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The Use of Systemic and Topical Fluoroquinolones

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Appropriate prescribing practices for fluoroquinolones, as well as all antimicrobial agents, are essential as evolving resistance patterns are considered, additional treatment indications are identified, and the toxicity profile of fluoroquinolones in children has become better defined. Earlier recommendations for systemic therapy remain; expanded uses of fluoroquinolones for the treatment of certain infections are outlined in this report. Prescribing clinicians should be aware of specific adverse reactions associated with fluoroquinolones, and their use in children should continue to be limited to the treatment of infections for which no safe and effective alternative exists or in situations in which oral fluoroquinolone treatment represents a reasonable alternative to parenteral antimicrobial therapy.

OVERVIEW

Fluoroquinolones are highly active in vitro against both Gram-positive and Gram-negative pathogens, with pharmacokinetic properties that are favorable for treating a wide array of infections. The prototype quinolone antibiotic agent, nalidixic acid, was first 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 represented the prototypic fluoroquinolone approved by the FDA and was available for children 3 months and older, but it is no longer available. Subsequent chemical modifications resulted in a series of fluoroquinolone agents with an increased antimicrobial spectrum of activity and better pharmacokinetic characteristics.

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

Levofloxacin is often referred to as a respiratory fluoroquinolone because it has increased activity against many of the respiratory pathogens, such as *Streptococcus pneumoniae, Mycoplasma pneumoniae,* and *Chlamydophila pneumoniae,* while retaining activity against many of the

abstract

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Gram-negative pathogens. A fourth-generation agent, moxifloxacin, displays increased activity against anaerobes while maintaining Gram-positive and Gram-negative activity and also has excellent activity against *Mycobacterium tuberculosis*; however, there are limited safety and dosing data available in children.

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

A policy statement summarizing the assessment of risks and benefits of fluoroquinolones in pediatric patients was published by the American Academy of Pediatrics (AAP) in 2006, and earlier recommendations remain, with updates as appropriate covered in this document.[3] The statement indicated that the parenteral fluoroquinolones were appropriate for the treatment of infections caused by multidrug-resistant pathogens for which no alternative safe and effective parenteral agent existed. However, for outpatient management, oral fluoroquinolones were only indicated when other options were intravenous (IV) treatment with other classes of antibiotic agents. In 2011, the AAP published an updated clinical report because of the increased ophthalmologic and topical use of fluoroquinolones as well as data on lack of toxicity when used in children.[4]

Quinolones that are currently approved for pediatric patients by the FDA and available in an IV and oral suspension formulation are ciprofloxacin for the indications of inhalational anthrax, plague, complicated urinary tract infections (UTIs), and pyelonephritis and levofloxacin for the indications of inhalational anthrax and plague. A randomized, prospective, double-blind multicenter study of moxifloxacin for complicated intraabdominal infection in children, in which patients were randomly assigned to receive either moxifloxacin plus comparator drug placebo or comparator drug plus moxifloxacin placebo, was completed in July 2015, but no data are available at this time. Systemic quinolones licensed in the United States will be discussed in this report. In addition, this review will contain no discussion of the use of fluoroquinolones in infants younger than 6 months.

SAFETY

Animal Models

The original toxicology studies with quinolones documented cartilage injury in weight-bearing joints in canine puppies, with damage to the joint cartilage proportional to the degree of exposure.[1,2] Each quinolone has a different potential to cause cartilage toxicity,[5] but given a sufficiently high exposure, cartilage changes will occur in all animal models with all quinolones.

Although initial reports focused on articular cartilage, subsequent studies suggested the possibility of epiphyseal plate cartilage injury,[6] leading to fluoroquinolone clinical study designs lasting several years to assess growth potential. 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, resulting in the impairment of integrin function and cartilage matrix integrity in the weight-bearing joints, which undergo chronic trauma during routine use.[7]

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.[8,9] 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 of ciprofloxacin. At this exposure level, the observed clinical signs all occurred during and shortly after treatment but resolved by 2 months after cessation, with no recurrent signs noted during the 5-month follow-up period. Histopathologic evidence of cartilage injury was also observed at 30 mg/kg per day, the dose currently recommended for children, and inflammation occurred in fewer than half the animals at this dose but persisted for 5 months after treatment, at full skeletal maturation. The "no observed adverse event level" (NOAEL) was 10 mg/kg per day, a dose at which neither clinical nor histopathologic evidence of toxicity was present, but a dose too low for therapeutic benefit.

Similar data were developed before FDA approval of levofloxacin for adults, documenting a NOAEL at 3 mg/kg per day for IV dosing for 14 days (approximately one-quarter the current FDA-approved dose of 16 mg/kg per day for children who weigh less than 50 kg). Levofloxacin has virtually 100% bioavailability, with total drug exposure being equivalent between IV and oral formulations at the same milligram per kilogram dose.[10]

Data from a lamb model, with growth rates and activity more closely mirroring humans than juvenile beagle dogs or rats, have been reported. Gross examination of articular cartilage and microscopic examination of epiphyseal cartilage did not reveal abnormalities consistent with cartilage injury or inflammation after a 14-day drug exposure to either gatifloxacin or

TABLE 1 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-week follow-up,[a] n (%)	31 (9.3)	21 (6.0%)
95% CI, %	(–0.8 to 7.2)	
Cumulative arthropathy rate at 1-year follow-up,[a] n (%)	46 (13.7)	33 (9.5%)
95% CI, %	(–0.6 to 9.1)	
Selected musculoskeletal adverse events[b] in patients with arthropathy at 1-year follow-up	Ciprofloxacin n = 46 patients[c]	Comparator n = 33 patients[c]
Arthralgia	35 (76)	20 (61)
Abnormal joint and/or gait examination	11 (24)	8 (24)
Accidental injury	6 (13)	1 (3)
Leg pain	5 (11)	1 (3)
Back pain	4 (9)	0
Arthrosis	4 (9)	1 (3)
Bone pain	3 (7)	0
Joint disorder	2 (4)	0
Pain	2 (4)	2 (6)
Myalgia	1 (2)	4 (12)
Arm pain	0	2 (6)
Movement disorder	1 (2)	1 (3)

Data are from ref 8. CI, confidence interval.

[a] The study was designed to show 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% CI indicated that it could not be concluded that ciprofloxacin had findings comparable to the comparator.

[b] Events occurring in 2 or more patients.

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

ciprofloxacin that was equivalent to that achieved in children receiving therapeutic doses.[11]

Human Studies

In 2004, the FDA released data about the safety of ciprofloxacin[8] from an analysis of clinical trial 100169, which evaluated ciprofloxacin for the treatment of complicated UTI or pyelonephritis in children 1 through 17 years of age. The study was a prospective, randomized, double-blind, active-controlled, parallel-group, multinational, multicenter pediatric trial. Ciprofloxacin oral suspension was compared with oral cefixime or trimethoprim-sulfamethoxazole (TMP-SMX) in 1 stratum, and in the second stratum ciprofloxacin (IV alone or IV followed by oral suspension) was compared with a number of comparator regimens, including IV ceftazidime alone or IV ceftazidime followed by oral cefixime or TMP-SMX. Clinical end points were designed to capture any sign of cartilage or tendon toxicity. Arthropathy rates were 9.3% for ciprofloxacin versus 6% for the comparator group (Table 1).

Adefurin et al[12] performed a systematic review of the safety data for 16 184 pediatric patients treated with ciprofloxacin by using case reports and case series and reported 1065 (6.6%) adverse events. The most frequently reported events were musculoskeletal (24%), followed by abnormal liver function tests (13%), nausea (7%), white blood cell count derangements (5.3%), vomiting (5.2%), and rash (4.7%). Arthralgia (50% of the 258 musculoskeletal adverse events) was the most common musculoskeletal adverse event reported. These data showed an estimated risk of 16 musculoskeletal adverse events per 1000 patients receiving ciprofloxacin (1.6%; 95% confidence interval: 0.9% to 2.6%), or 1 event for every 62.5 patients. All cases of arthropathy resolved or improved with medical management, which included drug withdrawal in some cases, and none of the studies found growth inhibition.

Levofloxacin safety data were collected on a large cohort of 2523 children who participated in prospective, randomized, unblinded clinical efficacy trials. Data were collected from a community-acquired pneumonia trial in children 6 months to 16 years of age (a randomized 3:1, prospective, comparative trial in 533 levofloxacin-exposed and 179 comparator-exposed evaluable subjects) and from 2 trials assessing therapy for acute otitis media in children 6 months to 5 years of age (1 open-label noncomparative study in 204 evaluable subjects and another randomized 1:1, prospective, comparative trial in 797 levofloxacin-exposed and 810 comparator-exposed evaluable subjects).[13] In addition, after completion of the treatment trials, all subjects from both treatment arms were also offered participation in an unblinded, 12-month follow-up study for safety assessments, including musculoskeletal events.

The definitions of musculoskeletal events for tendinopathy (inflammation or rupture of a tendon as determined by physical examination and/or MRI or ultrasonography), 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 because reports of musculoskeletal events and any other adverse events were collected during the follow-up period. An analysis of these events occurred at 1, 2, and 12 months after treatment. The analysis of disorders involving weight-bearing joints documented a statistically greater

rate between the levofloxacin-treated group and comparator group 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, with 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 long-term follow-up study (5 years) in selected subjects from this cohort was published recently.[14] The selection of the children for this long-term follow-up study was based on meeting 1 of the following criteria: (1) growth impaired or possibly growth impaired, defined as a documented height <80% of the expected height increase 12 months after treatment; (2) assessed by the investigator as having abnormal bone or joint symptoms during the original 12-month follow-up; (3) persisting musculoskeletal adverse events at the end of the original 12 months of follow-up; and (4) follow-up requested by the drug safety monitoring committee because of concerns for possible tendon/joint toxicity associated with a protocol-defined musculoskeletal disorder. Of the 2233 subjects participating in the previously described 12-month follow-up study, 124 of 1340 (9%) from the levofloxacin group and 83 of the 893 (9%) subjects in the comparator group were enrolled (207 total subjects), and 49% from each group completed the study. Although an increase in musculoskeletal events in the levofloxacin group had been noted at 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 group (0.1%) than in the levofloxacin group (0.07%). A total of 174 of 207 (84%) reviewed subjects were identified by the growth-impaired or possible growth-impaired criteria. Children from levofloxacin and comparator treatment groups had similar growth characteristics at the 5-year assessment, with equal percentages of children from each treatment group having (1) no change in height percentile, (2) an increase in percentile, or (3) a decrease in percentile. Of the 9 children that had less growth than predicted (6 of 104 [6%] from the levofloxacin group, 3 of 70 [4%] from the comparator group), none were believed by the drug monitoring safety committee to have drug-attributable growth changes. 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.

A rare complication associated with quinolone antibiotic agents, tendon rupture, has a predilection for the Achilles tendon (and is often bilateral) and is estimated to occur at a rate of 15 to 20 per 100 000 treated patients in the adult population.[15] 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. Although rare cases of Achilles tendon rupture can follow overuse injuries in children, to date there have been no reports of Achilles tendon rupture in children in association with quinolone use. In summary, although isolated studies of fluoroquinolone antimicrobial agents have suggested possible musculoskeletal toxicity in children, there is no evidence for long-term harm at this time.

Other potential adverse reactions of fluoroquinolone-class antibiotic agents, although very uncommon in children, include central nervous system adverse effects (seizures, headaches, dizziness, lightheadedness, sleep disorders, hallucinations) and peripheral neuropathy. In data from clinical trial 100169, the rate of neurologic events described were similar between ciprofloxacin-treated and comparator-treated children.[8] Reported rates of neurologic events in the levofloxacin safety database were statistically similar between fluoroquinolone- and comparator-treated children.[16,17]

Cardiotoxicity (see Additional Risks/Conditions), disorders of glucose homeostasis (hypo- and hyperglycemia), hepatic dysfunction, renal dysfunction (interstitial nephritis and crystal nephropathy), and hypersensitivity reactions have also been reported. Practitioners should be aware that fluoroquinolone-associated photosensitivity has been described, and patients should be counseled to use appropriate sun-protection measures. Rashes were more commonly noted in association with the use of >7 days of gemifloxacin in women younger than 40 years.

RESISTANCE

Resistance has been a concern since the approval of quinolone agents, given the broad spectrum of activity and the large number of clinical indications. Multiple mechanisms of resistance have been described, including mutations leading to changes in the target enzymes DNA gyrase and DNA topoisomerase, as well as efflux pumps and alterations

in membrane porins.[18] The role of plasmid-mediated quinolone resistance determinants such as *qnr* genes, continues to increase. The phenotype conferred by these genes generally shows a low-level resistance to fluoroquinolones, but it also appears to encourage additional fluoroquinolone resistance mechanisms that lead to high-level resistance.[19] Several surveillance studies have shown that after the introduction of fluoroquinolones into clinical practice, resistance rapidly develops, although less commonly in pediatric patients given the reduced use of these medications in children. In large-scale pediatric studies of levofloxacin for acute otitis media, the emergence of levofloxacin-resistant pneumococci was not shown after treatment, suggesting that the emergence of resistance during treatment is not a common event.[20] In adult patients, *Pseudomonas* resistance to both fluoroquinolones and other antimicrobial agents is problematic.[21] Data on resistance in *Escherichia 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%,[22] although in specific locations, rates of resistance for outpatients are closer to 10%.[23,24] Similar published data do not exist for children, although in current reports that include outpatient data, stratified by age, rates of fluoroquinolone resistance in *E coli* in children have been generally well below 3%.[24,25]

Recent data from Canadian hospitals revealed that antimicrobial resistance rates continue to be higher in older age groups as compared with children and that there is considerable variability in age-specific resistance trends for different pathogens.[26] Data available from 4 large tertiary care children's hospitals (Houston, Kansas City, San Diego, and Philadelphia) document ciprofloxacin resistance to *E coli* to range from 5% to 14% for 2014 (G.E. Schutze, MD, M.A. Jackson, MD, J. Bradley, MD, and T. Zaoutis, MD, personal communication, 2015) with rates that appear to be stable for the last 3 years. As fluoroquinolone use in pediatrics increases, it is expected that resistance will increase, as has been documented in adults. There is a clear risk of resistance in patients exposed to repeated treatment courses. Susceptibility data in patients with cystic fibrosis revealed a sharp increase in resistance to *Pseudomonas* strains when comparing rates from 2001 and 2011.[27] There is a correlation between fluoroquinolone use and the emergence of ciprofloxacin and levofloxacin resistance among Gram-negative bacilli in hospitalized children.[28] As expected, when the use of the fluoroquinolones (in particular levofloxacin) increased, the susceptibility of Gram-negative bacilli to ciprofloxacin and levofloxacin significantly decreased.[29]

ADDITIONAL RISKS/CONSIDERATIONS

The incidence of *Clostridium difficile*–associated disease in children continues to increase across the United States. The AAP Committee on Infectious Diseases emphasizes the risks related to the development of *C difficile*–associated disease, which includes exposure to antimicrobial therapy.[30] Current data suggest that clindamycin, oral cephalosporins, and fluoroquinolone-class antibiotics are associated with an increased risk of both community-acquired and hospital-acquired *C difficile*–associated disease.[31,32]

Cardiotoxicity of fluoroquinolones is well described in adults and relates to the propensity of such drugs to prolong the QT interval through blockage of the voltage-gated potassium channels, especially the rapid component of the delayed rectifier potassium current I(Kr), expressed by *HERG* (the human ether-a-go-go–related gene). Moxifloxacin has the greatest risk to prolong the QT interval and should be avoided in patients with long QT syndrome, those with hypokalemia or hypomagnesemia, those with organic heart disease including congestive heart failure, those receiving an antiarrhythmic agent from class Ia or class III (eg, quinidine and procainamide or amiodarone and sotaolo, respectively), those who are receiving a concurrent drug that prolongs the QTc interval independently, and those with hepatic insufficiency–related metabolic derangements that may promote QT prolongation. Levofloxacin also appears to prolong the QT interval, although at a lower risk than moxifloxacin. Ciprofloxacin appears to confer the lowest risk.[33] No cases of cardiotoxicity or torsades de pointes in children associated with fluoroquinolones have been reported to date.[34]

USE OF FLUOROQUINOLONES IN PEDIATRIC INFECTIONS

Conjunctivitis

Although most clinicians use a polymyxin/trimethoprim ophthalmologic solution or polymyxin/bacitracin ophthalmic ointment for the treatment of acute bacterial conjunctivitis, an increasing number of topical fluoroquinolones are approved by the FDA for this indication in adults and children older than 12 months, including levofloxacin, ofloxacin, moxifloxacin, gatifloxacin, ciprofloxacin, and besifloxacin (Table 2). Conjunctival tissue pharmacokinetic studies that use conjunctival biopsies in healthy adult volunteers with besifloxacin, gatifloxacin, and moxifloxacin have been performed. All 3 agents reached peak concentrations after 15 minutes.[35] Although drug

TABLE 2 Most Common Infections for Which Fluoroquinolones Are Effective Therapy

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	*S pneumoniae, Mycoplasma pneumoniae* (macrolides preferred for *Mycoplasma* infections)	Levofloxacin[d]
Gastrointestinal infections	*Salmonella* species, *Shigella* species	Ciprofloxacin[c]
Topical antibiotic requirement[e]		
Conjunctivitis	*S pneumoniae, H influenza*	Besifloxacin, levofloxacin, gatifloxacin, ciprofloxacin, moxifloxacin, ofloxacin
Acute otitis externa, tympanostomy tube–associated otorrhea	*P aeruginosa, Staphylococcus aureus*, mixed Gram-positive/Gram-negative organisms	Ciprofloxacin,[f] ofloxacin

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

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,[35] and slower corneal reepithelialization with specific agents.[36] Bacterial eradication and clinical recovery of 447 patients aged 1 through 17 years with culture-confirmed bacterial conjunctivitis were evaluated in a post hoc multicenter study investigating besifloxacin and moxifloxacin ophthalmic drops.[37] Although better clinical and microbiologic response was noted for besifloxacin compared with placebo, similar outcomes were noted when compared with moxifloxacin. Both agents were reported to be well tolerated.

External Otitis, Tympanostomy Tube–Associated Otorrhea

Recommendations for optimal care for patients with otitis externa are outlined in a review of 19 randomized controlled trials, including 2 from a primary care setting, yielding 3382 participants.[38] Topical antibiotic agents containing corticosteroids appeared 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 to treat 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.[38] The paucity of high-quality studies of antimicrobial agent–based topical therapy limited conclusions in this review. A small, prospective, randomized, open-label study in 50 patients with tympanostomy tube otorrhea or a tympanic membrane perforation showed comparable outcomes with either topical antibiotic therapy or topical plus systemic antibiotic agents.[39] For children with severe acute otitis externa, systemically administered antimicrobial agents should be considered in addition to topical therapy.[40]

Which topical antibiotic agent is best for external otitis is unclear.[41] High-quality studies that evaluated quinolone versus nonquinolone topical solutions are 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 microbiologic cure ($P = .035$). Safety profiles were similar between groups.[40] Similarly, Mösges et al[42] reviewed 12 relevant randomized controlled clinical studies involving 2682 patients and concluded that quinolone therapy achieved a higher cure rate ($P = .01$) and superior eradication rate ($P = .03$) than a non–fluoroquinolone-containing antibiotic-steroid combination. The clinical significance of these 2 reviews is reduced, however, when considering that bacterial persistence in the ear canal after treatment does not necessarily imply persistent acute otitis externa symptoms. A conclusion that quinolone and nonquinolone agents are similar in both microbiologic and clinical cure rates was reached in a study in more than 200 children, 90 of whom were evaluated for microbiologic response

in a multicenter, randomized, parallel-group, evaluator-blinded study comparing once-daily ofloxacin drops with a 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.[43] Treatment with fluoroquinolone agents has been well tolerated.

Acute Otitis Media, Sinusitis, and Lower Respiratory Tract Infections

Newer fluoroquinolones show 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, such as serotype 19A pneumococcus. Current otitis media and acute bacterial sinusitis guidelines from the AAP and Pediatric Infectious Diseases Society/Infectious Diseases Society of America guidelines on community-acquired pneumonia in children support the use of levofloxacin as an alternative therapy for those with severe penicillin allergy and for those infected with suspected multidrug-resistant pneumococcus (ie, patients in whom amoxicillin and amoxicillin-clavulanate have failed).[44–46] Pharmacokinetic data for children 6 months and older are well defined for levofloxacin, the only currently available fluoroquinolone studied for respiratory tract infections in children.[47]

Acute Bacterial Otitis Media

Clinical studies of levofloxacin and gatifloxacin have been conducted in children with recurrent or persistent otitis media but in those with not simple acute bacterial otitis media. Although 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 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 who had treatment failure or 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, with vomiting in 4% of patients documented as the most common adverse effect.[48] An evaluator-blinded, active-comparator, noninferiority multicenter study comparing levofloxacin with amoxicillin-clavulanate (1:1) involving 1305 evaluable children older than 6 months documented equivalent clinical cure rates of 75% in each treatment arm. Because tympanocentesis was not required, microbiologic cure rates could not be determined.[17]

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 the treatment of pneumococcal pneumonia in adults at dosages initially studied 30 years ago. Failures are most likely the result of increasing pneumococcal resistance to ciprofloxacin and other fluoroquinolones documented since their first approval.[49] Ciprofloxacin is currently not considered appropriate therapy for community-acquired pneumonia in adults because of its resistance profile.

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 show in vitro activity against the most commonly isolated pathogens: *S pneumoniae, H influenzae* (nontypeable), and *Moraxella catarrhalis* as well as *M pneumoniae, C pneumoniae*, and *Legionella pneumophila*.[50–52] 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 are, therefore, more likely to be infected with antibiotic-resistant pathogens.[53] Failures in the treatment of pneumococcal pneumonia have been reported with levofloxacin at 500 mg daily as a result of the emergence of resistance while receiving therapy or resistance from previous exposures to fluoroquinolones.[54] 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 recognized to overcome the most common mechanism for the development of fluoroquinolone resistance.[55]

Of the fluoroquinolones, only levofloxacin has been studied prospectively in children with community-acquired pneumonia, documenting efficacy in a multinational, open-label, noninferiority-design trial, compared with standard antimicrobial agents for pneumonia.[16] For children 6 months to 5 years of age, levofloxacin (oral or IV) was compared with amoxicillin-clavulanate (oral) or ceftriaxone (IV). For children 5 years and older, levofloxacin (oral) was compared with clarithromycin (oral) and levofloxacin (IV) was compared with ceftriaxone (IV) in combination with either erythromycin (IV) or

clarithromycin (oral). Clinical cure rates were 94.3% in the levofloxacin-treated group and 94.0% in the comparator group, with similar rates of cure in both the younger and older age groups. Microbiologic etiologies were investigated, with *Mycoplasma* being the most frequently diagnosed pathogen, 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 the comparator. Of note, 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%), suggesting 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 end-point evaluation after a treatment course that could not identify possible differences in response that may have been present in the first days of therapy.

Levofloxacin is now recognized as the preferred oral agent for children as young as 6 months of age with highly penicillin-resistant isolates (minimum inhibitory concentration of ≥4 μg/mL).[44] Although fluoroquinolones may represent effective therapy, they are not recommended for first-line therapy for community-acquired respiratory tract infections 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[56] summarized the results of 12 efficacy trials by using a number of fluoroquinolone agents for infections caused by *Salmonella* and *Shigella* species, but only 2 of the 12 trials reported data on fluoroquinolones compared with nonquinolone agents. 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 microbiologic success with fluoroquinolone therapy for these infections was similar when comparing children with adults. Recent data, however, show that fluoroquinolone resistance among isolates responsible for enteric fever in South Asia is very high (>90%), and the use of these drugs has been severely limited because of this.[57,58] Therefore, fluoroquinolones would not be an appropriate option in visitors returning from South Asia with enteric fever.

A prospective, randomized, double-blind comparative trial of acute, invasive diarrhea in febrile children in Israel was conducted by Leibovitz et al[59] comparing ciprofloxacin with intramuscular ceftriaxone in a double-dummy treatment protocol. A total of 201 children were treated and evaluated for clinical and microbiologic cure as well as for safety. Pathogens, most commonly *Shigella* and *Salmonella* species, were isolated in 121 children. Clinical and microbiologic cures were equivalent between groups.[59]

In the United States, although cases of typhoid fever and invasive salmonellosis are uncommon, there are approximately 500 000 cases of shigellosis, with 62 000 of the cases occurring in children younger than 5 years.[60] Treatment is recommended, primarily to prevent the spread of infection. Ampicillin and TMP-SMX resistance is increasing, and multidrug-resistant strains are becoming common; the National Antimicrobial Resistance Monitoring System reported that 38% of strains isolated from 1999 to 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*[61]; 89% of strains were resistant to both agents, but 100% of strains were susceptible to ciprofloxacin. Recently, however, fluoroquinolone resistance has been noted to be increasing at an alarming rate in Asia and Africa, and these resistant isolates are also starting to be seen in the United States as well.[62,63] Treatment options for multidrug-resistant shigellosis, depending on the antimicrobial susceptibilities of the particular strain, include ciprofloxacin, azithromycin, and parenteral ceftriaxone. Nonfluoroquinolone options should be used if available.

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 to *Campylobacter* species is particularly problematic in patients with a history of international travel. Recent data from *Campylobacter* isolates from international travel revealed fluoroquinolone resistance of approximately 61%.[64] Therefore, fluoroquinolones would not be an appropriate option in the treatment of traveler's diarrhea unless a pathogen is defined and antimicrobial susceptibilities are confirmed.

UTI

Standard empirical 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 potential first-line agents 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. AAP policy continues to support the use of ciprofloxacin as oral therapy for UTI and pyelonephritis caused by *P aeruginosa* or other multidrug-resistant Gram-negative bacteria in children 1 through 17 years of age.[3] If ciprofloxacin is started as empirical therapy, but susceptibility data indicate a pathogen that is susceptible to other appropriate classes of antimicrobial agents, the child's therapy can be switched to a nonfluoroquinolone.

Mycobacterial Infections

The fluoroquinolones are active in vitro against mycobacteria, including *M tuberculosis* and many nontuberculous mycobacteria.[53,65] Increasing multidrug resistance in *M tuberculosis* has led to the increased use of fluoroquinolones as part of individualized, multiple-drug treatment regimens, with levofloxacin and moxifloxacin showing greater bactericidal activity than ciprofloxacin.[66] Treatment regimens that include 1 to 2 years of fluoroquinolones for multidrug-resistant and extensively drug-resistant tuberculosis have not been studied prospectively in children. Prevailing evidence supports the use of fluoroquinolones in the treatment of multidrug-resistant tuberculosis infections in children.[67,68] The extended administration of the fluoroquinolones in adults with multidrug-resistant tuberculosis has not shown serious adverse effects, and there is no evidence to date suggesting that this is different in children.[69] A recent study that focused on the use of levofloxacin for tuberculosis infection in an adult liver transplant patient population did show a risk of tenosynovitis in 18% of those treated, highlighting that the clinician needs to be aware that additional risk factors for poor wound healing (patients older than 60 years, those taking corticosteroid drugs, and those with kidney, heart, or lung transplants [black box warning for all fluoroquinolones]) may increase the risk of musculoskeletal adverse effects.[70]

Other Uses

Ciprofloxacin and levofloxacin are among the acceptable antimicrobial agents for use in postexposure prophylaxis against *Bacillus anthracis* as well as for the treatment of many forms of anthrax (eg, cutaneous, inhalation, systemic) in children 1 month or older.[71] Ciprofloxacin is one of the antimicrobial options in postexposure prophylaxis and/or treatment of plague as well.[72,73]

Ciprofloxacin is effective in eradicating nasal carriage of *Neisseria meningitidis* (single dose, 500 mg for adults and 20 mg/kg for those older than 1 month) and preferred in nonpregnant adults. It can also be considered in younger patients as an alternative to 4 days of rifampin if ciprofloxacin-resistant isolates of *N meningitidis* have not been detected in the community.

Good penetration into the cerebrospinal fluid by certain fluoroquinolones (eg, levofloxacin) is reported, and concentrations often exceed 50% of the corresponding plasma drug concentration. In patients with tuberculosis, cerebrospinal fluid penetration, measured by the ratio of the plasma area under the concentration time curve from 0 to 24 to the cerebrospinal fluid area under the curve (0–24), was greater for levofloxacin (median: 0.74; range: 0.58–1.03) than for gatifloxacin (median: 0.48; range: 0.47–0.50) or ciprofloxacin (median: 0.26; range: 0.11–0.77).[74] In cases of multidrug-resistant, Gram-negative meningitis for which no other agents are suitable, fluoroquinolones may represent the only treatment option.

P aeruginosa can cause skin infections (including folliculitis) after exposure to inadequately chlorinated swimming pools or hot tubs. The disease is self-limited and the majority of children will not require antimicrobial therapy, but if they do, oral fluoroquinolone agents offer a treatment option that may be preferred over parenteral nonfluoroquinolone antimicrobial therapy. In addition, fluoroquinolones may be considered as part of an antimicrobial regimen in cases of infections after penetrating skin/soft tissue injuries in the setting of water exposure when *P aeruginosa* or *Aeromonas hydrophila* may play a significant role.

A recent systematic review of empirical fluoroquinolone therapy for children with fever and neutropenia found excellent outcomes with short-term safety. It should be emphasized, however, that these data were from studies in patients with low-risk fever and neutropenia (leukemia/lymphoma), of whom only a small proportion would be expected to have a serious occult bacterial infection.[75] Ongoing investigations will help define the role for these antimicrobial agents in patients with fever and neutropenia.

SUMMARY

Fluoroquinolones are broad-spectrum agents that should be considered selectively for use in a child or adolescent for specific clinical situations, including the following: (1) infection caused by a multidrug-resistant pathogen for which there is no safe and effective alternative and (2) 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. If a fluoroquinolone is selected for therapy on the basis of the above considerations, practitioners should be aware that both ciprofloxacin and levofloxacin are costly.

Although adverse reactions are uncommon, because of the potential for risks of peripheral neuropathy, central nervous system effects, and cardiac, dermatologic, and hypersensitivity reactions in adults, in July 2016 the FDA added a safety announcement with updated box warnings restricting use of fluoroquinolone antibiotics in adults with acute sinusitis, acute bronchitis, and uncomplicated UTI to situations in which no other alternative treatment is available. 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 suggests the possibility of increased musculoskeletal adverse events. Although studies were not blinded, with the potential for bias, children treated with levofloxacin both immediately after treatment and at a 12-month follow-up had an increased rate of musculoskeletal complaints but no physical evidence of joint findings. However, 5 years after treatment, no differences were seen between levofloxacin-treated and comparator-treated children. In the case of fluoroquinolones, as is appropriate with all antimicrobial agents, prescribing clinicians should verbally review common, anticipated, potential adverse events, such as rash, diarrhea, and potential musculoskeletal or neurologic events, and indicate why a fluoroquinolone is the most appropriate antibiotic agent for a child's infection.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
FDA: Food and Drug Administration
IV: intravenous
TMP-SMX: trimethoprim-sulfamethoxazole
UTI: urinary tract infection

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The Use of Systemic and Topical Fluoroquinolones

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