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Fluoroquinolone Antibiotics in Infants and Children

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Despite class label warnings against use in children, prescriptions for quinolone antibiotics to treat infections in children have become increasingly prevalent. Many of the characteristics of the contemporary fluoroquinolones, the derivatives of the first quinolone antibiotic, nalidixic acid, are particularly appealing for certain pediatric populations. The fluoroquinolones are rapidly bactericidal and have an extended antimicrobial spectrum that includes *Pseudomonas,* gram-positive cocci, and intracellular pathogens. They have advantageous pharmacokinetic properties, such as absorption from the gastrointestinal tract, excellent penetration into many tissues, and good intracellular diffusion. These antimicrobials have been effective in the treatment or prevention of a variety of bacterial infections in adults, including infections of the respiratory and urinary tracts, skin and soft tissue, bone and joint, and eye and ear. Overall, fluoroquinolones are generally well tolerated; the most frequent adverse events during treatment are gastrointestinal disturbances, reactions of the central nervous system, and skin reactions [1,2].

The use of fluoroquinolones in children has been limited because of their potential to induce arthropathy in juvenile animals [3–5]. This extraordinary form of age-related drug toxicity has been shown with all the fluoroquinolones tested so far and has led to important restrictions: Their use has been considered to be contraindicated in children, in growing adolescents, and in women during pregnancy and lactation. Since the mid-1980s, many children have received treatment with fluoroquinolones (mainly ciprofloxacin), however, because they are the only oral antimicrobials with potential activity against such multiply resistant and difficult-to-treat infections as *Pseudomonas aeruginosa* infections in children with cystic fibrosis, complicated urinary tract infections, and enteric infections in developing countries. Results of these trials indicate that prolonged therapy with the fluoroquinolones is effective

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and well tolerated in pediatric patients, with no significant evidence of arthropathy, bone abnormalities, or other serious adverse events [6]. Besides feared arthrotoxicity, the second major concern regarding use of fluoroquinolones in children is the potential impact on bacterial resistance development [6].

Quinolone arthropathy

History

Soon after the marketing of nalidixic acid in 1962, a child with soreness in one wrist during therapy for urinary tract infection was described [7]. Nalidixic acid was not initially contraindicated in children, but approved for use in children with urinary tract infections in March 1964. Eight years later, another report described a 22-year-old woman who developed severe polyarthritis during a second course of nalidixic acid [8]. These "incapacitating" cases of arthralgia/arthritis were considered as allergic manifestations. Data on file of the manufacturers were cited to contain "about a dozen such reports." These clinical observations with nalidixic acid prompted experimental exposure of laboratory animals to quinolone compounds. The first observations of quinolone-induced cartilage toxicity made with nalidixic, oxolinic, and pipemidic acid administration to young beagle dogs were reported by Ingham et al in 1977 [9], Tatsumi et al in 1978 [10], and Gough et al in 1979 [3].

Use of nalidixic acid in children

Four groups performed a retrospective matched control search for cartilage toxicity in pediatric patients who had received nalidixic acid therapy, in most cases for acute or recurrent urinary tract infections [11–14]. Details of patients and therapies are shown in Table 1. History of symptoms and clinical/radiologic examinations compatible with possible arthropathies

Table 1
Retrospective matched control search for cartilage toxicity in nalidixic acid–treated pediatric patients: details of patients and therapies

Investigators, country	Year of report	No. patient pairs	Age at therapy (y)[a]	Duration of Nalidixic acid therapy (d)[a]	Follow-up time (y)[a]
Schaad, et al Switzerland [11]	1987	11	0.3–9.6 (1.4)	9–600 (17)	3–12 (8)
Rumler and von Rodhden, Germany [12]	1987	201	1–7.2 (6.5)	27–1689 (168)	≥2
Adam, Germany [13]	1989	50	0.1–11 (4.8)	10–815 (118)	≥2
Nuutinen et al, Finland [14]	1994	39	0.3–10.1 (5.3)	6–570 (86)	15–25 (20)

[a] Ranges (mean value).

was recorded, and at follow-up examination growth curves and functional and radiologic joint findings were obtained. The results were similar in the index and control cases. All reports concluded that nalidixic acid does not cause arthropathy in children, even after long-term and high-dose therapy.

Animal experiments

All quinolones tested, including the older compounds and the newer derivatives, have been shown to induce changes in immature cartilage of weight-bearing joints in all laboratory animals tested (mice, rats, dogs, marmosets, guinea pigs, rabbits, and ferrets) [2,4,5,15]. Quinolone-induced arthropathy is limited to juvenile animals except when pefloxacin has been used. Juvenile dogs are generally more sensitive to the arthropathic effects of quinolones than are other species. Healing of quinolone-induced arthropathy is incomplete even after complete clinical recovery; structural changes are at least in part irreversible.

Typical histopathologic lesions after quinolone exposure include fluid-filled blisters, fissures, erosions, and clustering of chondrocytes, usually accompanied by noninflammatory joint effusion. Under the electron microscope, necrosis of the chondrocytes and swelling of the mitochondria are observed initially, followed by disruption of extracellular matrix [16]. Loss of collagen and glycosaminoglycan is an early sequela to the degeneration of chondrocytes [17]. When clinically manifested, the quinolone-induced joint lesions present as acute arthritis, including limping and swelling. The specific mechanism responsible for the initiation of quinolone-induced arthropathy has not been determined. At present, inhibition of mitochondrial DNA replication [18] and the role of magnesium deficiency [19,20] are the most discussed hypotheses.

Neither pharmacokinetic nor pharmacodynamic data can explain the variable arthropathic ''power'' of different compounds. There also is no clear effect of the molecular structure of the given compound regarding its cartilage toxicity (e.g., quinolones that are fluorinated versus quinolones that are not fluorinated).

Possible monitoring for quinolone-induced cartilage toxicity in patients

The available methods for monitoring for quinolone-induced cartilage toxicity are the following:

- Histopathology—the gold standard [21]
- MRI—the parameters are surface, thickness, and structure of cartilage; presence of effusion (especially recessus suprapatellaris); and bone/cartilage integrity [22–24]; predictive value of MRI has been shown in studies with rabbits, pigs, and dogs [25]
- Sonography—measurement includes presence/absence of effusion and thickness and surface of cartilage [23–26]

- Clinical examination—indicating symptoms and signs would be arthralgia, limping, and joint swelling and for long-term follow-up growth rate; in many animal experiments, cartilage toxicity was documented without any clinical manifestation

Review of published data

A comprehensive review of published reports including monitoring for quinolone-induced cartilage toxicity in patients was performed [27–32]. The reviewed studies included all case reports of suspected quinolone-associated arthralgia/arthropathy in children and adolescents and all multipatient studies on the use of quinolone compounds in skeletally immature patients (open-label and controlled trials) in which there were data on safety, especially regarding potential arthropathy. Most of the data were based on clinical findings—musculoskeletal complaints and joint examination. Such findings do not allow one to distinguish between coincidental joint problems and quinolone-induced arthropathy. As outlined before, only rarely MRI, ultrasonography, and growth curve have been used for either short-term or long-term evaluation. With the exception of the findings in two cystic fibrosis patients [21], the gold standard parameter ''histopathology'' is lacking. There are four conclusions:

1. To date, there is no unequivocal documentation of quinolone-induced arthropathy in patients as described in juvenile animals; quinolone arthropathy remains an experimental laboratory phenomenon in juvenile animals.
2. Clinical observations temporally related to quinolone use are reversible episodes of arthralgia with and without effusions that do not lead to long-term sequelae when treatment with the agents is discontinued.
3. Most joint complaints associated with quinolone use are coincidental and do not represent adverse effects. Possible coincidental conditions include arthropathy and hypertrophic pulmonary osteoarthropathy associated with cystic fibrosis [33] and reactive, traumatic, and rheumatic joint diseases.
4. It is postulated that the so-called allergic arthritis initially described in nalidixic acid–treated patients does exist but is not the same as the quinolone-induced arthropathy in animals. These adverse events are always transient arthralgic or arthritic manifestations, usually involving large joints and occurring during the first and second week of therapy. The overall incidence is 1% to 3% (−18%) depending on the studied patient group and quinolone compound.

Tendinopathy

Other musculoskeletal adverse effects of quinolones are tendinitis and tendon rupture. Clinical information on quinolone-induced tendinopathy is

relatively scarce. Review of the literature on fluoroquinolone-associated tendinopathy [34–37] reveals the following. The incidence in a healthy population is very low, especially in children [36]. In most cases, the Achilles tendon is affected with symptoms compatible with painful tendinitis or with rupture—usually occurring during the second week of treatment. Fluoroquinolone-associated tendinopathy increases in patients who have renal dysfunction (hemodialysis, after renal transplantation). There is a correlation between long-term cortical steroid therapy and age 60 years or older; the male-to-female ratio is approximately 2:1.

Development of bacterial resistance

As mentioned before, there is great concern regarding the potential impact of widespread fluoroquinolone use in children on bacterial resistance development [6,15,30,38,39]. Historically, antimicrobial use has led to the development of drug resistance. The relevant drivers are overuse (volume of antibiotic used in humans and in animals), misuse (inappropriate use), clonal spread (global travel, hygiene, hospital, daycare, family, switch of serotypes), and type of antibiotic. Overuse (eg, for viral infection, as prophylaxis, many veterinarian indications) reflects inadequate knowledge of the prescribing physician and unavailability of diagnostic methods. Appropriate use (avoidance of misuse) includes not only classic selection of an optimal, antibiotic but also individual optimization of dosage and duration of therapy. Well-defined antibiotic policies, good hygiene measures, and strong infection control programs represent key points for limiting the spread of antibiotic resistance.

Bacteria can become resistant to quinolones by mutations in the target molecules (gyrase protein, topoisomerase) or by active drug efflux. With regard to quinolone resistance, great variations exist between bacterial species, clinical settings, and local epidemiology. Resistance is the phenotypic expression corresponding to genetic changes caused by either mutation or acquisition of new genetic information. In some cases, multidrug resistance occurs. *Streptococcus pneumoniae* is one of the most important respiratory pathogens, playing a major role in upper and lower respiratory tract infections. Pneumococcal resistance to antimicrobials may be acquired by means of horizontal transfer followed by homologous recombination of genetic material from the normal flora of the human oral cavity or by means of mutation. Resistance in pneumococci to penicillins and macrolides has been increasing for some time, but more recently fluoroquinolone resistance has become an issue as well [40,41]. Fluoroquinolone resistance is not limited to *S pneumoniae* and has been documented in other pathogens, including those responsible for urinary, respiratory, and gastrointestinal tract infections; skin and soft tissue and bone and joint infections; sexually transmitted diseases; and ulcers [38,39].

Evidence is accumulating that multidrug resistance in pneumococci is related to prescription of antimicrobial agents to a crucial reservoir of these organisms—children. This multidrug resistance likely occurs because children, more often than adults, are colonized with high-density populations of pneumococci in the nasopharynx, which increases the potential for resistance development [38]. Supporting this concern are studies of daycare centers and pediatric long-term care centers that have found a very high prevalence of nasopharyngeal carriage of drug-resistant strains of *S pneumoniae* [42,43]. Overcrowding facilitates the transmission of resistance strains from colonized to susceptible infants and children, who serve as a source for further transmission to family members and ultimately to the general population [44].

A new concern about widespread use of fluoroquinolones to treat children and adults is the recognition of horizontal transfer of fluoroquinolone resistance from viridans group streptococci (eg, *S oralis* and *S mitis*) to *S pneumoniae* [45,46]. When resistance mutations develop in these naturally commensal organisms as a result o fluoroquinolone exposure (even in the absence of pathogenic pneumococci), any subsequent pneumococcal infection carries the risk that the infecting strain of *S pneumoniae* will readily acquire fluoroquinolone resistance–determining DNA regions when antimicrobial therapies are instituted. These fluoroquinolone-resistant *S pneumoniae* can be spread easily from child to parent, followed by widespread dissemination to the adult population. The dangerous triad of antibiotic overuse and misuse, a reservoir of resistant genes, and a closed-space pneumococcal infection (eg, otitis media) could come together with widespread, uncontrolled use of fluoroquinolones in pediatric patients [38].

Pharmacology

The pharmacokinetic data on fluoroquinolones in pediatric patients are limited, and for neonatal patients, the data are anecdotal only [47–51]. The results of available studies, most of which were conducted in cystic fibrosis patients, indicate that systemic clearance is increased in young children; this has led to recommendations for higher doses as shown in Table 2. In

Table 2
Current dosage recommendations

Drug	Route	Dose (mg/kg)	No. doses/day	Maximum daily dose (mg)
Ciprofloxacin	PO	15–20	2	1500
	IV	10–15	2	800
Ofloxacin[a]	PO	7.5	2	800
	IV	5	2	600
Norfloxacin[b]	PO	10–15	2	800

[a] Most pediatric experience in cystic fibrosis patients.
[b] Most pediatric experience in urinary tract infections.

general, fluoroquinolones are absorbed rapidly from the gastrointestinal tract. The range for bioavailability is vast, however, with norfloxacin being 10% to 30% and ofloxacin 80% to 90%. All of the newer compounds except norfloxacin have excellent tissue and intracellular penetration at the recommended therapeutic doses. Quinolones generally are excreted either predominantly in the urine (often as parent compound) or through the bile, in which some undergo enterohepatic recirculation.

Potential indications

Established use

Since the mid-1980s, fluoroquinolones have been used in pediatric patients primarily in circumstances where they were the only antimicrobial choice for infections caused by multiply-resistant organisms [6,15,30]. These included pseudomonal infections in children with cystic fibrosis [23,26,31,51,52], complicated urinary tract infections [53,54], enteric infections in developing countries [27,55,56], and chronic ear infections [57]. Results of controlled clinical trials in patients with these four indications have shown comparable efficacy of the fluoroquinolones and conventional regimens.

Preliminary experience in pediatric patients also indicates that the fluoroquinolones are effective and safe for the prevention or therapy of infections in neutropenic cancer patients [58,59] and for the eradication of nasopharyngeal carriage of meningococci [60]. Fluoroquinolones also have been used successfully when severe infections, including meningitis during the neonatal period, are due to enterobacteria resistance to standard treatment [32,61].

Future use

Research on chemical modifications of the quinolones has been aimed at (1) more potent derivatives, (2) less frequent resistance, (3) better penetration into cerebrospinal fluid, and (4) improved patient tolerability. Some of the newer compounds have achieved many of these goals.

Of major interest for pediatricians are the effective cerebrospinal fluid penetration and the excellent in vitro activity of the new fluoroquinolones against the pathogens that commonly cause bacterial meningitis in children older than 3 months of age, including strains of *S pneumoniae* resistant to β-lactams and to other antibiotics. Based on efficacy data in experimental animals and good cerebrospinal fluid penetration data in humans, a large multicenter, randomized, clinical trial was conducted in children with bacterial meningitis to compare the safety and efficacy of trovafloxacin with that of ceftriaxone with or without vancomycin therapy [62]. This study was terminated earlier than planned because of concerns regarding potential, life-threatening liver toxicity associated with the use of trovafloxacin in

adults with severe infections. Of the initially planned 284 children to be evaluable, only 203 (71%) were available for analysis at the time of trial closure. Although optimal statistical power required to draw firm conclusions was not reached, study results suggested that trovafloxacin is therapeutically equivalent to ceftriaxone with or without vancomycin for the management of bacterial meningitis in infants and children. Rates of bacterial eradication, cure, severe sequelae, and death were similar for both treatment groups at the end of treatment and at follow-up assessments. Future trials with other new fluoroquinolone compounds are warranted in pediatric patients with meningitis, but they will be difficult to conduct in view of the risk of rare side effects and possible treatment delays, which are a more important factor than resistance in the occurrence of sequelae.

Other potential future uses of newer fluoroquinolone compounds include childhood otitis media [63]. Increased resistance of pneumococci and other pathogens to available antibiotics raises concerns about bacteriologic and clinical failure in children with acute otitis media. Few therapeutic options exist for patients with recurrent infections or recent treatment failure. The good efficacy of the fluoroquinolone gatifloxacin in pediatric patients with refractory acute otitis media was shown in two trials [64,65]. For recurrent otitis media and otitis media treatment failure, the new fluoroquinolones seem to fill an unmet need.

Summary

The two major concerns regarding use of fluoroquinolones in children are development of bacterial resistance and cartilage toxicity as described in juvenile animals. The risk for rapid emergence of resistance among pneumococci and other common bacterial pathogens, associated with widespread, uncontrolled use of fluoroquinolones in pediatric patients, is a realistic threat. Cartilage toxicity with fluoroquinolones is a laboratory phenomenon in juvenile animals, and no arthropathy has been documented unequivocally in the large numbers of children treated with these agents. Nevertheless, expectant observation is warranted for any new quinolone use in pediatric patients.

Based on available data showing the safety and efficacy of the fluoroquinolones, selected pediatric patients should not be deprived of the therapeutic advantages that these agents have to offer. The quinolones should never be used in pediatric patients for routine treatment, however, when alternative safe and effective antimicrobials are known. To date, established pediatric indications for the fluoroquinolones include bronchopulmonary exacerbation in cystic fibrosis, complicated urinary tract infection, invasive gastrointestinal infection, and chronic ear infection. Potential pediatric indications are bacterial meningitis and refractory acute otitis media.

In most countries, fluoroquinolones so far are approved for use only in pediatric patients with cystic fibrosis and complicated urinary tract infection.

Authorization for broader use of new fluoroquinolones in children must combine efforts of experts in microbiology and infectious diseases, regulatory authorities, and pharmaceutical manufacturers. Postmarketing surveillance must include an adequate risk management plan feasible for patients, parents, and drug companies.

The fluoroquinolones must continue to serve mainly for second-line use in children, only after failure of an earlier treatment and when other antibiotics approved for pediatrics cannot be used. These guidelines would ensure that these agents remain effective for selected infants and children with difficult-to-treat infections.

References

[1] Stahlmann R. Safety profile of the quinolones. J Antimicrob Chemother 1990;26(Suppl D): 31–44.
[2] Stahlmann R, Lode H. The quinolones—safety overview: toxicity, adverse events, and drug interactions. In: Andriole VT, editor. The quinolones. London: Academic Press; 1988. p. 201–3.
[3] Gough A, Barsoum NJ, Mitchell L, McGuire EJ, de la Iglesia FA. Juvenile canine drug-induced arthropathy: clinicopathological studies on articular lesions caused by oxolinic and pipemidic acids. Toxicol Appl Pharmacol 1979;51:177–87.
[4] Christ W, Lehnert T, Ulbrich B. Specific toxicologic aspects of the quinolones. Rev Infect Dis 1988;10(Suppl 1):141–6.
[5] Schluter G. Ciprofloxacin: toxicologic evaluation of additional safety data. Am J Med 1989; 87(Suppl 5A):37–9.
[6] Schaad UB, Salam MA, Aujard Y, et al. Use of fluoroquinolones in pediatrics: consensus report of an International Society of Chemotherapy commission. Pediatr Infect Dis J 1995; 14:1–9.
[7] McDonald DF, Short HB. Usefulness of nalidixic acid in treatment of urinary tract infections. Antimicrob Agents Chemother 1964;64:628–31.
[8] Bailey RR, Natale R, Linton AL. Nalidixic acid arthralgia. Can Med Assoc J 1972;107: 604–7.
[9] Ingham B, Brentnall DW, Dale EA, McFadzean JA. Arthropathy induced by antibacterial fused n-alkyl-4-pyrodoine-3-carboxylic acids. Toxicol Lett 1977;1:21–6.
[10] Tatsumi H, Senda H, Yatera S, Takemoto Y, Yamayoshi M, Onishi K. Toxicological studies on pipedimic acid: V. effect on diarthrodial joints of experimental animals. J Toxicol Sci 1978;3:357–67.
[11] Schaad UB, Wedgwood-Krucko J. Nalidixic acid in children: retrospective matched controlled study for cartilage toxicity. Infection 1987;15:165–8.
[12] Rumler W, von Rodhden L. Does nalidixic acid produce joint toxicity in childhood? In: Book of Abstracts of the 15th International Congress of Chemotherapy, Istanbul, Turkey; 1987. p. 1029–31.
[13] Adam D. Use of quinolone in pediatric patients. Rev Infect Dis 1989;11(Suppl 5):S1113–6.
[14] Nuutinen M, Turtinen J, Uhari M. Growth and joint symptoms in children treated with nalidixic acid. Pediatr Infect Dis J 1994;13:798–800.
[15] Schaad UB. Use of the quinolones in pediatrics. In: Andriole VT, editor. The Quinolones. 3rd ed. San Diego: Academic Press; 2000. p. 455–75.
[16] Stahlmann R, Merker HJ, Hinz N, Chahoud I, Webb J, Neubert D. Ofloxacin in juvenile non-human primates and rats: arthropathia and drug plasma concentrations. Arch Toxicol 1990;64:193–204.

[17] Burkhardt JE, Hill MA, Carlton WW. Morphologic and biochemical changes in articular cartilages of immature beagle dogs dosed with difloxacin. Toxicol Pathol 1992;20:246–52.
[18] Kato M, Takada S, Ogawara S, Takayama S. Effect of levofloxacin on glycosaminoglycan and DNA synthesis of cultured rabbit chondrocytes at concentrations inducing cartilage lesions in vivo. Antimicrob Agents Chemother 1995;39:1979–83.
[19] Forster C, Kociok K, Shakibaei M, et al. Integrins on joint cartilage chondrocytes and alterations by ofloxacin or magnesium deficiency in immature rats. Arch Toxicol 1996;70: 261–70.
[20] Vormann J, Forster C, Zippel U, et al. Effects of magnesium deficiency on magnesium calcium content in bone and cartilage in developing rats in correlation to chondrotoxicity. Calcif Tissue Int 1997;61:230–8.
[21] Schaad UB, Sander E, Wedgwood J, Schaffner T. Morphologic studies for skeletal toxicity after prolonged ciprofloxacin therapy in two juvenile cystic fibrosis patients. Pediatr Infect Dis J 1992;11:1047–9.
[22] Schaad UB, Stoupis C, Wedgwood J, Tschaeppeler H, Vock P. Clinical, radiologic and magnetic resonance monitoring for skeletal toxicity in pediatric patients with cystic fibrosis receiving a three-month course of ciprofloxacin. Pediatr Infect Dis J 1991;10:723–9.
[23] Richard DA, Nousia-Arvanitakis S, Sollich V, Hampel B, Sommerauer B, Schaad UB, and the Cystic Fibrosis Study Group. Oral ciprofloxacin versus intravenous ceftazidime plus tobramycin in pediatric cystic fibrosis patients: comparison of antipseudomonas efficacy and assessment of safety using ultrasonography and magnetic resonance imaging. Pediatr Infect Dis J 1997;16:572–8.
[24] Arico M, Bossi G, Caselli D, et al. Long-term magnetic resonance survey of cartilage damage in leukemic children treated with fluoroquinolones. Pediatr Infect Dis 1995;14:713–4.
[25] Gylys-Morin VM, Hajek PC, Sartoris DJ, Resnick D. Articular cartilage defects: detectability in cadaver knees with MR. Am J Radiol 1987;148:1153–7.
[26] Church DA, Kanga JF, Kuhn RF, et al. Sequential ciprofloxacin therapy in pediatric cystic fibrosis: comparative study vs. ceftazidime/tobramycin in the treatment of acute pulmonary exacerbations. Pediatr Infect Dis J 1997;16:97–105.
[27] Pradhan KM, Arora NK, Jena A, Susheela AK, Bhan MK. Safety of ciprofloxacin therapy in children: magnetic resonance images, body fluid levels of fluoride and linear growth. Acta Paediatr 1995;84:555–60.
[28] Bethell DB, Hien TT, Phi LT, et al. Effects on growth of single short courses of fluoroquinolones. Arch Dis Child 1996;74:44–6.
[29] Burkhardt JE, Walterspiel JN, Schaad UB. Quinolone arthropathy in animals versus children. Clin Infect Dis 1997;25:1196–204.
[30] Gendrel D, Chalumeau M, Moulin F, Raymond J. Fluoroquinolones in paediatrics: a risk for the patient or for the community? Lancet Infect Dis 2003;3:537–46.
[31] Chalumeau M, Tonnelier S, d'Athis P, et al. Fluoroquinolone safety in pediatric patients: a prospective, multicenter, comparative cohort study in France. Pediatrics 2003;111: e714–9.
[32] Drosso-Agakidou V, Roilides E, Papakyriakidou-Koliouska P, et al. Use of ciprofloxacin in neonatal sepsis: lack of adverse effects up to one year. Pediatr Infect Dis J 2004;23:346–9.
[33] Phillips BB, David T. Pathogenesis and management of arthropathy in cystic fibrosis. J R Soc Med 1996;79(Suppl 12):44–50.
[34] van der Linden PD, van de Lei J, Nab HW, Knol A, Stricker BH. Achilles tendinitis associated with fluoroquinolones. Br J Clin Pharmacol 1999;48:433–7.
[35] van der Linden PD, Sturkenboom MCJM, Herings RMC, Leufkens HGM, Stricker BH. Fluoroquinolones and risk of Achilles tendon disorders: case-control study. BMJ 2002;324: 1306–7.
[36] Yee CL, Duffy C, Gerbino PG, Stryker S, Noel GJ. Tendon or joint disorders in children after treatment with fluoroquinolones or azithromycin. Pediatr Infect Dis J 2002;21: 525–9.

[37] Khaliq Y, Zhanel GG. Fluoroquinolone-associated tendinopathy: a critical review of the literature. Clin Infect Dis 2003;36:1404–10.
[38] Mandell LA, Peterson LR, Wise R, et al. The battle against emerging antibiotic resistance: should fluoroquinolones be used to treat children? Clin Infect Dis 2002;35:721–7.
[39] Hooper DC. New uses for new and old quinolones and the challenge of resistance. Clin Infect Dis 2000;30:243–54.
[40] Chen DK, McGeer A, De Azavedo JC, Low DE. Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. N Engl J Med 1999;341:233–9.
[41] Ho PL, Yung RW, Tsang DN, et al. Increasing resistance of *Streptococcus pneumoniae* to fluoroquinolones: results of a Hong Kong multicentre study in 2000. J Antimicrob Chemother 2001;48:659–65.
[42] Yagupsky P, Porat N, Fraser D, et al. Acquisition, carriage, and transmission of pneumococci with decreased antibiotic susceptibility in young children attending a day care facility in southern Israel. J Infect Dis 1998;177:1003–12.
[43] Mannheimer SB, Riley LW, Roberts RB. Association of penicillin-resistant pneumococci with residence in a pediatric chronic care facility. J Infect Dis 1996;174:513–9.
[44] Kronenberger CB, Hoffmann RE, Lezotte DC, Marine WM. Invasive penicillin-resistant pneumococcal infections: a prevalence and historical cohort study. Emerg Infect Dis 1996;2: 121–4.
[45] Gonzales J, Georgiou M, Alcaide F, Balas D, Linares J, de la Campa AG. Fluoroquinolone resistance mutations in the parC, parE, and gyrA genes of clinical isolates of viridans group streptococci. Antimicrob Agents Chemother 1998;42:2792–8.
[46] Ferrandiz MJ, Fernoll A, Linares J, de la Campa AG. Horizontal transfer of parC and gyrA in fluoroquinolone-resistant clinical isolates of *Streptococcus pneumoniae*. Antimicrob Agents Chemother 2000;44:840–7.
[47] Blumer JL, Stern RC, Myers CM, et al. Pharmacokinetics and pharmacodynamics of ciprofloxacin in cystic fibrosis. Abstracts of 14th Internationl Congress on Chemotherapy, Kyoto, 1985.
[48] Stutman HR, Shalit I, Marks MI, Greenwood R, Chartrand SA, Hillman BC. Pharmacokinetics of two dosage regimens of ciprofloxacin during a two-week-therapeutic trial in patients with cystic fibrosis. Am J Med 1987;82(Suppl 4A):142–5.
[49] Peltola H, Vaarala M, Renkonen O, Neuvonen PJ. Pharmacokinetics of single dose of oral ciprofloxacin in infants and small children. Antimicrob Agents Chemother 1992;36: 1086–90.
[50] Schaeffer HG, Strass H, Wedgwood J, et al. Pharmacokinetics of ciprofloxacin in pediatric cystic fibrosis patients. Antimicrob Agents Chemother 1996;40:29–34.
[51] Rubio TT, Miles MV, Lettiere JT, Kuhn RJ, Echols RM, Church DA. Pharmacokinetic disposition of sequential intravenous/oral ciprofloxacin in pediatric cystic fibrosis patients with acute pulmonary exacerbation. Pediatr Infect Dis J 1997;16:112–7.
[52] Schaad UB, Wedgwood J, Ruedeberg A, Kraemer R, Hampel B. Ciprofloxacin as antipseudomonal treatment in patients with cystic fibrosis. Pediatr Infect Dis J 1997;16: 106–11.
[53] Fujii R. The use of norfloxacin in children in Japan. Adv Antineopl Chemother 1992;11: 219–32.
[54] Koyle MA, Barqawi A, Wild J, Passamaneck M, Furness PD. Pediatric urinary tract infections: the role of fluoroquinolones. Pediatr Infect Dis J 2003;22:1133–7.
[55] Green S, Tillotson G. Use of ciprofloxacin in developing countries. Pediatr Infect Dis J 1997; 16:150–9.
[56] Salam MA, Dhar U, Khan WA, Bennish ML. Randomised comparison of ciprofloxacin suspension and pivmecillinam for childhood shigellosis. Lancet 1998;352:522–7.
[57] Lang R, Goshen S, Raas-Rothschild A. Oral ciprofloxacin in the management of chronic suppurative otitis media without cholesteatoma in children. Pediatr Infect Dis J 1992;11: 925–9.

[58] Freifeld A, Pizzo P. Use of fluoroquinolones for empirical management of febrile neutropenia in pediatric cancer patients. Pediatr Infect Dis J 1997;16:140–6.
[59] Patrick CC. Use of fluoroquinolones as prophylaxis agents in patients with neutropenia. Pediatr Infect Dis J 1997;16:135–9.
[60] Cuevas LE, Kazembe P, Mughogho GK, Tilloston GS, Hart CA. Eradication of nasopharyngeal carriage of *Neisseria meningitidis* in children and adult in rural Africa: a comparision of ciprofloxacin and rifampicin. J Infect Dis 1995;171:728–31.
[61] Krcmery V, Filka J, Uher J, et al. Ciprofloxacin in treatment of nosocomial meningitis in neonates and in infants: report of 12 cases and review. Diag Microbiol Infect Dis 1999;35: 75–80.
[62] Saez-Llorens X, Mccoig C, Feris JM, et al. Quinolone treatment for pediatric bacterial meningitis: a comparative study of trovafloxacin and ceftriaxone with or without vancomycin. Pediatr Infect Dis J 2002;21:14–22.
[63] Dagan R, Arguedas A, Schaad UB. Potential role of fluoroquinolone therapy in childhood otitis media. Pediatr Infect Dis J 2004;23:390–8.
[64] Leibovitz E, Piglansky L, Raiz S, et al. Bacteriologic and clinical efficacy of oral gatifloxacin for the treatment of recurrent/nonresponsive acute otitis media: an open label, non-comparative, double tymopanocentesis study. Pediatr Infect Dis J 2003;22:943–9.
[65] Arguedas A, Sher L, Lopez E, et al. Open label, multicenter study of gatifloxacin treatment of recurrent otitis media and acute otitis media treatment failure. Pediatr Infect Dis J 2003; 22:949–55.