Quinolone Arthropathy in Animals Versus Children

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The use of quinolones in children and accumulation of data on the pharmacodynamics of these drugs have been limited and delayed by concern regarding their chondrotoxicity. A comprehensive review of the findings in animals compared with the cumulative published findings in children and adolescents (>7,000 to date) allows the conclusion that such concern is not justified. Prospective controlled studies in children are justifiable in view of a continuing lack of correlation between findings in juvenile animals and those in children and because of the selected therapeutic advantages of the current and newer quinolones.

The first quinolone antibiotic, nalidixic acid, whose use was limited to the treatment of urinary tract infections, was a by-product of antimalarial research and was approved for use in children in March 1964. Subsequent modifications of the chemical structure of this drug led to the development of the contemporary fluoroquinolones. These drugs offered, for the first time, a wide spectrum of activity against gram-negative and gram-positive aerobes; favorable pharmacodynamics, allowing for treatment of systemic infections, including those caused by intracellular pathogens; and the flexibility of either intravenous or oral administration.

A new finding was the potential for all fluoroquinolones to cause damage to the weight-bearing cartilage of juvenile animals; however, the significance of this finding with respect to children remains unclear. For example, nalidixic acid was found to cause significant arthropathy in beagle puppies at a dose that is only half of that approved for treatment of children [1]. The drug continues to be used in children >3 months of age, and no lasting untoward effects on the skeletal system of children have been reported in over three decades of use.

The unique appeal of the newer-generation quinolones for children is the fact that they can be used to treat acute bronchopulmonary exacerbations in cystic fibrosis patients infected with *Pseudomonas aeruginosa* on an outpatient basis [2, 3]. Other indications for which fluoroquinolones show promise in children include treatment of urinary tract infections [4] and enteric infections in developing countries [5–9] and eradication of nasopharyngeal carriage of *Neisseria meningitidis* [10]. Some of the latest compounds of the class have inflammation-independent CSF penetration [11]; increased activity against gram-positive cocci, including multiresistant pneumococci [12]; and potential benefits in the treatment of CNS infections, as recently shown in a meningococcal epidemic in Nigeria [13]. These advantages underscore the importance of critically assessing our knowledge of quinolone-induced arthropathy in juvenile animals in the context of actual clinical experience with these agents in children and adolescents treated with these agents.

Received 5 February 1997; revised 27 June 1997.

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Clinical Infectious Diseases 1997; 25:1196–1204

1058–4838/97/2505-0041$03.00

Methods for the Literature Search

The following databases were searched from their date of inception through January 1997: MEDLINE, TOXLINE, and CANCERLIT (National Library of Medicine); CAB Abstracts (CAB International); AGRICOLA (Agricultural Online Access); BIOSIS PREVIEWS (Biosis); SEDBASE (Side Effects of Drugs; Elsevier); EMBASE (Electronic Excerpta Medica; Elsevier); International Pharmaceutical Abstracts (American Society of Health-System Pharmacists); Life Sciences Collection (Cambridge Scientific Abstracts); AGRIS (Food and Agriculture Organization); Derwent Drug File (Derwent); CA SEARCH (Chemical Abstracts Service); and SCISEARCH (Institute for Scientific Information). *Quinolone* or *fluoroquinolone* and *human* or *animal* were the initial search terms used to identify all relevant citations. The searches were subsequently narrowed by limiting to citations with the keywords (1) *arthropath*? or *joint cartilage* or *cartilage* or *skeletal system* or *joint disease* or (2) *effect* or *event* or *pharmacokinetic* or *pharmacodynamic* or *patholog*? or *histo*? or *toxicit*? or *clinical*? or *stud*? or *trial*?.

Quinolone Arthropathy in Animals

Quinolone-induced changes in immature articular cartilage of weight-bearing joints have been observed in all laboratory animals tested. These animals include mice [14], rats [15], dogs [16, 17], marmosets [18], guinea pigs [19], rabbits [1, 20], and ferrets [21]. Quinolone-induced arthropathy is limited to juvenile animals, except when pefloxacin has been used; this drug has produced characteristic lesions in both skeletally immature and mature dogs [22]. Juvenile dogs are generally more sensitive to the arthropathic effects of quinolones than are other species [23]. Inflammation of synovial membranes occurs, al-

though inconsistently, with some analogues [24]. Although the clinical manifestation of lameness in dogs resolves despite continued dosing [23], complete resolution of structural changes in affected cartilage has not been reported. MRI of joints in affected immature rabbits has identified thickened articular cartilage, surface irregularities consistent with ruptured vesicles, and separation of opposing articular surfaces, consistent with synovial effusion [25]. After various recovery periods ($\leqslant$17 weeks), healing of quinolone-induced arthropathy is incomplete in rats [26]. Microscopic examination has revealed that the lesions also fail to completely resolve in dogs after withdrawal periods of 14 [27], 30 [24], or 87 days (one animal) [28]. Results of multiple studies have corroborated the importance of weight-bearing forces in determining the location of lesions in dogs [17, 24, 29].

For all of the compounds tested, the quinolone-induced changes in dogs begin exclusively within the intermediate zone of the articular-epiphyseal-cartilage complex [23]. The initial changes are detectable by electron microscopy and consist of cytoplasmic vacuolation and mitochondrial dilatation within the chondrocytes [30]. Cellular changes are followed by formation of fissures in the extracellular matrix and subsequent loss of collagen and glycosaminoglycans [17, 31]. The seemingly characteristic microscopic changes were formerly believed to be pathognomonic for quinolone-induced arthropathy [32]; however, selective nutritional deprivation of magnesium [33, 34] and injection of various agents into the joint spaces [35] have been shown to produce similar lesions in rats.

Possible mechanisms reported from animal studies. The specific mechanism(s) responsible for the initiation of quinolone-induced arthropathy has not been determined. In vitro studies of cartilage from various species have implicated inhibitions of synthesis of either collagen or glycosaminoglycans [36–42]. Quinolone-induced oxidative injury to chondrocytes has been described [43, 44], as have inhibition of chondrocyte DNA synthesis [37, 42, 45] and compromised mitochondrial integrity [41, 42, 45]. It is unclear whether any of the perturbations listed above are primary or secondary events.

The most recent and, perhaps, most plausible postulate for the mechanism of quinolone-induced arthropathy involves the chelation of magnesium ions by quinolones, resulting in changed function of chondrocyte surface integrin receptors. Signal transduction via integrins seems to play a role in the maintenance of the integrity of the cartilage matrix [46, 47]. It has been observed that chondrocytes adjacent to fissures in articular cartilage in rats dosed with ofloxacin have reduced integrin expression [48], and this observation was confirmed in mice [49]. This hypothesis is further supported by the finding that nutritional magnesium deficiency in juvenile rats induced articular cartilage lesions that were histologically and ultrastructurally identical to those of quinolone-induced arthropathy [33, 34]. The combination of ofloxacin administration and magnesium deficiency produced greater cartilage damage than did either the drug or the deficiency alone. In addition, the normal magnesium concentrations in rat joint cartilage decrease to a nadir at the time of early postnatal growth, coinciding with the period of vulnerability for the seemingly similar magnesium deficiency and quinolone-induced cartilage lesions [50].

Comparison of Quinolone Pharmacokinetics in Children vs. Animals

The pharmacokinetics of quinolones in animals have been well described [51]. Conversely, pharmacokinetic data for children are limited, and those for neonates are only anecdotal [52–60]. The results of these studies, most of which were conducted in patients with cystic fibrosis, indicate that systemic clearance of the drugs is faster in young children beyond the neonatal period compared with adolescents [58]. This finding has led to recommendations for the use of higher doses of ciprofloxacin in patients weighing 14–28 kg [58, 59]. In general, quinolones are rapidly absorbed from the gastrointestinal tract. However, the bioavailability range is wide, with that of norfloxacin as low as 10%–20% and that of ofloxacin as high as 80%–90%. All of the newer compounds except norfloxacin have excellent tissue and intracellular penetration at the recommended therapeutic doses. Quinolones are generally excreted either predominantly in the urine (often as parent compound) or through the bile, where some of these drugs undergo enterohepatic recirculation.

Extrapolation of pharmacokinetic data across species lines (i.e., from animals to humans, especially to children of different ages) is complicated by significant interspecies differences. Increasing oral doses in dogs to levels at which chondrotoxicity is observed produces a corresponding increase in plasma concentrations [22]. Such proportional increases in dose and plasma concentration are similar to those observed in children [61]. Within the ranges that encompass arthropathic doses in rats, however, increasing doses of ofloxacin result in markedly subproportional increases in plasma concentrations [18]. Therefore, with respect to quinolone pharmacokinetics, humans and dogs share greater similarity than rats share with either of these species. Comparisons of doses of various quinolones in children with minimum arthropathic doses in dogs have shown that the two are poorly correlated [23]. For example, the minimal arthropathic doses of nalidixic acid in dogs is 25 mg/kg, or one-half the therapeutic dose in children (55 mg/kg) [1]. For ciprofloxacin, the doses are equal, at $\sim$30 mg/kg [29], whereas for trovafloxacin, the minimal arthropathic dose in dogs is 50 mg/(kg$\cdot$d), or five times the projected maximum dose in children of 10 mg/(kg$\cdot$d) [23].

Despite the propensity for quinolones to cause arthropathy in animals, information about their concentrations in articular cartilage is surprisingly scant. Studies of articular cartilages from rats dosed with quinolones [32] and femoral head cartilage from adult humans (obtained during hip replacement procedures) receiving ofloxacin therapy [62] revealed that the concentrations of quinolones are higher in cartilage than in plasma.

Machida et al. [1] demonstrated that minimum arthropathic doses in dogs were 50 mg/kg and 25 mg/kg for nalidixic acid and norfloxacin, respectively; however, in arthropathic cartilages the ranges of concentrations were similar (4.58 μg/g to 6.90 μg/g of tissue) and sometimes exceeded the values in serum. Studies of levofloxacin in rabbits indicated that concentration of the drug in articular cartilage initially failed to reach the maximum serum concentration [42]. However, the cartilage concentration later exceeded the concomitant serum concentration for a period of 2–24 hours after dosing, indicating a far greater exposure of cartilage to the drug than would have been predicted on the basis of serum concentrations alone.

In addition, Kato et al. [42] defined an arthropathic concentration of levofloxacin in rabbit articular cartilage as $\geqslant$12.2 μg/g of tissue. Kesseler et al. [63] described a concentration of 8.4 μg/mL of pefloxacin in synovial fluid, vs. a concentration of 5 μg/mL in serum, obtained 1 hour after 400 mg was administered to a 17-year-old boy. This boy was receiving the drug twice daily. Data on concentrations of quinolones in the cartilage of children, as well as information on concentrations in different strata of cartilage or the possible influence on quinolone penetration into cartilage by application and release of pressure during weight bearing in vivo, are lacking.

Influence of Age and Growth on Quinolone Arthropathy

Age is the single most critical factor in the development of quinolone arthropathy in animals. Dogs develop quinolone arthropathy when exposed at ages of >2 weeks or <8 months [24, 64], whereas rats are susceptible shortly after birth to age 8 weeks [15, 65]. Pefloxacin is the reported exception to the ''juvenile rule,'' as histologically confirmed arthropathy was produced in both juvenile and adult dogs after prolonged exposure [66]. Because the period of increased sensitivity to the development of quinolone arthropathy in dogs corresponds with the period of maximal growth, a high rate of growth could be a contributing factor [23].

Whether differences in growth can be incorporated into animal vs. human risk assessments is unclear. Dogs initially outgrow children by a wide margin. A beagle pup gains 8 kg during the period 1–6 months of age. In contrast, a child of similar age gains only 4 kg over the same period. Such differences become even more pronounced when the periods of growth from birth to adulthood for animals vs. humans are compared. Assuming a growth span from birth to adulthood of 1 year for a dog and 18 years for a human, a day of growth (and quinolone treatment) for a juvenile dog would correspond to 18 days of growth for a young child. It is possible that the extremely rapid extrauterine growth rates and nutritional requirements of the skeletons of laboratory animals are an explanation for their relative sensitivity to the chondrotoxic effects of quinolones.

Case Reports of Suspected Quinolone-Associated Arthralgia in Children and Adolescents

Although quinolone arthropathy in juvenile animals has been meticulously characterized, practical and ethical limitations have restricted the histological characterization of suspected cases of quinolone-induced arthralgia in children. The resultant lack of information makes it impossible to interpret suspected clinical cases of quinolone-associated arthralgia as being equivalent to quinolone arthropathy in animals. We review and comment on published case reports and studies in premature infants, children, and adolescents who were treated with a variety of quinolones.

Joint swellings or pain concurrent with quinolone therapy have been described by Kesseler et al. [63], McDonald and Short [67], Alfaham et al. [68], Ollier et al. [69], Jawad [70], Seigneuric et al. [71], Le Löet et al. [72], Chevalier et al. [73], and Chang et al. [74]. The 10 cases of suspected quinolone-associated arthropathy involved five girls and five boys ranging in age from 14 to 17 years. In seven of these 10 reports, the joint manifestations occurred after treatment with pefloxacin. Only two of these seven patients were treated for exacerbation of cystic fibrosis–related *P. aeruginosa* infection. Three of the other patients had invasive infections with *Staphylococcus aureus,* and two had cerebral abscess due to various organisms. Seven of the 10 cases involved pefloxacin patients with a variety of infections (often, but not limited to, cystic fibrosis). Two of the 10 cases involved ciprofloxacin-treated patients with cystic fibrosis, and one case involved the use of nalidixic acid for treatment of a urinary tract infection.

Consistent signs and symptoms were joint swelling or pain that involved one or more joints, usually including the knees (8 of 10 cases). Analysis of synovial fluid from swollen joints of seven patients treated with pefloxacin revealed that cell counts ranged from normal to elevated (i.e., 120–3,000/mm^3). The predominant cell types were monocytes and lymphocytes. Radiographs, which were obtained in nine cases, did not reveal bone or joint changes during either the acute stages of arthralgia or on follow-up, except in one case [73]. With the exception of this one case, complete clinical recovery was observed over a period of a few days to 3 months for most patients and over a period of >1 year for one [63].

The exception to these benign observations is the patient described by Chevalier et al. [73]. This 17-year-old patient was continuously treated with pefloxacin over a period of >2 months. He began to have joint pains and, subsequently, swelling of the knees during the first month of continued treatment. His initial source of infection was a perforated appendix, which was complicated by the development of endocarditis because of an atrial septum defect, resulting in a cerebral abscess. Septic emboli to the bones were a distinct possibility despite the fact that cultures performed later were negative. Concomitant medications included steroids to reduce brain edema and, later, calcitonin for suspected reflex

sympathetic dystrophy. No baseline radiographic findings were described, but within 1 month after treatment, the patient had limited range of motion, and there was radiographic evidence of cartilage loss in the knees. Arthroscopy and biopsies later showed epiphyseal bone necrosis with attendant fibrosis of synovium and articular cartilage. The patient later required bilateral knee and right hip replacement.

In a child treated with nalidixic acid [67], only reversible soreness of a wrist (without swelling) was reported during two separate courses of treatment. In the two case reports that involved ciprofloxacin therapy in children with cystic fibrosis [68, 70], the joint symptoms did not differ from those that can occur in patients with cystic fibrosis alone as a manifestation of either immune complex disease or hypertrophic osteopathy [75, 76]. The relationship between pefloxacin therapy, as with the other agents, and the reported joint symptoms [63, 69, 71–73, 74] has been temporal but is supported by the frequency of the reports. Although limited histological evaluations have been described, evaluation of articular cartilage (the site for development of quinolone arthropathy in animals) has not been reported.

In the case described by Chevalier et al. [73], the anatomic and morphological changes were consistent with alternative processes involving epiphyseal bone rather than articular cartilage. In the case reported by Ollier et al. [69], examination of a synovial biopsy specimen showed nonspecific changes compatible with chronic or subacute irritation. In the case described by Kesseler et al. [63] (a 17-year-old male with cystic fibrosis), the resolution of effusion and symptoms in both knees took several months, and mild bony alterations were observed on radiographs and MRIs. However, no cartilage lesions were observed, and examination of a synovial biopsy specimen, obtained 10 months after the onset of symptoms, revealed only nonspecific fibrosis. Bone scintigraphy, performed 1 year after the patient was first given pefloxacin, showed symmetrical uptake at the knee level that was interpreted as unusually marked for a patient who was only 18 years old. However, the cartilage of the knees appeared normal by magnetic resonance imaging. Similarly, follow-up MRIs showed normal results 9 months after pefloxacin-associated arthropathy was detected in the case described by Chang [74]. A technetium bone scan also revealed persistent minor abnormalities in this case.

In summary, these case reports of quinolone-associated effusion and arthralgia in children and adolescents draw attention to the possibility that chondrotoxicity will occur during therapy with these drugs. Reports implicating pefloxacin (seven of 10), are notably overrepresented. There were no long-term sequelae in any of the patients, with the exception of the one described by Chevalier et al. [73], in whom etiologies other than pefloxacin therapy cannot be ruled out. Assuming a causal relationship in that case, it is also possible that the continuation of pefloxacin treatment for at least 4 more weeks after appearance of symptoms was a contributing factor.

Because the areas of articular cartilage (the first site of quinolone arthropathy of animals) described above were not evaluated for the presence of primary changes, the comparability of these cases to those of quinolone arthropathy in animals remains uncertain. Adequate evaluation of articular cartilages for the presence of primary changes appears warranted for the publication of any future credible cases. MRIs, obtained with a special surface coil on formalin-fixed rabbit limbs, detected quinolone-induced changes in articular cartilage [25]. This method would be capable of detecting hypothetical human cartilage defects as small as those caused by quinolones in dogs [16, 77]. In the rabbit study [25], each contrast-weighted image required an acquisition time of 10–12 minutes without movements.

Nevertheless, adequate histopathologic studies would be the most appropriate technique for detecting cartilage lesions comparable to those in animals with quinolone-induced arthropathy [78]. Ultrasonograms of the knee and hip joints allow detection of articular effusion and measurement of the thickness of the synovia and, sometimes, the cartilage. Therefore, ultrasonography might be useful for screening purposes before and after quinolone therapy.

Review of Series of Children and Adolescents Treated with Quinolones

A total of 31 reports from various multipatient studies have described the use of ciprofloxacin, nalidixic acid, norfloxacin, or ofloxacin in >7,000 skeletally immature patients who did not develop arthralgia beyond the level of severity expected as a result of the underlying disease [3, 6–9, 52, 61, 78–105] (table 1). Clinical observations and studies for joint changes collectively included magnetic resonance imaging for 152 patients, ultrasonography for 55, and histopathology for two. Clinical and other studies for joint changes, performed ⩽6 months (magnetic resonance imaging [88]), 3 years (magnetic resonance imaging and histopathology [78]), 7 years (magnetic resonance imaging [89]), and 12 years (clinical observation only [80]) after quinolone treatment, did not show any quinolone-induced effects (table 2). In addition, none of the evaluated quinolones (ciprofloxacin, ofloxacin, or nalidixic acid) had negative effects on the linear growth of children.

Two multipatient studies of premature infants have been published. In one of these studies [52], ciprofloxacin (10 mg/kg b.i.d.) was administered to six premature infants; the peak plasma concentrations ranged between 0.15 μg/mL and 0.57 μg/mL, with a mean concentration of 0.31 μg/mL. On the basis of measurements in two infants with meningitis, the CSF penetration was ~60%–70%. Bacteriologic cure and no untoward side effects were observed. In another study [104], two premature infants were treated with ciprofloxacin, and five were treated with pefloxacin. No untoward effects were noted, and there were no differences in weight gain, growth, or increase in head circumference when these infants were compared with another group of equally ill premature infants during follow-up at 6-month intervals until age 30–42 months.

Table 1. Summary of skeletal safety data from multipatient studies of quinolones in skeletally immature patients.

Reference	No. of patients treated	Age of patients (mean or range)	Quinolone administered	Incidence of definitive quinolone arthropathy
[92]	3,341	<18 y	Ciprofloxacin	0
[105]	1,795	<5–17 y	Ciprofloxacin	0*
[8]	438	14 y	Ofloxacin	0
[61]	406	2–>9 y	Norfloxacin	0
[84]	233	<1–18 y	Ciprofloxacin	0
[7]	108	1–15 y	Ofloxacin	0
[95]	85	3–10 y (87%)	Ciprofloxacin	0
[103]	73	1.5–18 y 8.4 y	Ciprofloxacin	0
[86]	62	50 mo	Ciprofloxacin	0
[91]	58	8 mo–13 y	Ciprofloxacin	0
[9]	55	6.2 y	Ofloxacin	0
[3]	55	5–17 y	Ciprofloxacin	0
[97]	54	6 mo–13 y	Nalidixic acid, norfloxacin	0
[82]	32	39 mo	Nalidixic acid	0
[96]	25	15.4 y	Ciprofloxacin	0
[85]	24	11.5 y	Ciprofloxacin	0
[83]	21	7.5 y	Norfloxacin	0
[98]	21	4.4 y	Ciprofloxacin	0
[79]	21	5–26 y	Ofloxacin	0
[102]	20	22 y	Ciprofloxacin	0
[88]	18	6–24 y	Ciprofloxacin	0
[100]	18	6.4 y	Ciprofloxacin	0
[99]	16	3.6 y	Pefloxacin	0
[90]	14	14 y	Ciprofloxacin, ofloxacin	0
[101]	13	4 d–1 mo	Ciprofloxacin	0
[80]	11	3 mo–9.6 y 1.4 y	Nalidixic acid	0
[94]	8	2–13 y	Ciprofloxacin	0
[104]	7	32 w (gestational age)	Ciprofloxacin, pefloxacin	0
[52]	6	5–29 d	Ciprofloxacin	0
[89]	5	9–12 y	Norfloxacin	0
[78]	2	7–13 y	Ciprofloxacin	0
Total	7,045			0

* In this report, the incidence of arthralgia was ~1.5%; however, we considered the relationship to treatment uncertain because the prevalence of such symptoms was less than or equal to that for the non-quinolone-treated cystic fibrosis patient population.

A review of the approval studies for norfloxacin use in Japanese children contains 406 cases where norfloxacin was given at various dosages to children whose ages ranged from 2 to 11 years; no arthropathy was observed [61]. In the discussion of that study, anecdotal data about 433 cases of diarrhea in Chinese children, who were treated with norfloxacin without any adverse reactions, are mentioned.

By the end of 1994, there were 1,795 case report forms on file at the Bayer Corporation (Wuppertal, Germany), with data on children treated with ciprofloxacin [105, 106]. Arthralgia with and without clinical signs of arthritis occurred in 31 of 2,030 treatment courses (1.5%); 26% of the patients were between 12 and 17 years of age, and 28% of them had cystic fibrosis. The outcome was good, and there was no unequivocal documentation of ciprofloxacin-induced arthropathy in any case.

An exception to these studies with no adverse findings is a review of 63 children with cystic fibrosis who were treated with pefloxacin [107]. The authors describe nine, predominantly adolescent patients with joint manifestations that occurred in conjunction with treatment. Two of these cases should probably be excluded because the manifestations were present at the onset of treatment in one and began 6 days after completion of treatment in another. A pattern of swelling of the large joints, predominantly the knees, with complete resolution and no long-term sequelae was observed. Examination of synovial fluid from two patients revealed 390 cells/mm^3 and 700 cells/mm^3; these cells were predominantly mononuclear cells and lymphocytes. The most notable finding in this report was that five of the patients with joint manifestations later tolerated therapeutic courses of ofloxacin, without any problems. Kesseler et al. [63] similarly refers to unpublished experience presented by Reinert in 1987 [63], where five of 50 children treated with pefloxacin developed reversible joint manifestations but tolerated ofloxacin later.

The most recent experience is a prospective, randomized comparative study of oral ciprofloxacin (15 mg/kg b.i.d.) with conventional ceftazidime/tobramycin for treatment of acute bronchopulmonary exacerbations associated with *P. aeruginosa* infection in 108 children and adolescents with cystic fibrosis [3]. Before and after the 2-week treatments, ultrasonograms were obtained for 96 patients (48 patients in both treatment groups), and nuclear MRIs were obtained for 29 patients (14 patients treated with ciprofloxacin and 15 patients treated with ceftazidime/tobramycin). No evidence of any cartilage toxicity was found.

According to statistical equations derived by Hanley and Lippman-Hand [108], a 95% confidence interval (for absence of occurrence) can be constructed around x number of patients by the equation x/3. By using this equation for the 7,045 patients treated with quinolones described in this article, it can be concluded with 95% confidence that a maximum risk for the occurrence of chondrotoxicity, as seen in juvenile animals, would currently be not greater than 1 in 2,348 patients (7,045/3) or ~0.04%. The real number is probably much smaller, since we do not know how many more children have received quinolones to date for whom the outcomes have not been published.

Summary and Interpretation

Our comprehensive review of published data leads to the conclusion that quinolone arthropathy, as described in juvenile

Table 2. Summary of follow-up data on skeletal safety from multipatient studies of quinolone therapy in skeletally immature patients.

Reference	Duration of follow-up period	No. of patients	Diagnostic technique	Adverse findings	Quinolone used	Skeletal growth
[80]	3–12 y	11	Clinical evaluation	None	Nalidixic acid	Normal
[83]	24–62 mo	21	Radiography	None	Norfloxacin	NA
[101]	12–23 mo	13	Clinical evaluation	None	Ciprofloxacin	Normal
[88]	4–6 mo	18	MRI	None	Ciprofloxacin	Normal
[78]	3 y	2	MRI and histopathology	None	Ciprofloxacin	Normal
[89]	7 y	5	MRI	None	Norfloxacin	Normal
[60]	2 y	326	Clinical evaluation	None	Ciprofloxacin, ofloxacin	Normal
[90]	1 w–16 mo	14	MRI	None	Ofloxacin + ciprofloxacin	Normal
[91]	6 mo	58	MRI (acute phase); clinical evaluation (6 mo)	None	Ciprofloxacin	Normal
[104]	30–42 mo	7	Clinical evaluation	None	Ciprofloxacin, pefloxacin	Normal
[3]	Concurrent with therapy	55	MRI and ultrasonography	None	Ciprofloxacin	NA

NOTE. NA = data not available.

animals, is to date not convincingly correlated with use of these compounds in children and adolescents. The 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. Pefloxacin is the agent most frequently implicated in such reports; however, the incidence of this clinical observation with the other compounds does not appear to be higher than expected in a population with similar chronic disease. We conclude that it is ethically justifiable to perform prospective studies of selected quinolone agents in children.

References

1. Machida M, Kusajima H, Aijima H, Maeda A, Ishida R, Uchida H. Toxicokinetic study of norfloxacin-induced arthropathy in juvenile animals. Toxicol Appl Pharmacol **1990**;105(suppl. 3):403–12.
2. Schaad UB, Salam MA, Aujard Y, Use of fluoroquinolones in pediatrics: consensus report of an International Society of Chemotherapy commission. Pediatr Infect Dis J **1995**;14(suppl 1):1–9.
3. Richard DA, Nousia-Arvanitakis S, Sollich V, et al. Oral ciprofloxacin versus intravenous ceftazidime plus tobramycin in pediatric cystic fibrosis patients: comparison of antipseudomonas efficacy and assessment of safety with ultrasonography and magnetic resonance imaging. Pediatr Infect Dis J **1997**;16:572–8.
4. Van Wijk JAE, de Jong TPVM, Van Gool JD, Boemers TM, Voorman M. Using quinolones in urinary tract infections in children. Advances in Antimicrobial and Antineoplastic Chemotherapy **1992**;11(suppl 2): 157–61.
5. Gendrel D, Moreno JL, Nduwimana M, Baribwira C, Raymond J. One-dose treatment with pefloxacin for infection due to multidrug-resistant Shigella dysenteriae type 1 in Burundi. Clin Infect Dis **1997**;24:83.
6. Bethell DB, Day NPJ, Dung NM, et al. Pharmacokinetics of oral and intravenous ofloxacin in children with multidrug-resistant typhoid fever. Antimicrob Agents Chemother **1996**;40:2167–72.
7. Vinh H, Wain J, Hahn VTN, et al. Two or three days of ofloxacin for uncomplicated multi-drug resistant typhoid fever in children. Antimicrob Agents Chemother **1996**;40:958–61.
8. Hien TT, Bethell DB, Hoa NTT, et al. Short course of ofloxacin for treatment of multidrug-resistant typhoid. Clin Infect Dis **1995**;20: 917–23.
9. Rathore MH, Bux D, Hasan M. Multidrug-resistant *Salmonella typhi* in Pakistani children: clinical features and treatment. South Med J **1996**; 89:2:235–7.
10. Cuevas LE, Kazembe P, Mughogho GK, Tilloston GS, Hart CA. Eradication of nasopharyngeal carriage of *Neisseria meningitidis* in children and adults in rural Africa: a comparison of ciprofloxacin and rifampicin. J Infect Dis **1995**;171(suppl 3):728–31.
11. Arguedas-Mohs A, Loaiza C, Riviera R, et al. CSF penetration of iv trovafloxacin in children [abstract 4]. In: Program and abstracts of the First International Pediatric Infectious Disease Conference (Monterey, CA). Pediatric Infectious Diseases Society of America and European Society for Paediatric Infectious Diseases, **1995**.
12. Barry AL, Fuchs PC, Brown SD. In vitro activities of five fluoroquinolone compounds against strains of *Streptococcus pneumoniae* with resistance to other antimicrobial agents. Antimicrob Agents Chemother **1996**;40:2431–3.
13. Hopkins S, Williams D, Dunne M, Marinovich L, Edeline M, Utt E, Dutse AI. A randomized, controlled trial of oral or iv trovafloxacin vs. ceftriaxone in the treatment of epidemic meningococcal meningitis [LB 21 (late breaker)]. In: program addendum to Abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy (New Orleans). American Society for Microbiology, Washington, D.C., **1996**:11.
14. Linseman DA, Hamptom LA, Branstetter DG. Quinolone-induced arthropathy in the neonatal mouse: morphological analysis of articular lesions produced by pipemidic acid and ciprofloxacin. Fundam Appl Toxicol **1995**;28:59–64.
15. Kato M, Onodera T. Morphological investigation of cavity formation in articular cartilage induced by ofloxacin in rats. Fundam Appl Toxicol **1988**;11:110–9.
16. Gough A, Barsoum NJ, Mitchell L, McGuire EJ, La Iglesia FA. Juvenile canine drug-induced arthropathy: clinicopathological studies on articu-

lar lesions caused by oxolinic and pipemidic acids. Toxicol Appl Pharmacol **1979**;51:177–87.
17. Burkhardt JE, Hill MA, Carlton WW, Kesterson JW. Histologic and histochemical changes in articular cartilages of immature beagle dogs dosed with difloxacin, a fluoroquinolone. Vet Pathol **1990**;27:162–70.
18. Stahlmann R, Merker HJ, Hinz N, et al. Ofloxacin in juvenile non-human primates and rats. Arthropathia and drug plasma concentrations. Arch Toxicol **1990**;64:193–204.
19. Bendele AM, Hulman JF, Harvey AK, Hrubey PS, Chandrasekhar S. Passive role of articular chondrocytes in quinolone-induced arthropathy in guinea pigs. Toxicol Pathol **1990**;18:304–12.
20. Sharpnack DD, Mastin JP, Childress CP, Henningsen GM. Quinolone arthropathy in juvenile New Zealand white rabbits. Lab Anim Sci **1994**;44:436–42.
21. Ewing PJ, Ness DK. Quinolone arthropathy in juvenile ferrets. Vet Pathol **1995**;32:599.
22. Christ W, Lehnert T. Toxicity of the quinolones. In: Siporin C, Heifetz CL, Domagala JM, eds. The new generation of quinolones. New York: Marcel Dekker, **1990**;165–87.
23. Burkhardt JE. Review of quinolone arthropathy in the dog. Chemotherapie Journal **1996**;5(suppl 13):14–8.
24. Tatsumi H, Senda H, Yatera S, Takemoto Y, Yamayoshi M, Ohnishi K. Toxicological studies on pipemidic acid. V. Effect on diarthrodial joints of experimental animals. J Toxicol Sci **1978**;3:357–67.
25. Gough A, Johnson R, Campbell E, et al. Quinolone arthropathy in immature rabbits treated with the fluoroquinolone, PD 117596. Exp Toxicol Pathol **1996**;48:225–32.
26. Förster C, Kociok K, Shakibaei M, Merker HJ, Stahlmann R. Quinolone-induced cartilage lesions are not reversible in rats. Arch Toxicol **1996**;70:474–81.
27. Gough AW, Barsoum NJ, Renlund RC, Sturgess JM, de la Iglesia FA. Fine structural changes during reparative phase of canine drug-induced arthropathy. Vet Pathol **1985**;22:82–4.
28. 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.
29. Schmidt M, Hoffman K. The use of quinolones in children—toxicological aspects. In: Adam D, Rubio TT, eds. The use of new quinolones in pediatric medicine. Munich: Futuramed Publishers, **1992**;251–5.
30. Burkhardt JE, Hill MA, Turek JJ, Carlton WW. Ultrastructural changes in articular cartilages of immature beagle dogs dosed with difloxacin, a fluoroquinolone. Vet Pathol **1992**;29:230–8.
31. 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.
32. Gough AW, Kasali OB, Sigler RE, Baragi V. Quinolone arthropathy—acute toxicity to immature articular cartilage. Toxicol Pathol **1992**;20:436–9.
33. Stahlmann R, Förster C, Shakibaei M, Vormann J, Günther T, Merker HJ. Magnesium deficiency induces joint cartilage lesions in juvenile rats which are identical to quinolone-induced arthropathy. Antimicrob Agents Chemother **1995**;39:2013–8.
34. Shakibaei M, Kociok K, Förster C, et al. Comparative evaluation of ultrastructural changes in articular cartilage of ofloxacin-treated and magnesium-deficient immature rats. Toxicol Pathol **1996**;24:580–7.
35. Takada S, Kato M, Takayama S. Comparison of lesions induced by intra-articular injections of quinolones and compounds damaging cartilage components in rat femoral condyles. J Toxicol Environ Health **1994**;42:73–88.
36. Amacher DE, Schomaker SJ, Gootz TD, McGuirk PR. In: Goldberg AM, ed. In vitro toxicology: new directions. New York: Mary Ann Liebert, **1989**;307–12.
37. Brand HS, van Kampen GPJ, van der Korst JK. Effect of nalidixic acid, pipemidic acid, and cinoxacin on chondrocyte metabolism in explants of articular cartilage. Clin Exp Rheumatol **1990**;8:393–5.
38. Burkhardt JE, Hill M, Carlton W, Lamar C. Difloxacin reduces glycosaminoglycan synthesis in organ cultures of articular cartilage. In: Goldberg AM, ed. In vitro toxicology: mechanisms and new technology. New York: Mary Ann Liebert, **1991**;371–7.
39. Schröter-Kermani C, Hinz N, Risse P, Stahlmann R, Merker HJ. Effects of ofloxacin on chondrogenesis in murine cartilage organoid culture. Toxicology in Vitro **1992**;6:465–74.
40. Burkhardt JE, Hill MA, Lamar CH, Smith GN, Carlton WW. Effects of difloxacin on the metabolism of glycosaminoglycans and collagen in organ cultures of articular cartilage. Fundam Appl Toxicol **1993**;20:257–63.
41. Hildebrand H, Kempka G, Schlüten G, Schmidt M. Chondrotoxicity of quinolones in vivo and in vitro. Arch Toxicol **1993**;67:411–5.
42. 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.
43. Hayem G, Petit PX, Levacher M, Gaudin C, Kahn MF, Pocidalo JJ. Cytofluorometric analysis of chondrotoxicity of fluoroquinolone antimicrobial agents. Antimicrob Agents Chemother **1994**;38:243–7.
44. Thuong-Guyot M, Domarle O, Pocidalo JJ, Hayem G. Effects of fluoroquinolones on cultured articular chondrocytes. Flow cytometric analysis of free radical production. J Pharmacol Exp Ther **1994**;271:1544–9.
45. Mont MA, Mathur SK, Frondoza CG, Hungerford DS. The effects of ciprofloxacin on human chondrocytes in cell culture. Infection **1996**;24:151–5.
46. Ruoslahti E. Integrins. J Clin Invest **1991**;87:1–5.
47. Hynes RO. Integrins: versatility, modulation, and signaling in cell adhesion. Cell **1992**;69:11–25.
48. Förster C, Kociok K, Shakibaei M, et al. Integrins on joint cartilage chondrocytes and alterations by ofloxacin or magnesium deficiency in immature rats. Arch Toxicol **1995**;9:261–70.
49. Shakibaei M, Förster C, Merker HJ, Stahlmann R. Effects of ofloxacin on integrin expression on epiphyseal mouse chondrocytes in vitro. Toxicology in Vitro **1995**;9:107–6.
50. Vormann J, Förster 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 (in press).
51. Toothaker RD. Preclinical quinolone pharmacokinetics. In: Siporin C, Heifetz CL, Domagala JM, eds. The new generation of quinolones. New York: Marcel Dekker, **1990**;145–64.
52. Bannon MJ, Stutchfield PR, Weindling AM, Damjanovic V. Ciprofloxacin in neonatal Enterobacter cloacae septicaemia. Arch Dis Child **1989**;64:1388–9.
53. Cohen R, Bompard Y, Danan C, Auffrant C, Aujard Y. Indication des quinolones chez le nouveau-né. In: Aujard Y, Autret E, Jacqa-Aigrain E, eds. Pharmacol périnatale. Angers, France: Paquereau, **1991**:517–29.
54. LeBel M, Bergeron MG, Vallée F, et al. Pharmacokinetics and pharmacodynamics of ciprofloxacin in cystic fibrosis patients. Antimicrob Agents Chemother **1986**;30:260–6.
55. Goldfarb J, Wormser GP, Inchiosa MA, Guiden G, Diaz M, Mascia AV. Single dose pharmacokinetics of oral ciprofloxacin in patients with cystic fibrosis. J Clin Pharmacol **1986**;26:222–6.
56. Blumer JL, Stern RC, Reed MD, et al. Ciprofloxacin monotherapy for acute pulmonary exacerbations of cystic fibrosis. Am J Med **1987**;82(suppl 4A):174–9.
57. 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.
58. Peltola H, Väärälä M, Renkonen O, Neuvonen PJ. Pharmacokinetics of single dose of oral ciprofloxacin in infants and small children. Antimicrob Agents Chemother **1992**;36:1086–90.

59. Schaeffer HG, Stass H, Wedgwood J, et al. Pharmacokinetics of ciprofloxacin in pediatric cystic fibrosis patients. Antimicrob Agents Chemother **1996**;40:29–34.
60. Bethell DB, Day NPJ, Dung NM, et al. Pharmacokinetics of oral and intravenous ofloxacin in children with multidrug-resistant typhoid fever. Antimicrob Agents Chemother **1996**;40:267–72.
61. Fujii R. The use of norfloxacin in children in Japan. In: Adam D, Rubio TT, eds. The use of new quinolones in pediatric medicine. Munich: Futuramed Publishers, **1992**;219–30.
62. Meissner A, Borner K, Koeppe P. Concentrations of ofloxacin in human bone and in cartilage. J Antimicrob Chemother **1990**;26(suppl D): 69–74.
63. Kesseler A, LaCassie A, Hugot JP, Talon P, Thomas D, Astier L. Arthropathies consécutives à l'administration de péfloxacine chez un adolescent atteint de mucoviscidose. Ann Pédiatr (Paris) **1989**; 36:275–8.
64. Howard LD, Van Sickle DC, Deshmukh K, Griffing WJ, Owen NV. Cinoxacin induced arthropathy in juvenile beagle dogs [abstract]. Toxicol Appl Pharmacol **1979**;48:A145.
65. Mayer DG. Overview of toxicological studies (ofloxacin). Drugs **1987**; 34(suppl 1):150–3.
66. Christ W, Lehnert T, Ulbrich B. Specific toxicological aspects of the quinolones. Rev Infect Dis **1988**;10(suppl 1):S141–6.
67. McDonald DF, Short HB. Usefulness of nalidixic acid in treatment of urinary infection. Antimicrob Agents Chemother **1965**;628–31.
68. Alfaham M, Holt ME, Goodchild MC. Arthropathy in a patient with cystic fibrosis taking ciprofloxacin. Br Med J **1987**;295:699.
69. Ollier S, Laroche M, Arlet P, Montane P, Durroux R, LeTallec Y. Arthropathie a la péfloxacine. Rev Rhum Mal Osteoartic **1990**;5(suppl 9): 671.
70. Jawad ASM. Cystic fibrosis and drug-induced arthropathy. Br J Rheumatol **1989**;28:179–80.
71. Seigneuric C, Plantavid M, Bouygues D, Cassou M, Amar J, Cascarigny F. Manifestations articulaires sous péfloxacine chez l'adolescent. Presse Med **1990**;19:428.
72. Le Löet X, Fessard C, Noblet C, Ait Sait L, Moore N. Severe polyarthropathy in an adolescent treated with pefloxacin [letter]. J Rheumatol **1991**;18:1941–2.
73. Chevalier X, Albengres E, Voisin MC, Tillement JP, Larget-Piet B. A case of destructive polyarthropathy in a 17-year-old youth following pefloxacin treatment. Drug Saf **1992**;7:310–4.
74. Chang H, Chung MH, Kim JH, Kim JH. Pefloxacin-induced arthropathy in an adolescent with brain abscess. Scan J Infect Dis **1996**;28: 641–3.
75. Newman AJ, Ansell BM. Episodic arthritis in children with cystic fibrosis. J Pediatr **1979**;94:594–6.
76. Phillips BM, David TJ. Pathogenesis and management of arthropathy in cystic fibrosis. J R Soc Med **1986**;79(suppl 12):44–9.
77. Gylys-Morin VM, Hajek PC, Sartoris DJ, Resnick D. Articular cartilage defects: detectability in cadaver knees with MR. AJR Am J Roentgenol **1987**;148:1153–7.
78. 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.
79. Meyer H. Ofloxacin in cystic fibrosis. Drugs **1987**;34(suppl 1):177–9.
80. Schaad UB, Wedgwood-Krucko J. Nalidixic acid in children: retrospective matched controlled study for cartilage toxicity. Infection **1987**; 15:165–8.
81. Scully BE, Nakatomi M, Ores C, Davidson S, Neu HC. Ciprofloxacin therapy in cystic fibrosis. Am J Med **1987**;82(suppl 4A)196–201.
82. Salam MA, Bennish ML. Therapy for shigellosis. I. Randomized, double-blind trial of nalidixic acid in childhood shigellosis. J Pediatr **1988**; 113:901–7.
83. Cruciani M, Concia E, Navarra A, et al. Prophylactic co-trimoxazole versus norfloxacin in neutropenic children—prospective randomized study. Infection **1989**;17(2):65–9.
84. Black A, Redmond AOB, Steen HJ, Oborska IT. Tolerance and safety of ciprofloxacin in paediatric patients. J Antimicrob Chemother **1990**; 26(suppl F):25–9.
85. Rubio TT. Ciprofloxacin in the treatment of Pseudomonas infection in children with cystic fibrosis. Diagn Microbiol Infect Dis **1990**;13: 153–5.
86. Cheesbrough JS, Mwema FI, Green SD, Tillotson GS. Quinolones in children with invasive salmonellosis [letter]. Lancet **1991**;338: 127.
87. Chyský V, Kapila K, Hullmann R, Arcieri G, Schacht P, Echols R. Safety of ciprofloxacin in children: worldwide clinical experience based on compassionate use. Emphasis on joint evaluation. Infection **1991**;19: 289–96.
88. 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.
89. Aricò M, Bossi G, Caselli D, Cosi G, Villa A, Beluffi G, Genovese E. Long term magnetic resonance survey of cartilage damage in leukemic children treated with fluoroquinolones. Pediatr Infect Dis J **1995**;14: 713–4.
90. Danisovicová A, Brezina M, Belan S, et al. Magnetic resonance imaging in children receiving quinolones: no evidence of quinolone-induced arthropathy. Chemotherapy **1994**;40:209–14.
91. 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.
92. Karande SC, Kshirasagar NA. Adverse drug reaction monitoring of ciprofloxacin in pediatric practice. Indian Pediatr **1993**;20: 181–8.
93. Bethell DB, Hien TT, Phi LT, et al. Effects on growth of single short courses of fluoroquinolones. Arch Dis Child **1996**;74:44–6.
94. Sen S, Goyal RS, Dev R. Ciprofloxacin in the management of multiple drug resistant typhoid fever. Indian Pediatr **1991**;28:417–9.
95. Arora RK, Gupta A, Joshi NM, Kataria VK, Lall P, Anand AC. Multidrug resistant typhoid fever: study of an outbreak in Calcutta. Indian Pediatr **1992**;29:61–6.
96. Schaad UB, Wedgwood-Krucko J, Guenin K, Buehlmann U, Kraemer R. Antipseudomonal therapy in cystic fibrosis: aztreonam and amikacin versus ceftazidime and amikacin administered intravenously followed by oral ciprofloxacin. Eur J Clin Microbiol Infect Dis **1989**:858–65.
97. Lolekha S, Vibulbandhitkit S, Poonyarit P. Response to antimicrobial therapy for shigellosis in Thailand. Rev Infect Dis **1991**;13(suppl 4): S342–6.
98. Lang R, Goshen S, Raas-Rothschild A, et al. Oral ciprofloxacin in the management of chronic suppurative otitis media without cholesteatoma in children: preliminary experience in 21 children. Pediatr Infect Dis J **1992**;11:925–9.
99. Gendrel D, Raymond J, Legall MA, Bergeret M, Badoual J. Use of pefloxacin after failure of initial antibiotic treatment in children with severe salmonellosis. Eur J Clin Microbiol Infect Dis **1993**;12: 209–11.
100. Dutta P, Rasaily R, Saha MR, et al. Ciprofloxacin for treatment of severe typhoid fever in children. Antimicrob Agents Chemother **1993**;37:5: 1197–9.
101. Lumbiganon P, Pengsaa K, Sookpranee T. Ciprofloxacin in neonates and its possible adverse effect on the teeth. Pediatr Infect Dis J **1991**;10: 619–20.
102. Strandvik B, Hjelte L, Lindblad A, Ljundberg B, Malmborg AS, Nilsson-Ehle I. Comparison of efficacy and tolerance of intravenously and orally

administered ciprofloxacin in cystic fibrosis patients with acute exacerbations of lung infection. Scand J Infect Dis Suppl **1989**;60:84–8.

103. Bavdekar A, Chaudhari M, Bhave S, Pandit A. Ciprofloxacin in typhoid fever. Indian J Pediatr **1991**;58:335–9.
104. Martell M, de Ben S, Weinberger M, Beltrami G. Growth and development in preterm infants receiving fluoroquinolones. J Perinat Med **1996**;24:287–91.
105. Hampel B, Hullmann R, Schmidt K. Ciprofloxacin in pediatrics: worldwide clinical experience based on compassionate use—safety report. Pediatr Infect Dis J **1997**;16:127–9.
106. Chyský V, Kapila K, Hullmann R, Arcieri G, Schact P, Echols R. Safety of ciprofloxacin in children: worldwide clinical experience based on compassionate use. Emphasis on joint evaluation. Infection **1991**;4:289–96.
107. Pertuiset E, Lenoir G, Jehanne M, Douchain F, Guillot M, Menkes CJ. Tolérance articulaire de la péfloxacine et de l'ofloxacin chez les enfants et adolescents atteints de mucoviscidose. Rev Rhum Mal Osteoartic **1989**;56:735–40.
108. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? JAMA **1983**;249:1743–5.