

- Fluoroquinolones (FQs) are licensed for use in adults owing to their broad-spectrum antibacterial activity, their extensive tissue and intracellular penetration and their suitability for oral administration.
- They possess excellent pharmacodynamic and pharmacokinetic properties, even when administered in infants and children, which renders them a useful treatment option in several cases.
- Their potential indications for use in children are wide and include pneumonic exacerbations of *Pseudomonas aeruginosa* in cystic fibrosis patients, infections of the CNS or complicated otitis media due to penicillin-resistant strains of *Streptococcus pneumoniae*, gastrointestinal and urinary tract infections due to *Salmonella*, *Shigella* or *Campylobacter*, and even mycobacterial infections.
- Reports in pediatric populations so far have not shown any significant side effects affecting growth and development, even in infants. The FQ-induced arthropathy described in juvenile animal models does not appear to exist in humans.
- Newer FQs have been launched recently that appear to have even fewer side effects and an even wider antibacterial profile, extending not only to most Gram-negative microorganisms but also to many Gram-positive bacteria. These agents are promising and their use in children is anticipated to increase over the next few years.
- The major concern with the use of quinolones in children remains the possibility of the emergence of resistant strains as their use in day-to-day practice increases.
- This issue should be addressed promptly and FQs should not be prescribed as a first-line treatment in children when other therapeutic options are available.

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