The use of fluoroquinolones in children

Eugene Leibovitz

Purpose of review

The fluoroquinolones are an important group of antibiotics widely used in the treatment of various infectious diseases in adults, as a result of an excellent spectrum of activity, good tissue penetration and convenient ways of administration. Their use in children is limited as a result of possible fluoroquinolone-induced joint/cartilage toxicity observed mainly in juvenile animal studies.

Recent findings

Fluoroquinolones were successfully used in immunocompromised children 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.). The fluoroquinolones were shown to be efficacious and well tolerated in the treatment of complicated cases of acute otitis media. The emergence of *Streptococcus pneumoniae* with reduced susceptibility to fluoroquinolones has been described worldwide. No arthropathy associated with fluoroquinolone use in children was evident.

Summary

With the exception of cystic fibrosis and life-endangering infections, the use of fluoroquinolones in pediatrics should be limited to Gram-negative neonatal meningitis, *Salmonella* and *Shigella* spp. infections, chronic suppurative otitis media and some cases of complicated acute otitis media. Unskilled use of fluoroquinolones in children, particularly in community-acquired lower respiratory infections, could accelerate the emergence of pneumococcal resistance.

Keywords

adverse events, antibiotic resistance, arthropathy, enterobacteriaceae, fluoroquinolones, otitis, *S. pneumoniae*

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From the Pediatric Infectious Disease Unit, Soroka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Correspondence: Eugene Leibovitz, MD, Pediatric Infectious Disease Unit, Soroka University Medical Center, PO Box 151, Beer-Sheva 84101, Israel
Tel: (972-7) 640 0547, fax: (972-7) 623 2334; e-mail: eugenel@bgumail.bgu.ac.il

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Abbreviations

AOM	acute otitis media
UT	urinary tract infection

1040-8703

Introduction

Nalidixic acid, the first quinolone and the only one approved for use in children, is a non-fluorinated compound marketed in 1962 and is still in use today. The fluoroquinolones developed at the beginning of the 1980s – pefloxacin, ciprofloxacin and ofloxacin – are very active against *Enterobacteriaceae* spp. and methicillin-sensitive *Staphylococcus aureus*; ciprofloxacin is highly effective against *Pseudomonas aeruginosa* (see Fig. 1). The newer fluoroquinolones, developed at the end of the 1990s, have improved in-vitro activity against the Gram-negative pathogens (in particular, non-typeable *Haemophylus influenzae* and *Moraxella catarrhalis*) involved in community-acquired respiratory tract infections.

Quinolone usage in children has been limited following the observation of arthrotoxicity in juvenile animals. These compounds have been used in pediatrics only for infections occurring in cystic fibrosis patients or as second-line treatment in cases in which other antibiotics have failed. The rates of resistance to fluoroquinolones in both community-acquired and nosocomial infections occurring in adults is increasing and this phenomenon cannot be ignored when deciding on using these compounds in children. Their good activity against the main pathogens encountered in respiratory infections in children, particularly pneumococci, will most probably lead to an increase use with the major risk of further spread of fluoroquinolone resistance.

This review will discus the main issues related to the use of fluoroquinolones in children, the major problems of resistance developing among these compounds, with special emphasis on the potential side effects and skilled use of these alternative potent drugs in pediatric infections.

Mechanism of action, pharmacokinetics and spectrum of antibacterial activity

The primary targets of fluoroquinolone action are the bacterial topoisomerases – a class of enzymes essential in maintaining the bacterial DNA molecule stable and biologically active [1,2•]. They strongly inhibit the Type II enzymes (responsible for the replication of double-stranded DNA) including DNA gyrase (topoisomerase II) and topoisomerase IV. The presence of a methoxy group at position 8 in gatifloxacin and moxifloxacin increases their affinity for DNA gyrase and topoisome-

Figure 1 The quinolones – classification

First generation	*Second generation*
Nalidixic acid	Ciprofloxacin[1]
Oxolonic acid	Norfloxacin
Cinoxacin	Lomefloxacin
	Ofloxacin
Third generation[3]	***Fourth generation[4]***
Sparfloxacin[2]	Trovafloxacin[2]
Gatifloxacin	Moxifloxacin
Grepafloxacin	Gemifloxacin
Levofloxacin	

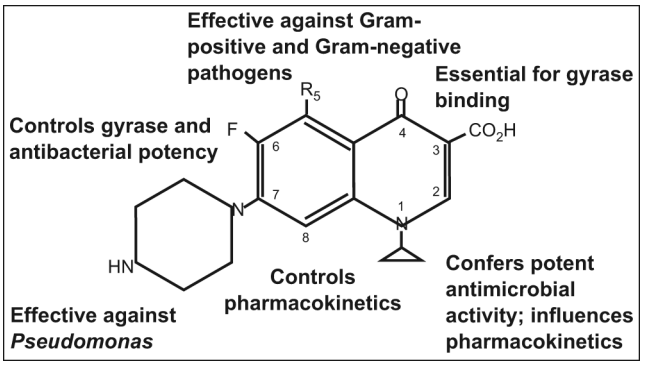
1 most potent against *Pseudomonas* spp.
2 withdrawn from market due to adverse effects
3 more potent against *S. pneumoniae* and anaerobes than early compounds
4 most potent against *S. pneumoniae* and anaerobes

rase IV conferring increased activity against *S. pneumoniae* and also a structural advantage that decreases the likelihood of emergence of resistance [2•] (see Fig. 2).

The newer fluoroquinolones have improved pharmacokinetic properties compared with the older ones, in terms of longer serum half-life, higher peak levels leading to maximal bacterial killing and large volumes of distribution with subsequent extensive tissue penetration.

Pharmacokinetic data of fluoroquinolones in pediatric patients are limited. Most pharmacological studies have been performed in older children with cystic fibrosis with *Pseudomonas* spp. infections and these have established the need for higher than usual doses in this group

Figure 2 Quinolones structure/antibacterial activity



of patients. Capparelli *et al.* [3•] reported rapid absorption and faster clearance of single-dose gatifloxacin in infants and children compared with adult patients and similar elimination half-life in older children to that of adults (while a shorter half-life was demonstrated in patients of less than 6 years of age). Two recent trials – one involving chronic otitis media children undergoing placement of tympanostomy tubes and the other patients with acute otitis media (AOM) – indicated that the concentration of levofloxacin in middle ear fluid rapidly approximates plasma concentrations after the drug has been taken [4].

All fluoroquinolones have excellent activity against aerobic Gram-negative bacilli while the newer ones are more active than their predecessors against *S. pneumoniae* and, in general, against Gram-positive cocci. The newer fluoroquinolones have lost some activity, however, *P. aeruginosa* as compared with ciprofloxacin. They all have enhanced activity against methicillin-susceptible *S. aureus*, but weak activity against methicillin-resistant *S. aureus* and coagulase-negative staphylococci. They have good activity against *S. pneumoniae*; the MIC_{50}–MIC_{90} of levofloxacin is the highest among these compounds. Activity against group A and group B β-hemolytic streptococci is optimal; the efficacy against enterococci and *Lysteria monocytogenes* was not yet clinically evaluated. Most *Haemophilus influenzae* strains and also *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumoniae* are uniformly susceptible to all fluoroquinolones. The fluoroquinolones, as a result of their excellent intracellular penetration, are effective against intracellular pathogens such as *Salmonella* spp. and mycobacteria. Only trovafloxacin (of all quinolones) has good activity (with clinical applicability) against anerobic bacteria [1,2•,5].

Resistance

Microorganisms become resistant to fluoroquinolones mainly by chromosomal mutations; single or multiple mutations in the genes encoding the DNA gyrase or topoisomerase IV are the specific sites of mutations. In resistant Gram-negative organisms, the resistance mechanism usually involves a primary mutation of the *gyr*A gene, and resistance is generalized for all fluoroquinolones [2•,5]. For Gram-positive cocci, the resistance derives from addition of mutations in different genes and increases with the number of mutations; resistance to one fluoroquinolones does not imply resistance to all others. Conceptually, it is mostly desirable to have a compound with preserved activity against single-step mutants and which will require the acquisition of two or more target site genetic mutations in order to express fluoroquinolone resistance; gatifloxacin and moxifloxacin may fulfill these requirements. As double mutations

occur rarely, the use of these two compounds may restrict the selection of resistance.

Increased fluoroquinolone resistance of *S. pneumoniae* isolates was reported during the past few years, mainly from Spain, Hong Kong and, to a lesser extent, North America. Among 2882 adult Spanish *S. pneumoniae* isolates, 75 (2.6%) were ciprofloxacin-resistant during 2002 [6•]; of 1968 invasive *S. pneumoniae* isolated in Spain (20% from children), ciprofloxacin MIC was more than 2 μg/ml for 2.1%, increasing from 0.4% in 2001 to 3.9% in 2003 [7•]. The fluoroquinolone resistance of *S. pneumoniae* reported from children in United States and Portugal remains minimal (less than 0.5%) [8•,9]. As however, the reservoir of *S. pneumoniae* is children. On whom quinolones have not yet been used routinely, careful monitoring of fluoroquinolone susceptibilities is mandatory. Meanwhile, as only a minority of pediatric *S. pneumoniae* isolates in respiratory infections is fully resistant to penicillin, it is appropriate not to use fluoroquinolones in the treatment of mild-to-moderate disease and to save them for non-improving patients and those in whom a delay in the initial response could be life-endangering.

Fluoroquinolone-resistant *H. influenzae* is rare; among 585 nasopharyngeal strains recovered from children aged 2–6 years in Hong Kong, five (0.9%) had decreased susceptibility to nalidixic acid and levofloxacin [10].

Fluoroquinolone use in hospitals has been linked to the emergence of resistance in *P. aeruginosa*, *S. aureus* and *Escherichia coli* [11•,12•].

Fluoroquinolone resistance has been reported in coagulase-negative staphylococci (an important cause of infection in premature babies and immunocompromised patients), group A streptococci, *Neisseria gonorrhea*, *Campylobacter jejuni* and *Mycobacerium* spp. [13,14,15•].

Resistance to fluoroquinolones is reported with increasing frequency in *Salmonella typhi* and non-*typhi* spp., most probably related to the broad use of these compounds in the community and also as additives to animal feed [16,17•]. Nalidixic acid, ciprofloxacin and other fluoroquinolone resistance in *Shigella* spp. has also been reported [18,19]. An increasing proportion of human infections with *Campylobacter* are caused by ciprofloxacin-resistant strains; a longer duration of diarrhea in such patients was described [20].

Tolerability

The most common side effects of fluoroquinolones are gastrointestinal, with these effects being reported in 1–4% of patients overall. Central nervous system (CNS) symptoms were more frequently reported with the use of trovafloxacin while photosensitivity reactions were mainly encountered with the use of sparfloxacin. Increased QT interval represents the main cardiac side effect associated with the entire quinolone class but its occurrence was particularly reported with the use of grepafloxacin, leading to its withdrawal from the market as a result of sudden death cases attributed to severe arrhythmia [1,2•,14]. Trovafloxacin was also withdrawn from use in 1999 owing to liver toxicity and reports of liver failure and subsequent death in a few patients during treatment.

Quinolone usage in children has been limited following the observation of arthrotoxicity in juvenile animals. The arthropathy evolves within days to weeks of drug administration and is characterized by typical histopathological lesions: fluid-filled blisters, fissures, erosions, and clusters of chondrocytes. These lesions are associated with noninflammatory joint effusions, and it is hypothesized that the effect of quinolones in some animal species may reflect inhibition of mitochondrial DNA replication in immature chondrocytes. One causal hypothesis is related to the chelation of magnesium ion by fluoroquinolones and blockade of the transduction signal at the level of the cell-surface receptors of the chondrocytes integrins that might have a role in maintaining the cartilaginous matrix [1,2•,14,21,22]. The lesions are reversible following immobilization and discontinuation of treatment. Ironically, the drug with the greatest arthropathic effect in animals, nalidixic acid, is the only one approved for use in children and has proved to be well tolerated in this population.

While clear-cut species and drug differences in the effect of quinolones on cartilage exist, the only evidence of any arthropathy in prepubertal humans was manifested by infrequent joint complaints occurring among pediatric patients (mainly [60%] in adolescent patients with cystic fibrosis, in whom arthropathy may also occur without administration of fluoroquinolones) [23]. Mild to moderate arthralgia occurred during 31/2030 (1.5%) ciprofloxacin treatments of 1795 children – an adverse event pattern similar to that seen in adults and resolving without intervention. A comprehensive review of 31 previous reports showed no quinolone-associated arthropathy in over 7000 children and adolescents who received ciprofloxacin, ofloxacin or nalidixic acid [22]. In an observational study, however, an overall adverse – events rate of 18% (similar to that reported in adults) was found in children with a 3.8% prevalence of musculoskeletal events (much higher than in adults, at 0.01-0.2%) [24]. The overall adverse–events rate was higher in the fluoroquinolone group for patients both with and without cystic fibrosis, and the rate of musculoskeletal

Table 1 Potential indications for use of fluoroquinolones in pediatric infections

1) Cystic fibrosis with suspected/confirmed *Pseudomonas* spp. infections
2) Immunocompromised patients
3) Neonatal sepsis/meningitis with multidrug-resistant Gram-negative bacilli
4) Severe enteric infections caused by *Salmonella* and *Shigella* spp.
5) Complicated urinary tract infections with multidrug-resistant organisms
6) Chronic suppurative otitis media with *Pseudomonas* spp.
7) Complicated acute otitis media failing to respond to initial antibiotic treatment

adverse events was also significantly higher for the fluoroquinolone-treated patients without cystic fibrosis.

Pediatric clinical uses

The main use of fluoroquinolones in pediatrics should be, understandably, in serious life-threatening infections for which other antibiotics therapies are not effective or available (see Table 1). Additional use of these compounds should be directed towards cystic fibrosis and immunocompromised patients and also those suffering from multidrug–resistant Gram-negative infections (including neonates), complicated urinary tract infections and multidrug-resistant enteric infections. Oral and topical quinolone therapy is very effective in chronic otitis due to *Pseudomonas* spp. The use of fluoroquinolones in nonresponsive AOM and lower respiratory tract infections should be cautious and restricted to patients that lack other therapeutic options.

Cystic fibrosis

Oral ciprofloxacin was shown to be as efficacious as a combination of β-lactams and aminoglycosides; the oral administration of the drug, thus making hospitalization unnecessary, contributed considerably to patients' quality of life. Therefore, cystic fibrosis is one of the conditions under which the agreement for use of fluoroquinolones in children is unanimous [1,2•,14,23].

Immunocompromised patients

Fluoroquinolones are not recommended today as first-line therapy in the treatment of infections in immunocompromised children or children on cancer chemotherapy with fever and neutropenia, but may be used for off-label indications in difficult-to-treat infections. These compounds are probably not superior to standard antibiotic combinations in children with febrile neutropenia [25], but the possibility of oral administration and avoidance of hospitalization in selected low-risk children is attractive. While prophylaxis with fluoroquinolones is common practice in adults with cancer, the emergence of resistant Gram-negative bacteria under this prophylaxis is alarming. Castagnola *et al.* [26•] reported a 10% rate of ciprofloxacin-resistant Gram-negative bacteria in children with cancer not receiving prophylaxis compared with 41% in adult leukemic patients receiving fluoroquinolone prophylaxis.

Enteric infections

Fluoroquinolones are recommended as first-line therapy for thyphoid and parathyphoid fever, but insufficient data and non-conclusive trials preclude any definitive recommendation regarding their superiority over other first-line antibiotics in children and adults [27•]. In children, a 5–7–day treatment with oral ciprofloxacin was bacteriologically and clinically effective in cases of *S. typhi* and *S. typhimurium* infections nonresponsive to initial ceftriaxone treatment [28]. Two or 3 days of ofloxacin were efficacious in 86.5 and 92.5%, respectively, in the treatment of typhoid fever caused by multidrug-resistant *S. typhi* in Vietnamese children [29].

Five days of oral ciprofloxacin were reported to be extremely efficacious in the treatment of shigellosis in children [30,31]. Fluoroquinolones were shown to have good in-vitro activity against *Helicobacter pylori* (including clarithromycin-resistant strains) isolated from children [32].

Urinary tract infections

The development of antimicrobial resistance (mainly against amoxicillin and trimethoprim-sulfamethoxazole, TMP/SMX) against UTI pathogens in children, particularly *E. coli*, is well documented [14,33]. While information on the use of quinolones (with the exception of nalidixic acid, which is successfully used for therapeutic and prophylactic purposes) in UTIs in children is limited and relates to complicated cases [14,34], the emergence of resistance among *E. coli* in adult patients with UTIs treated with ciprofloxacin is of major concern [35].

Complicated acute otitis media

Streptococcus pneumoniae causes 30–40% of all cases of AOM and is the least likely to resolve without treatment. A dramatic emergence of multiple-drug-resistant *S. pneumoniae* has been reported all over the world. A substantial amount of cross-resistance exists between macrolides, TMP/SMX and penicillin. Nonresponsive AOM (NR-AOM), defined as persistence of both clinical and otoscopic findings of tympanic membrane inflammation after 48–72 hours of antibiotic therapy, occurs in 20–30% of children treated with antibiotics. *S. pneumoniae*, and particularly the resistant strains, is found significantly more frequently in the MEF of children with NR-AOM or having recurrent episodes of AOM (R-AOM).

Fluoroquinolones have no place in the therapy of simple uncomplicated AOM. The paucity of the therapeutic armamentarium in the treatment of complicated AOM cases, however, makes the search for alternative therapeutic options imperative. The only new fluoroquinolones studied at the present time in the treatment of complicated AOM are gatifloxacin and levofloxacin.

Pichichero *et al.* [36••] performed a detailed analysis of all four pediatric clinical trials conducted with gatifloxacin in the treatment of 867 children with R-AOM or NR-AOM: two phase II noncomparative studies requiring pretreatment tympanocentesis (one of them requiring double-tympanocentesis) and two phase III comparative studies (the comparator being high-dose amoxicillin/clavulanate) with pretreatment tympanocentesis performed in 62% of cases. The gatifloxacin cure rate of AOM after completion of therapy was 89 and 88% in the two noncomparative and the two comparative studies, respectively. Gatifloxacin was associated with a significantly better clinical outcome than amoxicillin/clavulanate in AOM treatment failure cases, in AOM treatment failure cases in children under 2 years and in severe AOM cases in children under 2 years old. The adverse events occurring during treatment were similar for gatifloxacin and the comparator, with no evidence of arthrotoxicity, hepatotoxicity or any CNS adverse events in any child during therapy and during a 1-year follow-up period.

Noel *et al.* [37•] studied the eradication rates of MEF pathogens in 204 children (80%, aged 2 years or under) with, or at high risk for, NR-AOM and R-AOM, treated with levofloxacin in a multicenter double-tympanocentesis study. All 117 isolates of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* recovered were susceptible to levofloxacin. Bacteria were eradicated from MEF in 82/92 (89%) culture-positive patients (31/37 [84%] children with *S. pneumoniae* and 53/53 [100%] children with *H. influenzae*). Overall, the clinical success rate 1–5 days after therapy was 93.8%. Levofloxacin was well tolerated; no episodes of arthropathy occurred.

Topical ciprofloxacin was reported to be effective and well tolerated in the treatment of AOM in children with otorrhea through tympanostomy tubes [38•].

These preliminary results showed that fluoroquinolones were highly efficacious and well tolerated in the therapy of R-AOM and NR-AOM in children. These drugs, however, should be used with caution in the future in order to restrict the selection pressure on various bacterial populations.

Chronic suppurative otitis media/otitis externa

Ofloxacin otic solution was found to be efficacious in the treatment of chronic suppurative otitis media with *Pseudomonas spp.* and is approved for use in children 12 years of age and older [39]. Quinolone eardrops were more effective than nonquinolone ones both in reducing discharge and in eradicating bacteria [40].

Topical ciprofloxacin and ofloxacin were successfully used in acute external otitis ('swimmers ear') and provided a shorter and better-accepted alternative in children and adult patients [41,42].

Neonatal infections

Fluoroquinolones were successfully used in the treatment of neonatal meningitis caused by antibiotic-resistant enterobacteriaceae [43]. Drossou-Agakidou *et al.* [44•] reported on 116 neonates with microbiologically proven/probable sepsis treated with ciprofloxacin without any short-term hematologic, renal or hepatic adverse effects or evidence of clinical arthropathy/growth impairment at 1-year follow-up evaluation [44•].

Bacterial meningitis

The good activity of the newer fluoroquinolones against pneumococci, particularly those resistant to penicillin, coupled with excellent CNS penetration, made them a potential treatment for pneumococcal meningitis. Trovafloxacin was studied in a multicenter study in 108 children with bacterial meningitis and found comparable to ceftriaxone plus vancomycin in terms of clinical outcome, sequelae and death rates; there were no differences between the two regimens in terms of liver and joint toxicity [45].

Conclusion

The use of fluoroquinolones in children should be selective and skilled. These drugs are currently used in pediatrics as second-line antibiotics, mostly in cases in which all other previous treatments have failed. With the exception of cystic fibrosis and life-endangering infections, their use as first-line therapy should be limited to Gram-negative neonatal meningitis, severe *Salmonella* and *Shigella spp.* infections, chronic suppurative otitis media and to some cases of complicated AOM nonresponsive to initial treatment. While most of the published studies failed to detect an increased rate of articular adverse effects in children treated with fluoroquinolones, an increase in the use of these compounds, particularly in community-acquired lower respiratory infections, could accelerate the emergence of multidrug-resistant (including fluoroquinolone) pneumococcal strains.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p 91).

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