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Safety Concerns Surrounding Quinolone Use in Children

Karisma Patel, PharmD[1,3] and **Jennifer L. Goldman, MD, MS**[2,3,4]

[1]Department of Pharmacy, Children's Mercy Hospital, University of Missouri-Kansas City, Kansas City, MO, USA

[2]Department of Pediatrics, Children's Mercy Hospital, University of Missouri-Kansas City, Kansas City, MO, USA

[3]Divisions of Pediatric Infectious Diseases, Children's Mercy Hospital, University of Missouri-Kansas City, Kansas City, MO, USA

[4]Clinical Pharmacology, Children's Mercy Hospital, University of Missouri-Kansas City, Kansas City, MO, USA

Abstract

Fluoroquinolones are highly effective antibiotics with many desirable pharmacokinetic and pharmacodynamic properties including high bioavailability, large volume of distribution, and a broad spectrum of antimicrobial activity. Despite their attractive profile as anti-infective agents, their use in children is limited, primarily due to safety concerns. In this review we highlight the pharmacological properties of fluoroquinolones and describe their current use in pediatrics. In addition, we provide a comprehensive assessment of the safety data associated with fluoroquinolone use in children. Although permanent or destructive arthropathy remains a significant concern, currently available data demonstrate that arthralgia and arthropathy are relatively uncommon in children and resolve following cessation of fluoroquinolone exposure without resulting in long-term sequelae. The concern for safety and risk of adverse events associated with pediatric fluoroquinolone use is likely driving the limited prescribing of this drug class in pediatrics. However, in adults, fluoroquinolones are the most commonly prescribed broad-spectrum antibiotics, resulting in the development of drug-resistant bacteria that can be challenging to treat effectively. The consequence of misuse and overuse of fluoroquinolones leading to drug resistance is a greater, but frequently overlooked, safety concern that applies to both children and adults and one that should be considered at the point of prescribing.

Keywords

fluoroquinolones; pediatrics; safety

Nalidixic acid, the first synthetic quinolone agent discovered as a by-product of chloroquine synthesis, was approved by the United States Food and Drug Administration (FDA) in

Corresponding Author: Karisma Patel, PharmD, Clinical Specialist, Infectious Diseases, Children's Mercy Hospital, Kansas City, MO 64108, kbpatel@cmh.edu.

Conflict of Interest

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1964.[1] For several decades, this drug was prescribed to treat urinary tract infections (UTI) in children aged 3 months and older without restriction.[2] Subsequent fluorination of quinolone compounds led to the creation of new generations of fluoroquinolones, resulting in increased antimicrobial spectrum of activity and improved pharmacokinetic characteristics.

Since their introduction into the market, fluoroquinolones have been extensively studied and utilized in adults and have proven to be highly effective in the treatment of infections because of their broad spectrum of activity, excellent tissue and intracellular penetration, high oral bioavailability, and overall good tolerability profile. However, the quality of evidence supporting clinical use in children is less robust. In the early stages of fluoroquinolone development, studies in juvenile animals demonstrated the development of arthropathy and damage to immature cartilage of weight-bearing joints. Due to these effects seen in these young animals, the possibility of observing similar effects in infants and children raised extensive concerns. As a result, fluoroquinolone use was not recommended in children, and no further clinical studies were conducted to further evaluate their true safety in the pediatric population.

Despite the lack of available safety data, prescriptions for fluoroquinolones in children do occur, especially as antimicrobial-resistant pathogens continue to emerge. However, fluoroquinolone use in pediatrics is commonly reserved for specific indications due to safety concerns. Currently, fluoroquinolones are only FDA approved for individuals less than 18 years of age for complicated UTI including pyelonephritis and for postexposure prophylaxis and treatment of inhalation anthrax.[2] The American Academy of Pediatrics (AAP) policy statement supports strategies to limit fluoroquinolone use in children for the treatment of an infection caused by a multidrug-resistant organism for which there is no safe and effective alternative and when no other oral options are available. Although, overall, prescribing of fluoroquinolones to children remains uncommon, specific indications including the treatment of multidrug-resistant infections, complicated or recurrent UTI, or intra-abdominal infections are deemed appropriate for pediatric fluoroquinolone use.[2,3] Challenges exist for clinicians in assessing risks and benefits when prescribing fluoroquinolones to children based on the currently available safety data and drug label restrictions.

In this article, we provide an overview of the pharmacokinetic and pharmacodynamic properties of fluoroquinolones, review the current recommendations regarding fluoroquinolone use in children, critically evaluate the evidence regarding the safety of fluoroquinolones in children, focusing on musculoskeletal adverse effects, and address the role of antimicrobial stewardship in directing the optimal use of fluoroquinolones and in preventing widespread fluoroquinolone bacterial resistance.

Clinical Pharmacology

Fluoroquinolones are a unique class of antimicrobial agents that function as direct inhibitors of bacterial DNA synthesis by primarily targeting bacterial topoisomerases in the nucleus, including DNA gyrase and topoisomerase IV, blocking the progression of the DNA replication enzyme complex. Thus, fluoroquinolones exhibit bactericidal properties by

causing damage to bacterial DNA and rapid bacterial cell death.[4] Currently, there are 4 generations of quinolones, as outlined in Table 1.

Due to their broad spectrum of activity, fluoroquinolones are effective in treating a wide spectrum of infections. All fluoroquinolones are highly active in vitro against aerobic Gram-negative organisms, particularly *Enterobacteriaceae*, and the later generations provide additional activity against Gram-positive organisms. Activity against methicillin-susceptible *Staphylococcus aureus* and streptococci is also provided, with levofloxacin exhibiting the greatest activity against *Streptococcus pneumoniae*. Compared to nalidixic acid, the newer fluoroquinolones, predominantly ciprofloxacin, have additional activity against *Pseudomonas aeruginosa*. Later-generation fluoroquinolones, such as levofloxacin and moxifloxacin, uniformly possess antibacterial activity against atypical pathogens, such as *Mycoplasma pneumoniae, Chlamydia pneumoniae*, and *Legionella pneumophila*. Due to excellent intracellular penetration, fluoroquinolones are also effective against intracellular pathogens such as *Salmonella* spp and mycobacteria.[5] In addition, moxifloxacin shows good activity against anaerobic bacteria.

The bacterial killing effects of fluoroquinolones occur via concentration-dependent killing and a postantibiotic effect.[6] Based on in vitro studies, animal models, and human studies, the ratio of the peak free drug serum concentration to the minimum inhibitory concentration (C_{max}/MIC), and the ratio of the 24-hour area under the concentration-time curve (AUC_{24}) to the MIC are the parameters most closely correlated with adequate pharmacodynamic exposure in terms of successful clinical and microbiological outcomes.[7,8] There are no clear data defining the pharmacodynamic parameter most predictive of cure, although studies suggest that the target endpoints vary by specific pathogen. For Gram-negative infections, animal studies have suggested that fluoroquinolones producing a C_{max}/MIC >10:1 are associated with an increased survival rate.[8,9] Although a study evaluating the efficacy of ciprofloxacin in seriously ill adult patients suggested an AUC/MIC <125 was associated with inadequate antibacterial activity, a ratio between 125 and 250 represented acceptable activity, and an AUC/MIC >500 resulted in optimal antibacterial activity.[7] Conversely, the minimum AUC/MIC is significantly lower for Gram-positive organisms. An AUC/MIC >30 has been correlated with successful treatment of community-acquired pneumonia (CAP) caused by *Streptococcus pneumoniae*.[7,10] Analysis of the interactions among pharmacodynamic parameters, microbiological characteristics (ie, susceptibilities of the bacterial pathogens), and pharmacokinetic data aids in defining the optimal dosing of fluoroquinolones for the treatment of specific infections.

In addition to the broad spectrum of antimicrobial activity, fluoroquinolones are highly bioavailable and have a large volume of distribution, making them an attractive antimicrobial selection for a broad range of infections. Following rapid dissolution in the gastrointestinal tract, peak serum concentrations are typically achieved within 1 to 2 hours of administration in healthy patients and exhibit linear kinetics.[11–14] Food does not substantially affect absorption. The large volume of distribution of newer fluoroquinolones, together with low protein binding, results in extensive tissue and fluid distribution.[15] In terms of elimination, there is considerable variation among fluoroquinolones. Ofloxacin, levofloxacin, and gatifloxacin are predominantly excreted unchanged in the urine, whereas others undergo a

certain level of hepatic metabolism prior to elimination. Newer-generation fluoroquinolones also have a longer half-life, supporting the use of once-daily dosing.[16]

Data addressing fluoroquinolone pharmacokinetics are scarce in pediatrics, but available information appears to indicate that pharmacokinetic characteristics can be compound-dependent and influenced by age and disease status. Peltola et al conducted a study to evaluate the pharmacokinetics of a 15-mg/kg dose of oral ciprofloxacin using ground tablets in infants and small children.[13] The study showed that the mean elimination half-life of ciprofloxacin in children was significantly shorter than that in adults. However, infants experienced a higher systemic exposure due to reduced renal clearance, ultimately resulting in reduced plasma clearance. The impact of ontogeny on fluoroquinolone exposure directly influences dosing strategies. An increase in dosing frequency of ciprofloxacin to 3 times daily is recommended in children to avoid potential subtherapeutic concentrations, whereas infants and adults are recommended to receive twice-daily dosing.[13,17] Additional ciprofloxacin pharmacokinetic data are primarily limited to data specific to patients with cystic fibrosis. Data from 2 major studies in children with cystic fibrosis demonstrated a significantly faster clearance, necessitating the use of higher or more frequent dosing. In particular, it has been suggested that daily doses must be at least 30 mg/(kg·day) intravenously or 40 mg/(kg·day) orally.[18,19]

Data related to the pharmacokinetics of fluoroquinolones in neonates are minimal. Zhao et al conducted the first population pharmacokinetic study of ciprofloxacin in neonates and infants <3 months of age. Several factors were identified to impact ciprofloxacin pharmacokinetics, including gestational age at birth, postnatal age, current weight, serum creatinine, and the use of inotropic agents. Due to a decreased clearance in this population, 7.5 to 12.5 mg/(kg·dose) every 12 hours was sufficient to achieve the AUC/MIC target of >125.[20]

Levofloxacin absorption and distribution are not age dependent, but the drug half-life and clearance are directly influenced by age. Children <5 years of age cleared levofloxacin approximately twice as quickly as adults resulting in a significant decrease in exposure. This explains why children <5 years of age require twice-daily dosing to provide levofloxacin exposures similar to those associated with clinical effectiveness and safety observed in adults receiving once-daily dosing.[16,21] Similarly, in a prospective study, children being treated for multidrug-resistant tuberculosis had lower serum concentrations despite higher dosing of moxifloxacin, which again was attributed to an increase in drug elimination in children.[22] Evaluation of gatifloxacin in infants and children from 6 months to 16 years of age also revealed an increase in clearance as compared to adults.[11] Thus, the available pediatric pharmacokinetic data involving fluoroquinolones highlight the importance of recognizing key differences regarding drug exposure that are critical for optimizing fluoroquinolone use in children.

Clinical Use of Fluoroquinolones in Pediatric Practice

Currently, fluoroquinolones have a limited number of FDA-approved indications in children (Table 2). Ciprofloxacin is approved for the treatment of inhalation anthrax, complicated

UTIs, and pyelonephritis due to *Escherichia coli* in children aged 1 to 17 years, and ciprofloxacin and levofloxacin are approved for postexposure inhalation anthrax.[23,24] Moxifloxacin is not approved for pediatric use; however, it is clinically utilized off-label in the older pediatric population.[25]

Despite restricted FDA-approved pediatric indications, fluoroquinolones have been used off-label to treat a variety of infections in children due to their broad spectrum of activity, tolerability, high bioavailability, and easy oral dosing. *Pseudomonas aeruginosa* and other multidrug-resistant Gram-negative infections are often targeted with fluoroquinolones when oral therapy is indicated, specifically ciprofloxacin or levofloxacin.[26] Special populations, such as children with cystic fibrosis, commonly are infected with resistant pathogens for which fluoroquinolones may be effective. In addition, ciprofloxacin has been used as treatment for acute gastroenteritis by *Shigella* spp, *Salmonella* spp, *E coli*, and *Campylobacter* spp.[27]

Levofloxacin has been studied in children with CAP and has been shown to be comparable to standard antimicrobial agents.[28] In the 2011 Pediatric Infectious Diseases Society (PIDS) and Infectious Diseases Society of America (IDSA) clinical practice guidelines for CAP in infants and children, levofloxacin is recommended as an alternative treatment option for *Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae*, and *Chlamydia pneumoniae.* It is also the preferred oral therapy option for CAP caused by penicillin-resistant *S. pneumoniae* in adolescents.[29] Additionally, levofloxacin is now recommended by the IDSA as a treatment option for acute bacterial rhinosinusitis in children and adults with a history of type I hypersensitivity to penicillin, as a second-line agent for children with risk for antibiotic resistance, failed initial therapy, or severe infection requiring hospitalization.[30] Levofloxacin is also efficacious for the treatment of recurrent otitis media.[31] However, fluoroquinolones are not recommended as first-line agents for these indications, and are recommended to be used with caution and restricted to patients with no alternative options.

Recent studies have evaluated the use of fluoroquinolones for the treatment of multidrug-resistant tuberculosis, but there are limited data on efficacy, pharmacokinetics, and safety of fluoroquinolones in children with tuberculosis, especially with prolonged use.[22] In the 2011 World Health Organization guidelines for the treatment of drug-resistant tuberculosis, the use of fluoroquinolones such as levofloxacin, moxifloxacin, or gatifloxacin is included in second-line regimens.[32]

Oral fluoroquinolones have been introduced as an attractive option for low-risk patients for preventing fever in the presence of neutropenia due to their ease of administration, high bioavailability, and broad Gram-negative spectrum.[33] Data on bacterial prophylaxis in high-risk oncology patients are limited in children, but preliminary studies suggest that it may reduce the incidence of Gram-negative bacteremia.[34] Concurrently, prolonged use of fluoroquinolone prophylaxis may propose a significant risk for development of resistant bacterial strains in this population.[35]

Due to fluoroquinolones' excellent central nervous system penetration, their use for the treatment of pneumococcal meningitis has been a recent area of research. Trovafloxacin, which is no longer available, was compared to ceftriaxone in children with bacterial meningitis, and no differences in clinical outcomes, sequelae, and death rates were found.[36] Successful treatment of neonatal meningitis caused by antibiotic-resistant *Enterobacteriaceae* has been demonstrated, although fluoroquinolones should not be selected as first-line treatment.[37]

Although there are several clinical scenarios in which the use of fluoroquinolones has been shown to be effective, overall use should be monitored and restricted to prevent the emergence of resistance. According to an AAP policy statement, use of fluoroquinolones should be limited to the following indications: exposure to aerosolized *Bacillus anthracis* to decrease the incidence or progression of disease; UTIs caused by *P. aeruginosa* or other multidrug-resistant, Gram-negative bacteria; chronic suppurative otitis media or malignant otitis externa caused by *P. aeruginosa*; chronic or acute osteomyelitis or osteochondritis caused by *P. aeruginosa*; exacerbation of pulmonary disease in patients with cystic fibrosis who have colonization with *P. aeruginosa* and can be treated in an ambulatory setting; mycobacterial infections caused by isolates known to be susceptible to fluoroquinolones; Gram-negative bacterial infections in immunocompromised hosts in which oral therapy is desired or resistance to alternative agents is present; gastrointestinal tract infection caused by multidrug-resistant *Shigella* species, *Salmonella* species, *Vibrio cholerae*, or *Campylobacter jejuni*; documented bacterial septicemia or meningitis attributable to organisms with in vitro resistance to approved agents or in immunocompromised infants and children in whom parenteral therapy with other appropriate antimicrobial agents has failed; and serious infections attributable to fluoroquinolone-susceptible pathogens in children with life-threatening allergy to alternative agents.[26]

Fluoroquinolone Safety

Although fluoroquinolones are routinely prescribed for common infections such as UTIs and pneumonia in adults, their use is restricted in the pediatric population due to concern of significant adverse effects. Data on the safety of fluoroquinolones in children remain limited, and safety concerns have resulted in the termination of pediatric studies during clinical development, restriction of use due to toxicities by limiting exposure days, and withdrawal of several fluoroquinolones from the US market (Table 3).

Adverse reaction type and frequency differ among the various fluoroquinolones due to the differences in chemical structure of the compounds and their specific interactions with organ systems.[38] The overall incidence of adverse effects associated with fluoroquinolones is as high as 20% depending on the drug.[39] The most common adverse effects reported are gastrointestinal symptoms (eg, nausea, vomiting, diarrhea) including *C difficile*–associated colitis, followed by serious anaphylactic and allergic skin reactions and central nervous system effects such as dizziness, headache, and anxiety (Table 4).[39,40]

A life-threatening event linked with fluoroquinolone use is QT interval prolongation. Ciprofloxacin has limited proarrhythmic potential when compared to levofloxacin, as the

latter does have proarrhythmic potential that has been associated with an increased risk of cardiovascular death in adults; however, this is not commonly seen in children.[40–42] Risk for inducing torsade de pointes was the primary reason a new drug application for grepafloxacin was issued a withdrawal by the FDA in 2007.[43] More recently, in August 2013, the FDA required the drug labels and medication guides for all fluoroquinolones be updated to better describe the serious side effect of peripheral neuropathy. Review of the Adverse Event Reporting System database reveals that the onset of peripheral neuropathy is rapid and could potentially be severe, disabling, and permanent. Unfortunately, to date no clinical predictors exist to determine those at risk.[44]

Photosensitivity has also been reported, and the incidence is related to the fluoroquinolone structure. Agents containing a halogen substituent at the 8-position, such as sparfloxacin and lomefloxacin, are more likely to be associated with phototoxicity.[45] Other adverse effects described include metabolic disturbances, renal and liver toxicity, hemolytic syndrome, and, less commonly, myalgia and arthralgia resulting in the recall of temafloxacin.[46–48] There have been case reports of hypoglycemia and hyperglycemia with the use of levofloxacin and ciprofloxacin; however, these symptoms more commonly occur in elderly patients and patients with diabetes mellitus. Although similar observations have not been well described in the pediatric population, caution is advised when using these drugs in pediatric patients with diabetes.[38] Most adverse events are mild to moderate in severity and generally are reversible on discontinuation of the drug.[40]

Pediatric Safety Concerns

Arthropathy

Soon after the introduction of nalidixic acid, the concern for fluoroquinolone use in children was raised due to concerns of age-related drug toxicities stemming from observed cartilage toxicity in weight-bearing joints of immature animals during preclinical animal experiments. Based on these findings, the FDA recommended against the administration of fluoroquinolones in pediatric clinical trials involving individuals younger than 18 years of age. However, in 1989, the FDA did grant permission to conduct prospective clinical trials to evaluate the safety and efficacy of ciprofloxacin in cystic fibrosis patients and neutropenic patients undergoing chemotherapy for malignancy due to the medical need for fluoroquinolones in these specific populations who are at greatest risk for multidrug-resistant bacterial infections. The true potential for fluoroquinolone-induced arthropathy in children has been assessed in multiple studies as outlined in Table 5. Although musculoskeletal events account for fewer than 2% of reported fluoroquinolone adverse events, the concerns remain, resulting in clinician uncertainty when prescribing a fluoroquinolone to a child.[41] The following sections provide an extensive review of the animal and pediatric data assessing musculoskeletal safety data with fluoroquinolones.

Animal Toxicity Data—The adverse musculoskeletal effects of fluoroquinolones were first noted when young beagle dogs developed joint toxicity in weight-bearing joints after receiving pipemidic acid, a first-generation quinolone.[49] Since that time, all quinolones tested have been shown to have arthropathic effects on the joints of juvenile animals.[49–62]

However, the severity of the effects have been found to vary based on both the drug and animal species. From the various animals studied, dogs are the most sensitive to joint toxicities. Doses of oral ciprofloxacin at 30 mg/(kg·day) for 14 days were sufficient to cause cartilage damage,[61] whereas oral doses of pipemidic acid at 100 mg/(kg·day) resulted in arthropathy when given for as long as 90·days.[52,60] Rats required doses of nalidixic acid up to 50 mg/(kg·day), administered subcutaneously for 7 days, to observe similar effects.[56,63] On the other hand, mice did not show any effect at doses of nalidixic acid as high as 1000 mg/(kg·day) given orally for 7 days.[55,64] Monkey species also did not develop quinolone-induced cartilage toxicity with oral norfloxacin doses less than 500 mg/(kg·day) after 7 days of treatment.[56,58] In terms of drug, nalidixic acid is associated with the greatest arthropathic effects. The onset of arthropathy occurred within days to weeks.[49] Morphologic and histologic evaluation of the articular cartilage demonstrated localized fluid-filled blister formation, chondrocyte loss, matrix degeneration, and erosion accompanied by a noninflammatory effusion in the cavity of large weight-bearing joints.[49,52,54,55,60]

The mechanism of musculoskeletal toxicity remains unknown with several theorized hypotheses. The first hypothesis involves inhibition of mitochondrial DNA synthesis in immature chondrocytes.[51,58,65] It has also been suggested that fluoride may cause direct toxicity to cartilage; however, nonfluorinated quinolones can also induce cartilage toxicity in experimental animals, although other fluorinated agents do not cause the same effect, making fluoride alone unlikely to be the only contributor to these undesired effects.[66] The third hypothesis lies in the theory of a potential magnesium deficiency in the cartilage due to chelation with quinolones.[67] The final hypothesis involves defective proteoglycan and procollagen synthesis along with decreased incorporation of tritiated thymidine by chondrocytes as seen in in vivo studies.[50,51,62,68,69] Currently, there is no single mechanism clearly associated with the described arthropathy.

Human Data—The year 1962 marked the first human report of arthropathy in a child who developed unilateral wrist soreness during treatment with nalidixic acid for a UTI.[70] Eight years after nalidixic acid was FDA approved in children for the treatment of UTIs in 1964, another report of a 22-year-old woman who developed severe polyarthritis during her second course of nalidixic acid was described.[71] These clinical observations, including about a dozen cases of arthralgia and arthritis documented by the manufacturer, prompted further investigation in laboratory animals as described above. Simultaneously, several researchers performed retrospective matched control studies to evaluate the presence of cartilage toxicity in nalidixic acid–treated pediatric patients. Despite a thorough evaluation of growth-related problems and clinical symptoms of joint toxicity, no differences were detected in growth curves and functional and radiological joint findings when compared to control cases. All studies concluded that nalidixic acid did not cause arthropathy in children.[72–75]

Numerous additional studies have been performed to evaluate the safety of fluoroquinolones to determine the true incidence of musculoskeletal events in children. Many of the early studies were conducted using populations in which fluoroquinolones were initially approved on a compassionate use basis, most commonly in cystic fibrosis patients. Retrospective and prospective reviews of ciprofloxacin use for the treatment of acute bronchopulmonary infections in patients with cystic fibrosis have not demonstrated an increased incidence of

adverse musculoskeletal events. The use of MRI or plain radiographic studies confirmed the lack of joint findings.[76–78] Larger compassionate use studies showed a low incidence of arthralgias in children (1.5–1.8%). Arthralgias were generally mild to moderate in severity, self-limiting, and often occurred in patients with cystic fibrosis.[39,79] It is, however, difficult to assess the true underlying cause of these effects in patients with cystic fibrosis, as the presence of arthropathy can also be secondary to their underlying disease process.

Comprehensive literature reviews of children and adolescents treated with ciprofloxacin confirm the low rates of musculoskeletal events in the pediatric population. Burkhardt et al. conducted a comprehensive review of 31 previous reports in over 7000 children and adolescents who received ciprofloxacin, nalidixic acid, or ofloxacin and found no evidence of quinolone-associated arthropathy.[80] Another systematic search described a similar incidence rate of 1.6% as previously reported after reviewing data from 105 studies that included 16,184 patients who received ciprofloxacin. Arthralgia was the most common musculoskeletal complaint in patients 7 months to 17 years, accounting for 50% of all musculoskeletal events. All cases of arthropathy resolved or improved with either continuation of the drug, discontinuation of the drug, use of analgesics, dose reductions, or a combination of these interventions.[41]

Ciprofloxacin has also been utilized in neonates on a compassionate use basis as a “life-saving” drug for the treatment of multidrug-resistant pathogens in several studies (Table 6). Kaguelidou et al completed a systematic search of all literature evaluating the efficacy, safety, and pharmacokinetics of ciprofloxacin in neonates. In total, 32 studies met criteria for inclusion. From 5 cohort studies, 308 patients received ciprofloxacin, and 692 patients were used as controls if they either received an alternate antibiotic or no antibiotic therapy. An additional 143 infants treated with ciprofloxacin were identified through 27 case reports or clinical cases. No serious adverse events were reported during treatment or follow-up in either group. The short- and long-term impact of ciprofloxacin on cartilage damage and growth were not significantly different between the 2 groups.[81]

Conversely, a multicenter observational, comparative cohort study evaluated the safety of fluoroquinolones for the treatment of a variety of infections in 276 pediatric patients less than 19 years of age and compared them to 249 control patients. Musculoskeletal events occurred more frequently in the fluoroquinolone group versus the control group (3.8 vs. 0.4%). Events were more prevalent with pefloxacin (18.2%) than with ciprofloxacin (3.3%); however, no severe or persistent musculoskeletal injuries were observed.[40]

Bradley et al investigated the safety of levofloxacin in children 6 months and older with CAP or recurrent or persistent otitis media. The authors found a slight increase in incidence of musculoskeletal disorders in the levofloxacin group (n = 1534) compared to the comparator group (n = 989) (1.6% vs 0.7%, $P = .046$).[28] Noel et al evaluated the safety and tolerability of levofloxacin therapy in children treated for CAP and recurrent and/or persistent otitis media from 3 large multicenter efficacy trials. Patients between 6 months and 16 years were randomized to receive levofloxacin (n = 1340) or a nonfluoroquinolone antibiotic (n = 893). A total of 2233 children were included in a long-term 1-year surveillance trial. The study categorized musculoskeletal effects into 4 predefined categories:

arthralgia, arthritis, tendinopathy, and gait abnormality. During treatment or within the first month after therapy, no differences in incidence and character of adverse events were seen between the groups. The incidence of at least 1 musculoskeletal disorder was statistically greater in the levofloxacin group compared to the nonfluoroquinolone group at 2 months (2.1% vs 0.9%, $P = .038$) and at 12 months (3.4% vs 1.8%, $P = .025$). The majority of events reported in both groups were arthralgia in weight-bearing joints.[82] To further assess the long-term effects of fluoroquinolone use, Bradley et al enrolled 207 children who reported musculoskeletal adverse effects or with an increased risk of toxicity from the previous study in a supplemental long-term observational safety study for 4 additional years. Between years 2 and 5 of follow-up, 1 case in each group experienced a musculoskeletal event possibly related to the drug, but no cases were defined at the end of the 5-year period. Additionally, no children had growth abnormalities.[83]

The risk of arthropathy with moxifloxacin cannot be appropriately estimated, as there is limited evidence of use in children with no current prospective studies available for evaluation. A few cases in which moxifloxacin was used in combination with other antimicrobials for long-term treatment of multidrug-resistant tuberculosis at dosages of 10 mg/kg did not experience any adverse reactions.[84] From 2 prospective case series, 10 children received moxifloxacin for the treatment of tuberculosis. A single case of arthritis involving the ankle was reported after 3 months of moxifloxacin treatment. Symptoms spontaneously resolved days after moxifloxacin was discontinued.[85,86] Conversely, there was a case report of a 12-year-old boy in Venezuela who developed severe bilateral polyarthritis after mistakenly being prescribed 2 g/day (50 mg/[kg·day]) of moxifloxacin. Both knees had large effusions with suprapatellar and parapatellar swelling, and MRI revealed abundant joint and prepatellar bursae effusions. The patient was given steroids in the acute period, and monthly follow-up for 12 months did not reveal any sequelae or functional impairment of the affected joint.[87]

Similarly with gatifloxacin, there are limited data available to assess the incidence of musculoskeletal effects in children. A single study of 867 patients between 6 months and 7 years with recurring otitis media showed similar incidence of arthralgia in the gatifloxacin group (1.5%) compared to children treated with amoxicillin/clavulanic acid (1.3%). Additional safety follow-up data were collected for 671 gatifloxacin-treated children, and no evidence of arthropathy was noted after 1 year from completion of therapy.[88]

Tendinitis and Tendon Rupture

The occurrence of tendinopathy and tendon rupture associated with fluoroquinolones is minimal in adults and essentially negligible in children. The first documented report of tendinopathy emerged in 1983, and reports of tendon rupture followed in 1988.[89,90] In 2008, the FDA mandated a black box warning regarding the increased risk of tendinopathy and tendon rupture with fluoroquinolones.[91] Tendinopathies most commonly involve the Achilles tendon but have also been reported in tendons of the shoulder, hand, biceps, and thumb. The populations at highest risk are individuals over 60 years of age, transplant recipients, and those on concomitant steroid therapy.[92] Athletes are an additional group that is presumed to be at increased risk of fluoroquinolone-associated tendon disorders. Proposed

guidelines suggest that athletes should avoid all use of fluoroquinolone antibiotics if an alternative is available. If one is used, the athlete and athletic staff should be notified of the potential risks, and corticosteroids should not be administered concomitantly. Reduction in training activities and volume should be considered, and training activities should be ceased if the person becomes symptomatic. After completion of treatment, if the athlete is asymptomatic, then a gradual return to full activity should be initiated with close monitoring for musculoskeletal symptoms for a minimum of 6 months.[93] To date, there have been no reports of Achilles tendon rupture in children following fluoroquinolone exposure.

The Impact of Fluoroquinolone Use on Bacterial Resistance

The increased use of fluoroquinolones over time has been shown to correlate with emergence of bacterial resistance and decreased efficacy for the treatment of many infections in both adults and children. Resistance to fluoroquinolones can be acquired through 2 primary mechanisms. Spontaneous chromosomal mutations in the genes that encode DNA gyrase and topoisomerase IV can prevent binding of the quinolone to the target enzyme. Efflux pumps can also prevent quinolone binding intracellularly by altering drug permeation across the cell membrane.[4]

Numerous surveillance studies have reported fluoroquinolone resistance in *S pneumoniae* strains isolated primarily from adult patients with respiratory tract infections and in *E coli* isolated from adult patients with UTIs.[94,95] Resistance in other pathogens including *Pseudomonas aeruginosa*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, and *Streptococcus pyogenes* have also been described.[2] Fluoroquinolone-resistant pathogens have been identified as an independent risk factor for mortality among hospitalized patients, and antibiotic resistance has been identified as a global health threat.[96,97]

Following their introduction into the US market in the 1980s, fluoroquinolones became the leading antibiotic prescribed to adults in the outpatient setting by 2002, with 22 million outpatient visits resulting in a fluoroquinolone prescription.[98] In contrast, only 520,000 prescriptions were written for children less than 18 years in 2002, and only 3% of prescribing occurred in children less than 6 years of age.[26] Fluoroquinolones are the least frequently prescribed class of antibiotic for pediatric patients, accounting for less than 2% of all antibiotics prescribed in the ambulatory setting.[3] The concern for safety and risk of adverse events associated with pediatric fluoroquinolone use is likely limiting these drugs' overall use in pediatrics. A potential greater risk is that overuse or inappropriate use of fluoroquinolones will continue to drive the development of resistance. Thus, the future threat of continued antimicrobial resistance potentially outweighs the current concern of fluoroquinolone-associated adverse drug events. As fluoroquinolones remain an attractive antimicrobial option, usage and resistance will continue to increase.

Compared to adults, global resistance remains less prominent in children. However, children often have nasopharyngeal colonization with a high-density population of pneumococci increasing the risk of resistance selection.[99] The most recent reports available from the Centers for Disease Control and Prevention surveillance have not reported any levofloxacin resistance to pneumococci in children younger than 2 years between 1999 and 2004.[100] An

additional study evaluating the use of levofloxacin for the treatment of acute otitis media in children with persistent pneumococcal colonization did not document development of resistance after treatment.[101] This low prevalence of resistance is thought to be secondary to the minimal use of fluoroquinolones in children and the widespread use of the pneumococcal conjugate vaccine since 2000.[2]

In the setting of Gram-negative infections, a case-control study found only 8 (2.9%) of 271 bloodstream isolates of *E coli* and *Klebsiella* species in hospitalized children were resistant to fluoroquinolones.[102] Data available from 3 large pediatric hospitals document ciprofloxacin resistance for *E coli* ranging from 4% to 7% for 2010, which was stable for the last 3 years.[2] Rose et al conducted a study to assess the correlation between the use of fluoroquinolones, measured by doses administered and days of therapy, and resistance to fluoroquinolones in children. From 2001 to 2009 the susceptibility of Gram-negative bacilli to ciprofloxacin and levofloxacin decreased from 96.1% and 96.6% to 93.4% and 95.9% (P = .016), respectively. Increased use of fluoroquinolones was associated with reduced efficacy of ciprofloxacin and levofloxacin against Gram-negative infections in children, but overall susceptibility remained above 90%.[103] With the exception of children with cystic fibrosis, overall resistance in pediatric Gram-negative organisms is below 5%.[104]

To minimize the rapid emergence of multidrug-resistant organisms, it is essential to preserve the fluoroquinolone class, especially in the setting of a diminishing antibiotic development pipeline. Unfortunately, concomitant to the rise in quinolone use, bacteria have developed several methods of resistance, highlighting the importance of the need for greater scrutiny of fluoroquinolone prescribing.[105] Antimicrobial stewardship programs have the ability to provide guidance on appropriate antimicrobial prescribing to optimize usage, reduce resistance selection pressures, and improve patient outcomes. Specific management strategies include prescriber education, prospective audit and feedback, guideline and pathway development, parenteral-to-oral conversions, and formulary decision making.[106] In adults, these practices have been shown to effectively reduce inpatient empiric prescribing of fluoroquinolones by 30%, improve susceptibility for all antipseudomonal antibiotics by 10%, and decrease mortality associated with pseudomonal infections.[107] Therefore, incorporation of stewardship activities is critical to minimize the misuse and overuse of fluoroquinolones, reduce the development of resistant pathogens, and maintain efficacy of current limited therapeutic options.

Conclusions

Although fluoroquinolones have numerous benefits from a pharmacokinetic-pharmacodynamic perspective in treating multidrug-resistant infections, pediatricians have been skeptical about utilizing fluoroquinolones in children due to experimental findings of arthropathy in juvenile animals. To date, the majority of data have failed to demonstrate significant musculoskeletal sequalae associated with fluoroquinolone use in neonates, infants, and children. Frequently, the musculoskeletal adverse events observed in the pediatric population are arthralgias, which are transient and self-resolve after discontinuation of therapy. Currently, there are also no data demonstrating tendinopathy or tendon rupture occurring in children. Of greater concern is the increased risk of emergence of bacterial

resistance to fluoroquinolones with excessive and/or unnecessary use, primarily in the adult population. Thus, it is crucial to optimize the use of fluoroquinolones in both children and adults when indicated and to implement antimicrobial stewardship strategies to limit the use of fluoroquinolone when unnecessary.

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Table 1

Classification of Quinolones

Generation	Drugs	Spectrum of Activity		
		Gram Positive	Gram Negative	Anaerobes/Atypicals
First	Nalidixic acid[a] Cinoxacin	Minimal Gram-positive	*Enterobacteriaceae*	None
Second	Ciprofloxacin[b,c] Levofloxacin[b,d] Enoxacin Fleroxacin Ofloxacin Lomefloxacin Norfloxacin Pefloxacin	Methicillin-susceptible *Staphylcoccus aureus, Streptococcus pneumoniae*, Other streptococci	*Enterobacteriaceae Pseudomonas aeruginosa Haemophilus* spp., *Neisseria* spp., *Moraxella catarrhalis*	*Legionella pneumophila, Chlamydia* spp., *Mycoplasma* spp., *Ureaplasma urealyticum, Mycobacterium* spp
Third[e]	Gatifloxacin Grepafloxacin Sparfloxacin Temafloxacin	Methicillin-susceptible *S. aureus, S. pneumoniae, Listeria monocytogenes*, Other streptococci	*Enterobacteriaceae Haemophilus* spp., *Neisseria* spp., *Moraxella catarrhalis*	*Legionella pneumophila Chlamydia* spp., *Mycoplasma* spp., *Ureaplasma urealyticum Mycobacterium* spp
Fourth	Moxifloxacin[b,f] Trovafloxacin Gemifloxacin	Methicillin-susceptible *S. aureus*, *S. pneumoniae*, Other streptococci	*Enterobacteriaceae Haemophilus* spp., *Neisseria* spp., *Moraxella catarrhalis*	*Legionella pneumophila, Chlamydia* spp., *Mycoplasma* spp., *Ureaplasma urealyticum, Mycobacterium* spp. Anaerobes

[a] Only indicated for urinary tract infections due to low systemic exposure.

[b] Most commonly prescribed.

[c] Greatest activity against *Pseudomonas aeruginosa.*

[d] Greatest activity against *Streptococcus pneumoniae.*

[e] Not available in the United States or removed from the market.

[f] Additional activity against anaerobes.

Table 2

Clinical Uses for Most Commonly Prescribed Fluoroquinolones in Children

Drug	Pediatric FDA-Approved Indications	Additional Pediatric Clinical Uses	AAP Recommendations
Ciprofloxacin	Inhalation anthrax Complicated urinary tract infection/ pyelonephritis	*Salmonella typhi* infections *Shigella* dysenteriae Cystic fibrosis exacerbations from *Pseudomonas aeruginosa* Fever and neutropenia prophylaxis	Exposure to aerosolized *Bacillus anthracis* UTI caused by *P. aeruginosa* or other multidrug-resistant, Gram-negative bacteria Chronic suppurative otitis media or malignant otitis externa caused by *P. aeruginosa*
Levofloxacin	Inhalation anthrax	Acute otitis media Sinusitis Pneumonia Multidrug-resistant tuberculosis	Chronic or acute osteomyelitis or osteochondritis caused by *P. aeruginosa* Exacerbation of pulmonary disease in patients with cystic fibrosis who are colonized with *P. aeruginosa* and can be treated as outpatients Mycobacterial infections caused by fluoroquinolone-susceptible isolates
Moxifloxacin	Not indicated	Multidrug-resistant tuberculosis	Gram-negative bacterial infections in immunocompromised hosts in which oral therapy is desired or resistance to alternative agents is present Gastrointestinal tract infections caused by multidrug-resistant *Shigella* species, *Salmonella* species, *Vibrio cholerae*, or *Campylobacter jejuni* Documented bacterial septicemia or meningitis attributable to organisms with in vitro resistance to approved agents or in immunocompromised infants and children in whom parenteral therapy with other appropriate antimicrobial agents has failed Serious infections attributable to fluoroquinolone-susceptible pathogens in children with a life-threatening allergy to alternative agents

Table 3

Fluoroquinolones Withdrawn From US Market

Drug	Year Withdrawn	Reason for Withdrawal
Temafloxacin	1992	Hypoglycemia in elderly patients as well as a constellation of multisystem organ involvement characterized by hemolytic anemia, frequently associated with renal failure, markedly abnormal liver tests, and coagulopathy
Trovafloxacin	1999	Marketing authorization suspended due to hepatic events
Gatifloxacin	2006	Dysglycemia (hypoglycemia and hyperglycemia)
Grepafloxacin	2007	Voluntarily withdrawn, manifested as QTc interval prolongation on the electrocardiogram, which could put patients at risk of torsade de pointes

Table 4

Toxicological Profile of Fluoroquinolones

Gastrointestinal effects (eg, nausea, vomiting, diarrhea)[a]
Hepatotoxicity[a]
Skin reactions[a]
Central nervous system effects (eg, dizziness, headache, anxiety)
Nephropathy
Ocular toxicity
Cardiovascular effects (eg, QT prolongation)
Metabolic and nutritional adverse events
Phototoxicity
Arthropathy
Achilles tendinitis and rupture
Neuropathy
Exacerbation of myasthenia gravis

[a]Most frequent adverse effects per package inserts, with incidence ranging from 1% to 2.5%. Data not specific to children.

Table 5

Studies With Outcome Data of Fluoroquinolone-Associated Musculoskeletal Events in Children (Excluding Neonates)

First Author and Reference	Study Design	No. Treated With FLQ/Total	Age	Indication	FLQ	Duration of FLQ Exposure	Duration of Follow-Up	Incidence of FLQ-Associated MSK Event	Description of Events
Schaad 1987[75]	Retrospective observational study	11	0.3–9.6 years	Urinary tract infections (UTI)	Nalidixic acid	9–600 days	3–12 years	No difference with comparator group	Episodes of arthralgia were judged to have no relation to the drugs.
Rumler 1987[74]	Retrospective study	207/408	1–7.2 years, mean 6.5 years	Chronic UTI	Nalidixic acid	27–1689 days, mean 168 days	10 years	0%	No adverse effects to hip or knee joints.
Adam 1989[72]	Retrospective study	50/100	0.1–11 years, mean 4.8 years	Unknown	Nalidixic acid	10–815 days, mean 118 days	2 years	0%	Neither group showed evidence of joint damage confirmed by radiographic imaging.
Kuhn 1990[108]	Retrospective study	396	<18 years	Cystic fibrosis (CF)	Ciprofloxacin	5–48 days, mean 9.2 days	Unknown	2.5%	Reversible arthralgia, all tolerated subsequent courses with FLQ.
Schaad 1992[78]	Prospective review	18	6–24 years	CF exacerbation	Ciprofloxacin	90 days	22 months	0%	No evidence of arthropathies or joint abnormalities confirmed by radiological and MRI studies.
Danisovicova 1994[109]	Prospective observational study	14/29	4–18 years	CF-related infections	Ciprofloxacin Ofloxacin	4–28 days 1	week–16 months	43%	Transient arthralgia. Changes on MRI were seen in both groups at high rates.
Nuutinen 1994[73]	Controlled follow-up	78	<15 years	Recurrent UTI	Nalidixic acid	6–570 days, mean 86 days	14.8–24.7 years, mean 19.6 years	No difference with comparator group	No growth disturbances were found.
Pradhan 1995[66]	Case series	58	8 months–13 years	Fever ≥7 days, *Salmonella typhi* infection	Ciprofloxacin	9–16 days	10–15 days to 37 months	0%	No evidence of joint swellings, arthralgia or restriction of movements.
Bethell 1996[110]	Prospective cohort study	326/549	1–14 years	Typhoid fever	Ciprofloxacin Ofloxacin	3–7 days	2 years	0%	No evidence of acute joint toxicity. Height velocity was similar to control group at end of follow-up.
Richard 1997[77]	Randomized, controlled trial	55/108	5–17 years	Bronchopulmonary infections, CF	Ciprofloxacin	14 days	20–30 days	No difference with comparator group	Arthralgia and extremity pain.
Church 1997[111]	Prospective, randomized trial	41/84	5–17 years	CF exacerbation	Ciprofloxacin	Median 13 days	14–28 days	No difference with comparator group	Arthralgia of mild to moderate severity,

First Author and Reference	Study Design	No. Treated With FLQ/Total	Age	Indication	FLQ	Duration of FLQ Exposure	Duration of Follow-Up	Incidence of FLQ-Associated MSK Event	Description of Events
									majority resolved without intervention.
Jick 1997[112]	Retrospective study	1733	<17 years	Variety of infections	Ciprofloxacin	Unknown	45 days	0%	No new cases of acute arthritis or joint toxicity.
Hampel 1997[39]	Safety report	1795	<17 years	Compassionate use	Ciprofloxacin	1–303 days	Unknown	1.50%	Mild to moderate arthralgia, typically self-resolving.
Salam 1998[113]	Randomized, controlled trial	71/143	2–15 years	Shigellosis	Ciprofloxacin	5 days	180 days	18%, no difference with comparator group	Arthralgia, no patients had signs of arthritis.
Leibovitz 2000[27]	Randomized, controlled trial	95/201	6 months–10 years	Acute invasive diarrhea	Ciprofloxacin	3 days	21 ± 5 days	1%	One patient developed bilateral knee arthralgia within hours of treatment, but subsided without intervention after a few hours. Therapy was not discontinued.
Saez-Llorens 2002[36]	Randomized trial	108/203	3–12 years	Bacterial meningitis	Trovafloxacin	5–14 days	6–12 months	No difference with comparator group	Transient arthralgia and joint abnormalities. MRI in patient with joint inflammation negative for arthropathy, later resolved.
Yee 2002[114]	Observational	7897	<19 years	Variety of infections	Ofloxacin, Levofloxacin, Ciprofloxacin	Unknown	60 days	50 verified cases (<1%)	Most frequently involved the joint, tendon, cartilage and gait disorder.
Zimbabwe BSADSG 2002[115]	Randomized, controlled trial	253	1–12 years	Shigella	Ciprofloxacin	3–5 days	14 days	3.5%	Mild arthralgia with normal joint function at follow-up.
Chalumeau 2003[40]	Prospective, comparative cohort study	264/525	<19 years	Variety of infections	Ciprofloxacin Ofloxacin Pefloxacin	1–327 days	15 days	3.8% vs 0.4% (greater than comparator group)	Transient arthralgia of large joints or myalgia; no tendinopathy was observed.
Ciprofloxacin Package Insert 2005[23]	Prospective, comparative study	335/684	1–17 years	Complicated UTIs and pyelonephrtitis	Ciprofloxacin	10–21 days	1 year	13.7% vs 9.5% (statistically greater than comparator group)	Mild to moderate arthralgia, typically self-resolving within 30 days of end of treatment.

First Author and Reference	Study Design	No. Treated With FLQ/Total	Age	Indication	FLQ	Duration of FLQ Exposure	Duration of Follow-Up	Incidence of FLQ-Associated MSK Event	Description of Events
Sher 2005[116]	Randomized, comparative study	176/354	6 months–7 years	Otitis media (AOM)	Gatifloxacin	10 days	12 months	0%	No evidence of abnormal joint or gait findings.
Pichichero 2005[88]	Review of data from clinical trials	867	6 months–7 ears	AOM	Gatifloxacin	10 days	12 months (n = 671)	No difference with comparator group	Transient arthralgia, self-resolving. No evidenceof arthropathy.
Bradley 2007[28]	Open-label, active-comparator, non-inferiority trial	405/539	6 months–16 years	Community acquired pneumonia (CAP)	Levofloxacin	10 days	25–35 days	No difference with comparator group	Arthralgia and myalgia.
Noel 2007[82]	Database review of three clinical trials	2233	6 months–16 years	CAP or AOM	Levofloxacin	7–14 days	1 year	3.4% vs 1.8% (statistically greater than comparator group)	Myalgia, arthralgia, pathologic fracture, arthropathy, and pain in extremity. Incidence appeared to increase over time.
Pinon 2010[84]	Case series	2	11,23 months	Multidrug-resistant tuberculosis (TB)	Moxifloxacin	Unknown	18 months	0%	No evidence of adverse effects.
Chauny 2012[85]	Case series	6	9 months–14 years	TB	Moxifloxacin, Levofloxacin	1–16 months	Unknown	2 patients	Patient 1 had polyarthritis 1 month after starting therapy, which resolved after stopping. Patient 2 had arthralgia after 4 days, but symptoms spontaneously resolved while on treatment.
Garazzino 2014[86]	Case series	9	6 months–13 years	Pulmonary TB	Moxifloxacin	3–13.4 months	0–36 months	1 patient	One case of ankle arthritis after 3 months of therapy that spontaneously resolved after discontinuation.
Bradley 2014[83]	Follow-up safety study	124/207	6 months–16 years	CAP or AOM	Levofloxacin	7–14 days	5 years	<1%	Transient arthralgia of knee and elbow, synovitis of hip.

[a] FLQ, fluoroquinolone; MSK, musculoskeletal.

Table 6

Studies With Outcome Data on Fluoroquinolone-Associated Musculoskeletal Events in Neonates

First Author and Reference	Study Design	No. Tx With FLQ/Total	Age	FLQ Indication	FLQ	Duration of FLQ Exposure	Duration of Follow-Up	Description of Adverse Events
Lumbiganon 1991[117]	Follow-up study	11	Neonates >26 weeks	Nosocomial *Klebsiella* infections	Ciprofloxacin	10–20 days	12–23 months	Normal growth and development. No skeletal dysfunction or joint abnormalities. Greenish teeth discoloration was noted in two patients.
Martell 1996[118]	Longitudinal study	7/21	Mean 32 weeks	Clinical sepsis	Ciprofloxacin, Pefloxacin	10 days	42 months	No osteoarticular sequelae or joint deformities. No growth impairment noted with fluoroquinolone treatment.
Gurpinar 1997[119]	Longitudinal comparative survey	9/27	Mean 35 weeks	Clinical sepsis	Ciprofloxacin	14 days	42 months	No osteoarticular sequelae or joint deformities. No growth impairment noted with fluoroquinolone treatment.
Belet 2004[120]	Prospective study	30	25–38 weeks	Nosocomial *P aeruginosa* infections	Ciprofloxacin	8–24 days	1 week post-discharge	No evidence of joint toxicity.
Chaudhari 2004[121]	Prospective case-matched control study	30/60	Mean 33.2 ± 3.83 weeks	Neonatal septicemia	Ciprofloxacin	14 days	6 months	No effects on growing cartilage or joint involvement confirmed by ultrasound.
Drossou-Agakidou 2004[122]	Observational prospective matched study	77/160	25–40 weeks	Clinical sepsis	Ciprofloxacin	14 days	12 months	No evidence of articular damage or growth impairment.
Ahmed 2006[123]	Prospective cohort study	48/114	<33 weeks	Life-saving therapy in sepsis	Ciprofloxacin	15.4 ± 10.6 days	24.7 ± 18.5 months	No evidence of acute or subclinical joint toxicity. Growth and development were normal.
Dutta 2006[124]	Retrospective cohort study	61/205	<37 weeks	Various ne onatal infections	Ciprofloxacin	>3 days	12 months	No effect on linear growth.
Kaguelidou 2011[81]	Systematic literature review	451/1256	<4 weeks	Neonatal infections	Ciprofloxacin	5–75 days	1 week–36 months	No serious adverse events, including joint toxicity, observed.

FLQ, fluoroquinolone.