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Guidance for the Clinician in Rendering Pediatric Care

CLINICAL REPORT

The Use of Systemic and Topical Fluoroquinolones

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abstract

FREE

Appropriate prescribing practices for fluoroquinolones are essential as evolving resistance patterns are considered, additional treatment indications are identified, and the toxicity profile of fluoroquinolones in children becomes better defined. Earlier recommendations for systemic therapy remain; expanded uses of fluoroquinolones for the treatment of certain infections are outlined in this report. Although fluoroquinolones are reasonably safe in children, clinicians should be aware of the specific adverse reactions. Use of fluoroquinolones in children should continue to be limited to treatment of infections for which no safe and effective alternative exists. *Pediatrics* 2011;128:e1034–e1045

KEY WORDS

fluoroquinolones, pediatrics, infectious diseases, systemic therapy

ABBREVIATIONS

FDA—Food and Drug Administration
UTI—urinary tract infection
TMP-SMX—trimethoprim-sulfamethoxazole

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

OVERVIEW

Fluoroquinolones are highly active in vitro against both Gram-positive and Gram-negative pathogens and have pharmacokinetic properties that are favorable for treating a wide array of infections. The prototype quinolone antibiotic agent, nalidixic acid, was approved by the US Food and Drug Administration (FDA) for adults in 1964 and generally is considered to be the first generation of such agents. For more than 2 decades, nalidixic acid also has been approved by the FDA and available for children aged 3 months and older. Subsequent chemical modifications of the first quinolone compounds resulted in the development of a series of fluoroquinolone agents with an increased antimicrobial spectrum of activity and better pharmacokinetic tissue-exposure characteristics.

Second-generation agents have a greater Gram-negative spectrum (with activity against *Pseudomonas aeruginosa*) and include ciprofloxacin, levofloxacin, norfloxacin, and ofloxacin. In 2004, ciprofloxacin became the first fluoroquinolone agent approved for use in children 1 through 17 years of age.

Gemifloxacin, a currently marketed third-generation agent, has been approved by the FDA for adults for the treatment of community-acquired pneumonia and acute exacerbations of chronic bronchitis. Compared with earlier agents, gemifloxacin provides substantially increased activity against *Streptococcus pneumoniae* (while retaining activity against many Gram-negative pathogens), *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae*.

A fourth generation of fluoroquinolones, represented by moxifloxacin, displays increased activity against anaerobes while maintaining the Gram-positive and Gram-negative activity of the third-generation agents. Moxifloxacin also provides excellent activity against many my-

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cobacteria including most strains of *Mycobacterium tuberculosis* currently isolated in the United States.

Animal toxicology data available with the first quinolone compounds documented their propensity to create inflammation and subsequent destruction of weight-bearing joints in juvenile animals.[1,2] This observation effectively sidelined further development or large-scale evaluation of this class of antibiotic agents in children.

A policy statement summarizing the assessment of risks and benefits of fluoroquinolones in pediatric patients was published by the American Academy of Pediatrics in 2006.[3] At that time, parenteral fluoroquinolones were believed to be appropriate for the treatment of infections caused by multidrug-resistant pathogens for which no alternative safe and effective parenteral agent existed. For outpatient management, oral fluoroquinolones were reasonable for treatment of infections when the only other options were intravenous treatment with other classes of antibiotic agents.

Since publication of the previous American Academy of Pediatrics policy statement, the clinical value of fluoroquinolones for the treatment of specific infections in children, particularly those caused by Gram-negative pathogens, has been further documented. The use of topical fluoroquinolone therapy for external otitis is now recommended by the American Association of Otolaryngology.[4] In addition, results of the first randomized, prospective studies on the safety of the fluoroquinolones have been reported.[5,6] No published reports exist of physician-diagnosed cartilage damage in children in the United States, either from controlled clinical trials of fluoroquinolones or from unsolicited reporting to the FDA or drug manufacturers. Quinolones that are currently approved by the FDA and available for use in children are nalidixic acid for urinary tract infections (UTIs), ciprofloxacin for inhalational anthrax and complicated UTI and pyelonephritis, and levofloxacin for inhalational anthrax. Only ciprofloxacin and levofloxacin are available in a suspension formulation. Moxifloxacin is currently under investigation for treatment of complicated intraabdominal infections in children.[7] Other systemic quinolones that may be available in other countries but not the United States are not addressed in this report.

SAFETY

Animal Models

The original toxicology studies with quinolones documented cartilage injury in weight-bearing joints in juvenile animals; damage to the joint cartilage was proportional to the degree of exposure.[1,2] Each quinolone may demonstrate a different potential to cause cartilage toxicity.[8] However, given a sufficiently high exposure, cartilage changes will occur in all animal models with all quinolones, including nalidixic acid.

Although initial reports focused on articular cartilage, the results of subsequent studies suggested the possibility of epiphyseal plate cartilage injury,[9] which led to fluoroquinolone clinical study designs that lasted several years to assess growth potential. Recent data suggest that quinolone toxicity occurs as a result of concentrations present in cartilage that are sufficiently high to form chelate complexes with divalent cations, particularly magnesium, that result in impairment of integrin function and cartilage matrix integrity in the weight-bearing joints, which undergo chronic trauma during routine use.[10]

In studies of ciprofloxacin exposure to very young beagle puppies (one of the most sensitive animal models for quinolone toxicity), clinical evidence of arthrotoxicity was observed during a 14-day treatment course at 90 mg/kg per day but not at 30 mg/kg per day. Apparent joint tenderness at the higher exposure resolved 6 weeks after the last dose of ciprofloxacin.

Histopathologic evidence of cartilage injury was noted in virtually all animals given 90 mg/kg per day. At this exposure level, the observed clinical signs all occurred during and shortly after treatment but resolved by 2 months, with no recurrent signs noted during the 5-month follow-up period. In contrast, histopathologic evidence of cartilage injury was observed at 30 mg/kg per day, the dose currently recommended for children. Histopathologic evidence of inflammation occurred in fewer than half the animals at this dose but persisted for 5 months after treatment, at full skeletal maturation.[5,11] The "no-observed-adverse-event level" was 10 mg/kg per day, a dose at which neither clinical nor histopathologic evidence of toxicity was present.

Similar data, which documented a no-observed-adverse-event level of 3 mg/kg per day for intravenous dosing for 14 days (approximately one-quarter the current FDA-approved dose of 16 mg/kg per day for children who weigh $<$50 kg), were documented before FDA approval of levofloxacin for adults. Levofloxacin has virtually 100% bioavailability; total drug exposure is equivalent between intravenous and oral formulations at the same milligram-per-kilogram dose.[12]

Recent data from investigation of a lamb model, felt to approximate human growth rates and activity more closely than juvenile beagle dogs or rats, have been published. This study addressed epiphyseal cartilage and growth velocity after a 14-day drug exposure to either gatifloxacin or ciprofloxacin that was equivalent to that achieved in children receiving thera-

peutic doses. Gross examination of articular cartilage and microscopic examination of epiphyseal cartilage did not reveal abnormalities consistent with cartilage injury or inflammation.[13]

Preclinical toxicology data are available for all FDA-approved fluoroquinolones. These data document differences in the animal species susceptible to cartilage effects as well as differences between each quinolone in the ability to create cartilage toxicity.

Human Studies

At the time of publication of the last American Academy of Pediatrics policy statement, retrospective studies, case-control series, and case reports represented the published data on fluoroquinolone safety in children available in the peer-reviewed literature.[14–17] Some reports included children with cystic fibrosis, who can develop disease-related arthropathy, and some included more toxic fluoroquinolone agents that were never approved in the United States. These data provided conflicting reports regarding the safety of fluoroquinolones in children. The results of 2 large, prospective safety studies are now available for review; 1 study was performed at the request of the FDA by Bayer for ciprofloxacin, and the second study was performed by Johnson & Johnson for levofloxacin as part of their FDA-coordinated program of pediatric drug development.

In 2008, the FDA's analysis of study data for ciprofloxacin in the treatment of complicated UTI and pyelonephritis in children aged 1 through 17 years from 2004 was posted on the FDA Web site.[5] A series of prospective, randomized, double-blinded studies was performed to compare (1) intravenous ceftazidime with intravenous ciprofloxacin, permitting oral step-down therapy, and (2) oral ciprofloxacin with oral cefixime or trimethoprim-sulfamethoxazole (TMP-SMX). These large studies were conducted in several countries (Table 1). Clinical end points were designed to capture any sign of cartilage or tendon toxicity by eliciting a detailed history of a wide variety of complaints referable to bones and joints (Table 2). Comparing complaints and physical findings between the ciprofloxacin-treated group and the group treated with comparator antimicrobial agents, a difference was detected only in the United States. The difference in rates of complaints varied between countries; the lowest

TABLE 1 Rate of FDA-Defined Arthropathy (See Table 2) 6 Weeks After Treatment With Ciprofloxacin or Comparator, According to Selected Baseline Characteristics

	Ciprofloxacin ($N = 335$)	Comparator ($N = 349$)
All patients, *n*/*N* (%)	31/335 (9.3)	21/349 (6.0)
Country, *n*/*N* (%)		
Argentina	8/77 (10.4)	7/79 (8.9)
Canada	1/8 (12.5)	1/11 (9.1)
Costa Rica	4/21 (19.0)	0/20 (0.0)
Germany	1/13 (7.7)	1/11 (9.1)
Mexico	0/56 (0.0)	0/60 (0.0)
Peru	2/87 (2.3)	3/88 (3.4)
United States	13/62 (21.0)	8/71 (11.3)
South Africa	2/11 (18.2)	1/9 (11.1)
Race, *n*/*N* (%)		
White	18/130 (13.8)	13/134 (9.75)
Black	0/5 (0.0)	1/7 (14.3)
Asian	0/3 (0.0)	1/6 (16.7)
Hispanic	8/102 (7.8)	3/109 (2.8)
Uncoded	5/95 (5.3)	3/93 (3.2)
Gender, *n*/*N* (%)		
Male	6/62 (9.7)	4/65 (6.2)
Female	25/273 (9.2)	17/284 (6.0)

TABLE 2 Rate of FDA-Defined Arthropathy 6 Weeks and 1 Year After Treatment With Ciprofloxacin or a Comparator

	Ciprofloxacin ($N = 335$)		Comparator ($N = 349$)
Arthropathy rate at 6 wk of follow-up, *n* (%)	31 (9.3)		21 (6.0)
95% confidence interval[a]		(−0.8 to 7.2)	
Cumulative arthropathy rate at 1 y of follow-up, *n* (%)	46 (13.7)		33 (9.5)
95% confidence interval[a]		(−0.6 to 9.1)	
Selected musculoskeletal adverse events[b] in patients with arthropathy at 1 y of follow-up			
No. of patients	46[c]		33[c]
Arthralgia, *n* (%)	35 (76)		20 (61)
Abnormal joint and/or gait exam, *n* (%)	11 (24)		8 (24)
Accidental injury, *n* (%)	6 (13)		1 (3)
Leg pain, *n* (%)	5 (11)		1 (3)
Back pain, *n* (%)	4 (9)		0 (0)
Arthrosis, *n* (%)	4 (9)		1 (3)
Bone pain, *n* (%)	3 (7)		0 (0)
Joint disorder, *n* (%)	2 (4)		0 (0)
Pain, *n* (%)	2 (4)		2 (6)
Myalgia, *n* (%)	1 (2)		4 (12)
Arm pain, *n* (%)	0 (0)		2 (6)
Movement disorder, *n* (%)	1 (2)		1 (3)

[a] The study was designed to demonstrate that the arthropathy rate for the ciprofloxacin group did not exceed that of the comparator group by more than 6.0%. At both evaluations, the 95% confidence interval indicated that it could not be concluded that ciprofloxacin had findings comparable to those of the comparator.

[b] Events that occurred in 2 or more patients.

[c] A patient with arthropathy may have had more than 1 event.

rates were reported from Mexico (0% ciprofloxacin, 0% comparator), and the highest rates were reported from the United States (21% ciprofloxacin, 11% comparator). The study used a noninferiority design to assess musculoskeletal complaints between the 2 treatment groups across all countries, and as analyzed, the groups were sufficiently different to suggest potential musculoskeletal toxicity with ciprofloxacin (Table 2).

The levofloxacin safety data collection was prospective and randomized but not blinded. The published safety profile of levofloxacin included a large cohort of 2523 children from 3 large multicenter efficacy trials. Data were collected from a community-acquired pneumonia trial in children aged 6 months to 16 years (a randomized 3:1, prospective, comparative trial with 533 levofloxacin-exposed and 179 comparator-exposed evaluable subjects) and from 2 trials that assessed therapy of acute otitis media in children aged 6 months to 5 years (1 open-label noncomparative study with 204 evaluable subjects and another randomized 1:1, prospective, comparative trial with 797 levofloxacin-exposed and 810 comparator-exposed evaluable subjects).[6] In addition, after completion of the treatment trials, all subjects from both treatment arms were also offered participation in an unblinded, long-term, 12-month follow-up study for safety assessments, and 2233 of 2523 families participated. From these trials, a selected group of children who were judged to benefit from additional follow-up because of the presence of tendon/joint abnormalities or failure to achieve expected vertical growth over the year of observation were continued in the musculoskeletal long-term follow-up study, which consisted of yearly visits for 4 additional years.

The definitions of musculoskeletal events for tendinopathy (inflammation or rupture of a tendon as determined by physical examination and/or MRI or ultrasound), arthritis (inflammation of a joint as evidenced by redness and/or swelling of the joint), arthralgia (pain in the joint as evidenced by complaint), and gait abnormality (limping or refusal to walk) were determined before starting the studies. The identity of study medication was known by parents, study personnel, and the subject's care providers as reports of musculoskeletal events and any other adverse events were collected during the follow-up period. An analysis of these events occurred 1, 2, and 12 months after treatment. The analysis of disorders that involved weight-bearing joints revealed a statistically greater rate between the levofloxacin- and comparator-treated groups at 2 months (1.9% vs 0.7%; $P = .025$) and at 12 months (2.9% vs 1.6%; $P = .047$). A history of joint pain accounted for 85% of all events, and there were no findings of joint abnormality when assessed by physical examination. Computed tomography or MRI was performed for 5 of the patients with musculoskeletal symptoms; no signs of structural injury were identified. No evidence of joint abnormalities was observed at 12 months in the levofloxacin group.

A report on the 5-year safety assessment of the 2233 children who received levofloxacin treatment was recently completed by the manufacturer, Johnson & Johnson. Specified criteria for review included (1) documented height that was less than 80% of the expected height increase, (2) abnormal bone or joint findings, and (3) any other concerns for possible tendon/joint toxicity identified by the data safety monitoring board during treatment or in the 12 months after treatment. A total of 174 of 207 (84%) reviewed subjects were identified by the predetermined growth criteria (124 levofloxacin-treated and 83 comparator-treated subjects), and 49% of each group completed the entire 5-year follow-up. Although an increase in musculoskeletal events in the levofloxacin group had been noted 12 months after treatment, the cumulative long-term outcomes of children with musculoskeletal adverse events reported during the 5-year safety study (including ongoing arthropathy, peripheral neuropathy, abnormal bone development, scoliosis, walking difficulty, myalgia, tendon disorder, hypermobility syndrome, and pain in the spine, hip, and shoulder) were slightly higher in the comparator treatment group (2% levofloxacin, 4% comparator). Among all study participants identified by the growth criteria ($n = 174$), equal percentages of children from each treatment group were documented to fall into the previously defined categories at the 5-year visit: no change in height percentile; improvement; or deterioration in growth characteristics. This 5-year follow-up study enrolled 48% of study participants from US sites compared with 20% from US sites enrolled in the original clinical trials (unpublished data on file, J&J protocol LOFBO-LTSS-001, clinical study report, March 23, 2011).

A rare complication associated with quinolone antibiotic agents, tendon rupture, has a predilection for the Achilles tendon (often bilateral) and is estimated to occur at a rate of 15 to 20 per 100 000 treated patients in the adult population. Advanced age, along with antecedent steroid therapy and a particular subset of underlying diseases, including hypercholesterolemia, gout, rheumatoid arthritis, end-stage renal disease/dialysis, and renal transplantation, have been identified as risk factors and prompted an FDA warning about this serious adverse event for all quinolone agents. Achilles tendon rupture in the pediatric popu-

TABLE 3 Rate of FDA-Defined Neurologic Adverse Events by 6 Weeks After Treatment With Ciprofloxacin or Comparator

Neurologic Adverse Events	Ciprofloxacin ($N = 335$), *n* (%)	Comparator ($N = 349$), *n* (%)
Any event	9 (3)	7 (2)
Dizziness	3 (<1)	1 (<1)
Nervousness	3 (<1)	1 (<1)
Insomnia	2 (<1)	0 (0)
Somnolence	2 (<1)	0 (0)
Abnormal dreams	0 (0)	2 (<1)
Convulsion	0 (0)	2 (<1)
Hypertonia	0 (0)	1 (<1)
Abnormal gait	0 (0)	1 (<1)

lation, in general, is extremely rare, and although tendonitis in athletes is observed, this event usually follows overuse. To date, there have been no reports of this rare complication in a pediatric patient who was exposed to a quinolone, which precludes assessment of the risk of this complication in children.

Other potential toxicities of fluoroquinolone-class antibiotic agents do not occur commonly in children but include central nervous system adverse effects (seizures, headaches, dizziness, lightheadedness, sleep disorders), peripheral neuropathy, hypersensitivity reactions, photosensitivity and other rashes, disorders of glucose homeostasis (hypoglycemia and hyperglycemia), prolongation of QT interval, and hepatic dysfunction.

In the prospective ciprofloxacin study requested by the FDA, the rate of neurologic events was similar between ciprofloxacin- and comparator-treated children (Table 3).[5] Reported rates of neurologic events in the levofloxacin safety database were statistically similar between fluoroquinolone- and comparator-treated children.[18,19]

RESISTANCE

Quinolone resistance has been a concern since the first approval of these agents, given the broad spectrum of activity and the large number of clinical indications. Multiple mechanisms of resistance have been described, including mutations that lead to changes in the target enzymes DNA gyrase and DNA topoisomerase, as well as efflux pumps and alterations in membrane porins.[20] Newly described plasmid-encoded quinolone-resistance proteins have the ability to spread rapidly.[21]

Surveillance studies have tracked fluoroquinolone resistance in *S pneumoniae* strains isolated primarily from adult patients with respiratory tract infections and in *Escherichia coli* isolated from adult patients with UTIs. A number of studies also have assessed resistance in other enteric bacilli,[22–25] *Pseudomonas aeruginosa*,[26] *Neisseria gonorrhoeae*,[27] *Neisseria meningitidis*,[28] and *Streptococcus pyogenes*.[29,30] One recent study in North America addressed fluoroquinolone resistance in both Gram-negative and Gram-positive isolates, specifically from children younger than 7 years.[31] Previous concerns that continuing widespread use of respiratory fluoroquinolones would lead to substantial increases in pneumococcal resistance and subsequent lack of usefulness of this class of agents for respiratory tract infections[32–34] have, fortunately, not been confirmed by current published surveillance data, particularly for pneumococcal isolates from children.[31,35,36] The Active Bacterial Core Surveillance of the Centers for Disease Control and Prevention documented virtually no levofloxacin resistance in children younger than 2 years between 1999 and 2004.[37] In large-scale pediatric studies of levofloxacin for acute otitis media, emergence of levofloxacin-resistant pneumococci was not documented in children with persisting pneumococcal colonization after treatment, which suggests that emergence of resistance during treatment is not a common event.[38] Possible reasons for the lack of increasing multidrug-resistant serotypes in both children and adults in populations in North America and Europe include the almost universal use of conjugate pneumococcal vaccine in children since 2000 as well as the lack of widespread use of fluoroquinolones in children.[37,39–41]

In adult patients, *Pseudomonas* resistance to both fluoroquinolones and other antimicrobial agents is problematic.[42] Data on resistance in *E coli* isolated from adults with UTIs who were seen in emergency departments in the EMERGEncy ID NET, a network of 11 geographically diverse university-affiliated institutions, suggest a low but stable rate of resistance of approximately 5%,[24] although in specific locations, rates of resistance for outpatients are closer to 10%.[22,43] Similar published data do not exist for children, although in recent reports that included outpatient data, stratified according to age, the rates of fluoroquinolone resistance in *E coli* in children have been generally well below 3%.[23,43]

For hospitalized children in a major tertiary care pediatric center, only 3% of 271 bloodstream isolates of *E coli* and *Klebsiella* species collected over 4 years (1999–2003) were resistant to fluoroquinolones.[44] With the exception of children with cystic fibrosis, overall resistance in pediatric Gram-negative isolates, including *P aeruginosa*, has been lower than 5%.[31] Data available from 3 large tertiary care children's hospitals document ciprofloxacin resistance for *E coli* to range from 4% to 7% for 2010 (B. Connelly, MD [Cincinnati Children's Hospital and Medical Center, Cincinnati, OH], M. A. Jackson, MD [Mercy Children's Hospital, Kansas City, MO], and J. Bradley, MD [Rady Children's Hospital, San Diego, CA], verbal communication, May 2011), and the rates have seemed stable for the last 3 years.

TABLE 4 Most Common Infections for Which Fluoroquinolones Are Effective Therapy (See Text)

Infection	Primary Pathogen(s)[a]	Fluoroquinolone
Systemic antibiotic requirement[b]		
UTI	*Escherichia coli* *Pseudomonas aeruginosa* *Enterobacter* species *Citrobacter* species *Serratia* species	Ciprofloxacin[c]
Acute otitis media; sinusitis	*Streptococcus pneumoniae* *Haemophilus influenzae*	Levofloxacin[d]
Pneumonia	*Streptococcus pneumoniae* *Mycoplasma pneumoniae* (macrolides preferred for *Mycoplasma* infections)	Levofloxacin
Gastrointestinal infections	*Salmonella* species *Shigella* species	Ciprofloxacin[c]
Topical antibiotic requirement[e,f]		
Conjunctivitis	*Streptococcus pneumoniae* *Haemophilus influenzae*	Besifloxacin Levofloxacin Gatifloxacin Ciprofloxacin Moxifloxacin Ofloxacin
Acute otitis externa; tympanostomy tube–associated otorrhea	*Pseudomonas aeruginosa* *Staphylococcus aureus* Mixed Gram-positive/Gram-negative organisms	Ciprofloxacin[g] Ofloxacin

[a] Assuming that the pathogen is either documented to be susceptible or presumed to be susceptible for fluoroquinolones.
[b] If oral therapy is appropriate, use other classes of oral antibiotics if organisms are susceptible.
[c] Dose of ciprofloxacin: oral administration, 20 to 40 mg/kg per day, divided every 12 hours (maximum dose: 750 mg per dose); intravenous administration, 20 to 30 mg/kg per day, divided every 8 to 12 hours (maximum dose: 400 mg per dose).
[d] Dose of levofloxacin: oral or intravenous administration, 16 to 20 mg/kg per day divided every 12 hours (for children 6 months to 5 years of age) or 10 mg/kg per day once daily (for children 5 years of age and older) (maximum dose: 750 mg per dose).
[e] Systemic toxicity of fluoroquinolones is not a concern with topical therapy; use of topical agents should be determined according to suspected pathogens, efficacy for mucosal infection, tolerability, and cost.
[f] Other systemic therapy may be required for more severe infection.
[g] Available with and without corticosteroid.

As fluoroquinolone use in pediatrics increases, it is expected that resistance will increase, as has been documented in adults. Appropriate use of fluoroquinolones in children should limit the development and spread of resistance.

USE OF FLUOROQUINOLONES FOR PEDIATRIC INFECTIONS

Conjunctivitis

An increasing number of topical fluoroquinolones have been investigated and approved by the FDA for treatment of acute conjunctivitis in adults and children older than 12 months, including levofloxacin, moxifloxacin, gatifloxacin, ciprofloxacin, and besifloxacin (Table 4). Conjunctival tissue pharmacokinetic evaluation was conducted in healthy adult volunteers; besifloxacin, gatifloxacin, and moxifloxacin were compared by using conjunctival biopsy. All 3 agents reached peak concentrations after 15 minutes.[45] Bacterial eradication and clinical recovery of 447 patients aged 1 through 17 years with culture-confirmed bacterial conjunctivitis was evaluated in a posthoc multicenter study that investigated besifloxacin and moxifloxacin ophthalmic drops.[46] Although better clinical and microbiological response was noted for besifloxacin compared with placebo, similar outcomes were noted when compared with moxifloxacin. Both agents were reported to be well tolerated. Although drug concentrations are only 1 indicator of potential clinical efficacy, the utility of agents with higher concentrations is tempered by the observation of a potential increase in ocular adverse events, such as eye pain,[45] and slower corneal reepithelialization with specific agents.[47]

External Otitis, Tympanostomy Tube–Associated Otorrhea

Recommendations for optimal care for patients with otitis externa were outlined in a review of 19 randomized controlled trials, including 2 from a primary care setting, which yielded 3382 participants. Topical antibiotic agents containing corticosteroids seemed to be more effective than acetic acid solutions. Aminoglycoside-containing otic preparations were reported to cause ototoxicity if the tympanic membrane was not intact; fluoroquinolone-containing preparations represent a safer alternative for treating both otorrhea associated with tympanic membrane perforation and tympanostomy tube otorrhea. Eleven trials included aural toilet as a routine intervention, but the authors acknowledged that this treatment is not likely to be available in a typical primary care office setting.[48] The paucity of high-quality studies of antimicrobial-based topical therapy limited conclusions in this review. A small, prospective, randomized, open-label study of 50 patients with tympanostomy tube–associated otorrhea or a tympanic membrane perforation resulted in comparable outcomes with either topical antibiotic therapy or topical plus systemic antibiotic agents.[49] For children with severe acute otitis externa, systemically administered antimicrobial agents should be considered in addition to topical therapy.[50]

Which topical antibiotic agent is best for external otitis is unclear. High-quality studies that evaluated quinolone versus nonquinolone topical solutions have been limited. A systematic review of 13 meta-analyses confirmed

that topical antibiotic agents were superior to placebo and noted a statistically significant advantage of quinolone agents over nonquinolone agents in the rate of microbiological cure ($P = .035$), although the clinical import of this advantage is likely of limited value. Safety profiles were similar between groups.[50] A conclusion that quinolone and nonquinolone agents are similar in both microbiological and clinical cure rates was reached in a study of more than 200 children, 90 of whom were evaluated for microbiological response in a multicenter, randomized, parallel-group, evaluator-blinded study that compared once-daily ofloxacin drops to 4-times-daily neomycin sulfate/polymyxin B sulfate/hydrocortisone otic suspension. Microbial eradication was documented in 95% and 94%, respectively; clinical cure was achieved in 96% and 97%, respectively. Treatment was well tolerated with both regimens.[51]

Acute Otitis Media, Sinusitis, and Lower Respiratory Tract Infections

Newer fluoroquinolones display enhanced in vitro activity against *S pneumoniae* compared with ciprofloxacin. The clinical need for such agents to treat respiratory tract infections has largely been driven by the emergence of multidrug-resistant strains of this pathogen. Pharmacokinetic data for children 6 months of age and older are well defined for levofloxacin, the only currently available fluoroquinolone that has been studied for respiratory tract infections in children.[52] The pharmaceutical manufacturer is currently not intending to present data to the FDA to obtain approval for the use of levofloxacin for acute bacterial otitis media or community-acquired pneumonia in children (S. Maldonado, Johnson & Johnson, written communication, May 2011).

Acute Bacterial Otitis Media

Clinical studies of levofloxacin and gatifloxacin have been conducted in children with recurrent or persistent otitis media but not simple acute bacterial otitis media. Although the results of studies of several fluoroquinolones have been reported, only levofloxacin is currently available in the United States. A prospective, open-label, noncomparative study of levofloxacin was performed in 205 children 6 months of age and older, 80% of whom were younger than 2 years. Tympanocentesis was performed at study entry and at least at 3 to 5 days into therapy for children for whom treatment failed or who had persistent effusion. Bacterial eradication of middle-ear pathogens occurred in 88% of children, including 84% infected by pneumococci and 100% infected by *Haemophilus influenzae*. Levofloxacin treatment was well tolerated; vomiting in 4% of the patients was documented as the most common adverse effect.[53] An evaluator-blinded, active-comparator, noninferiority, multicenter study that involved 1305 evaluable children older than 6 months and compared levofloxacin to amoxicillin-clavulanate (1:1) found equivalent clinical cure rates of 75% in each treatment arm. However, because tympanocentesis was not required, microbiological cure rates could not be determined.[19]

Pneumonia

Although initially approved by the FDA for the treatment of pneumonia and acute exacerbation of chronic bronchitis in adults, ciprofloxacin therapy has not been uniformly successful in treatment of pneumococcal pneumonia in adults at dosages initially studied 30 years ago. Failures are most likely a result of the increasing pneumococcal resistance to ciprofloxacin and other fluoroquinolones documented since their first approval.[54] Ciprofloxacin is currently not considered appropriate therapy for community-acquired pneumonia in adults.

Fluoroquinolones with enhanced activity against *S pneumoniae* compared with ciprofloxacin (levofloxacin, moxifloxacin, gemifloxacin) have been used in adults for single-drug treatment of community-acquired pneumonia. These "respiratory tract" fluoroquinolones have demonstrated in vitro activity against the most commonly isolated pathogens: *S pneumoniae*, *Haemophilus influenzae* (nontypeable), and *Moraxella catarrhalis*, as well as *M pneumoniae*, *C pneumoniae*, and *Legionella pneumophila*.[55–57] Although these agents are not the drugs of choice for pneumonia in previously healthy adults, they are recommended for adults with underlying comorbidities and for those who have been exposed to antibiotic agents within the previous 3 months and, therefore, are more likely to be infected with antibiotic-resistant pathogens.[58] Failures in the treatment of pneumococcal pneumonia have been reported with levofloxacin at 500 mg daily as a result of emergence of resistance on therapy or resistance from previous exposures to fluoroquinolones.[59] An increased dose of levofloxacin—750 mg daily, given for 5 days—is currently approved by the FDA for adults with pneumonia. The increase in drug exposure at the higher dose is designed to overcome the most common mechanism for the development of fluoroquinolone resistance.[60]

Of the fluoroquinolones, only levofloxacin has been studied prospectively in children with community-acquired pneumonia; efficacy in a multinational, open-label, noninferiority-design trial compared with standard antimicrobial agents for pneumonia was documented. For children aged 6 months to 5 years, levofloxacin (oral or intravenous) was compared with amoxicillin/

clavulanate (oral) or ceftriaxone (intravenous). For children 5 years of age and older, levofloxacin (oral) was compared with clarithromycin (oral), and levofloxacin (intravenous) was compared with ceftriaxone (intravenous) in combination with either erythromycin (intravenous) or clarithromycin (oral). Clinical cure rates were 94.3% in the levofloxacin-treated group and 94.0% in the comparator group, and there were similar rates of cure in both the younger and older age groups. Microbiological etiologies were investigated, and *Mycoplasma* was the most frequently diagnosed pathogen (by serologic testing), representing 32% of those receiving levofloxacin in both older and younger age groups and approximately 30% of those receiving comparator agents in both age groups. Pneumococci were infrequently documented to be the cause of pneumonia in study patients, representing only 3% to 4% of those who received levofloxacin and 3% to 5% of those receiving comparator. It should be noted that the clinical response rate of 83% in children younger than 5 years diagnosed by serologic testing with *Mycoplasma* infection and treated with amoxicillin/clavulanate was similar to that in children treated with levofloxacin (89%), which indicates a high rate of spontaneous resolution of disease caused by *Mycoplasma* species in preschool-aged children, poor accuracy of diagnosis by serologic testing, or a clinical endpoint evaluation after a treatment course that could not identify possible differences in response that may have been present in the first days of therapy.[18]

Although fluoroquinolones may represent effective therapy, they are not recommended for first-line therapy of respiratory tract infection in children, because other better-studied and safer antimicrobial agents are available to treat the majority of the currently isolated pathogens.

Gastrointestinal Infections

Alghasham and Nahata[61] summarized the results of 12 efficacy trials that used a number of fluoroquinolone agents for infections caused by *Salmonella* and *Shigella* species. However, data from only 2 of the 12 trials that compared fluoroquinolones to nonquinolone agents were reported. Patients were treated for typhoid fever (8 studies, including 7 for multidrug-resistant strains), invasive nontyphoid salmonellosis (1 study), and shigellosis (3 studies). Clinical and microbiological success with fluoroquinolone therapy for these infections was similar for children and adults. A recent report suggested caution in the use of fluoroquinolones in visitors returning from India with typhoid fever, because antimicrobial-resistant *Salmonella typhi* strains, including strains with decreased susceptibility to fluoroquinolones, have been noted.[62]

A prospective, randomized, double-blind comparative trial of acute, invasive diarrhea in febrile children was conducted by Leibovitz et al,[63] who compared ciprofloxacin with intramuscular ceftriaxone in a double-dummy treatment protocol. Two hundred and one children were treated and evaluated for clinical and microbiological cure as well as for safety. Pathogens were isolated in 121 children, most commonly *Shigella* and *Salmonella* species. Clinical and microbiological cure were equivalent between groups. No arthropathy was detected during or up to 3 weeks after completion of therapy.[63]

In the United States, although cases of typhoid fever and invasive salmonellosis are uncommon, there are up to 280 000 cases of shigellosis per year, most of which occur in preschool-aged children with relatively mild disease. Treatment is recommended primarily to prevent spread of infection. Ampicillin and TMP-SMX resistance is increasing, and multidrug-resistant strains are becoming common; the National Antimicrobial Resistance Monitoring System (NARMS) reported that 38% of the strains isolated from 1999–2003 were resistant to both ampicillin and TMP-SMX. A 2005 outbreak of multidrug-resistant *Shigella sonnei* infection involving 3 states was reported in the *Morbidity and Mortality Weekly Report*[64]; 89% of the strains were resistant to both agents, but 100% of the strains were susceptible to ciprofloxacin. Treatment options for multidrug-resistant shigellosis, depending on the antimicrobial susceptibilities of the particular strain, include ciprofloxacin, azithromycin, and parenteral ceftriaxone.

Although ciprofloxacin has been regarded as an effective agent for traveler's diarrhea in the past, resistance rates are increasing for specific pathogens in many parts of the world. Resistance in *Campylobacter* species is particularly problematic in countries such as Taiwan, Thailand, and Sweden, where rates of 57%, 84%, and up to 88%, respectively, have been reported.[65,66]

Urinary Tract Infection

Standard empiric therapy for uncomplicated UTI in the pediatric population continues to be a cephalosporin antibiotic agent, because TMP-SMX- and amoxicillin-resistant *E coli* are increasingly common. The fluoroquinolones remain a potential first-line agent only in the setting of pyelonephritis or complicated UTI when typically recommended agents are not appropriate on the basis of susceptibility data, allergy, or adverse-event history. The previous American Academy of Pediatrics policy statement (2006) supported the use of

ciprofloxacin as oral therapy for UTI and pyelonephritis caused by *P aeruginosa* or other multidrug-resistant Gram-negative bacteria in children aged 1 through 17 years and remains current.[3]

Mycobacterial Infections

The fluoroquinolones are active in vitro against mycobacteria, including *M tuberculosis* and many nontuberculous mycobacteria.[58,67] Increasing multidrug resistance in *M tuberculosis* has lead to the increased use of fluoroquinolones as part of individualized, multiple-drug treatment regimens; levofloxacin and moxifloxacin have demonstrated greater bactericidal activity than has ciprofloxacin.[68] Treatment regimens that include fluoroquinolones for 1 to 2 years for multidrug-resistant and extensively drug-resistant tuberculosis have not been prospectively studied in children. However, the benefit of treatment of tuberculosis with an active compound when other active alternatives are not available is greater than the potential for arthropathy. No joint toxicity has yet been reported in children who have received long-term therapy for tuberculosis, but data on safety have not been collected systematically.

Other Uses

Ciprofloxacin is effective in eradicating nasal carriage of *Neisseria meningitidis* (single dose: 500 mg for adults and 20 mg/kg for children older than 1 month), is preferred in nonpregnant adult women, and can be considered for younger patients as an alternative to rifampin, depending on results of a risk/benefit assessment.

Good penetration into the cerebrospinal fluid by certain fluoroquinolones has been reported, and concentrations often exceed 50% of the corresponding plasma drug concentration. In cases of multidrug-resistant Gram-negative meningitis in which no other agents are suitable, fluoroquinolones may represent the only treatment option.[69]

P aeruginosa can cause skin infections (including folliculitis) after exposure to inadequately chlorinated swimming pools or hot tubs. For children who require systemic therapy, fluoroquinolone agents offer an oral treatment option that may be preferred over parenteral nonfluoroquinolone antimicrobial therapy.

SUMMARY

Use of a fluoroquinolone in a child or adolescent may be justified in special circumstances in which (1) infection is caused by a multidrug-resistant pathogen for which there is no safe and effective alternative and (2) the options for treatment include either parenteral nonfluoroquinolone therapy or oral fluoroquinolone therapy, and oral therapy is preferred. In other clinical situations outlined previously, fluoroquinolones may also represent a preferred option (eg, topical fluoroquinolones in the treatment of tympanostomy tube–associated otorrhea) or an acceptable alternative to standard therapy because of concerns for antimicrobial resistance, toxicity, or characteristics of tissue penetration.

No compelling published evidence to date supports the occurrence of sustained injury to developing bones or joints in children treated with available fluoroquinolone agents; however, FDA analysis of ciprofloxacin safety data, as well as posttreatment and 12-month follow-up safety data for levofloxacin, suggest the possibility of increased musculoskeletal adverse effects in children who receive fluoroquinolones compared with agents of other classes. Many drugs in common pediatric use lack specific FDA approval for children. In the case of fluoroquinolones, as is appropriate with all antimicrobial agents, practitioners should verbally review common, anticipated potential adverse events, and indicate why a fluoroquinolone is the most appropriate antibiotic agent for a child's infection.

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