

# Ciprofloxacin for the Treatment of Uncomplicated Gonorrhea Infection in Adolescents: Does the Benefit Outweigh the Risk?

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The highest rates of reported gonorrhea infections occur among adolescent females aged 15–19 years. Among the Centers for Disease Control and Prevention (CDC)–recommended single-dose gonorrhea treatment regimens, ciprofloxacin, a fluoroquinolone antibiotic, is approximately half the cost of other CDC-recommended oral treatment regimens. Fluoroquinolone use in patients aged <18 years has been limited because of irreversible articular cartilage damage demonstrated in large, weight-bearing joints of young animals. We reviewed the medical literature to assess whether the risks of a single 500-mg dose of ciprofloxacin to treat uncomplicated gonorrhea infection in adolescents appears to outweigh the benefits. We found no reports of irreversible cartilage toxicity or age-associated adverse events in 5236 human children and adolescents (aged 5 days–24 years) treated with a total of 5486 courses of fluoroquinolones.

The highest rates of reported gonorrhea infections occur among adolescent females aged 15–19 years [1]. Sociodemographic studies have mapped endemic gonorrhea and sporadic gonorrhea cases to impoverished urban areas with limited resources [2, 3]. Therefore, an inexpensive, effective, single-dose antibiotic would be beneficial for the treatment and control of gonorrhea.

Although *Neisseria gonorrhoeae* was once responsive to a wide spectrum of antibiotics, treatment options are now limited. In response to the progressive rise in *N. gonorrhoeae* resistance to penicillin and tetracycline, the Centers for Disease Control and Prevention (CDC) published guidelines in 1987 that include recommendations to discontinue use of these classes of antibiotics for treatment of gonorrhea infection [4]. Antimicrobial

resistance of *N. gonorrhoeae* remains a critical concern for gonorrhea treatment. Overall, 28.1% of isolates collected in 1999 by the CDC's Gonococcal Surveillance Project were resistant to penicillin, tetracycline, or both [1].

Some providers use azithromycin for the treatment of adolescent gonorrhea infection [5]. Published studies that have evaluated a 1-g single dose of azithromycin for gonorrhea treatment have demonstrated a suboptimal cure rate of only 93% [6–8]. A single 2-g azithromycin dose is effective in the treatment of uncomplicated gonorrhea infection, but the high frequency of gastrointestinal side effects and the high cost prohibit its practical use [6, 9].

The CDC's 1998 Guidelines for Treatment of Sexually Transmitted Diseases recommended the use of either 2 fluoroquinolone antimicrobials or 2 cephalosporins for the treatment of uncomplicated gonorrhea infection [6]. Among these recommended regimens, ciprofloxacin, a fluoroquinolone antibiotic, is one of the most affordable. Although ciprofloxacin has been

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**Table 1. Radiographic, anatomic, and histopathologic assessment of joints among adolescents and children treated with fluoroquinolones.**

Ref.	Study design	Subjects				Studies <sup>a</sup>	Outcomes	Exposure time, months <sup>b</sup>
		No.	Age (range)	Abx	Length of Rx			
[22]	P	24 pts, 39 courses	Mean, 11.5 (2.5–17) years	C	30.5 days (21–76)	X-ray of bilat knees and ankles during tx on 10 pts	All X-rays NL	1
[23]	R	1	15 years	C	4 weeks	X-ray of bilat knees, hips, and feet at 3 weeks of tx	All X-rays NL	2
[24]	R	1	16 years	C	22 days	X-ray of bilat knees, feet, and hands during tx and 4 months f/u	All X-rays NL	5
[25]	P	26	(6–16 years)	C	14 days	MRI of Rt knee	All MRIs NL	0.5
[26]	P	58	Mean, 11.7 (8 months–13 years) years	C	9–16 days	NMR scan of right knee at baseline and days 10–15 of tx	No changes of R knee NMR scans in 22/22	0.5
[27]	P	55	Mean, 10.2 (5–17) years	C	14 days	U/S bilat knees and hips before, during, and at end of tx in 48; MRI knee pre- and post-tx in 14	U/S, no changes; MRI, no cartilage abnormalities	0.5
[28]	P	219	(5 days–14 years)	C	NA	X-rays and MRIs of symptomatic joints during and 6 months after tx on 2 pts	All studies NL	6
[29]	P	18	(6–24 years)	C	3 months	X-ray of bilat knees at tx baseline and end; MRI of L knee at tx baseline and end for all and 4–6 months after for prepubertal pts	All studies NL	3–9
[30]	P	14 cases, 15 controls	Cases, mean 14.2 (7–18) years; controls, mean 11.9 (4–18) years	Case, C or O; control, other Abx	9.6 (7–10) days	X-rays of bilat knees and hips, MRI L knee after tx	Cases, 43% abn X-rays, 50% abn MRI; controls, 33% abn X-rays, 70% abn MRI	0.3
[31]	R	2	7 and 13 years	C	10 and 9 months	L knee autopsy	Cartilage, no histopathologic lesions, NL morphology; chondrocytes intact	9–10

**NOTE.** abn, abnormal; Abx, antibiotics; bilat, bilateral; C, ciprofloxacin; f/u, follow-up; L, left; NA, not available; NL, normal; NMR, nuclear magnetic resonance; O, ofloxacin; P, prospective; pts, patients; R, retrospective; Ref., reference; Rt, right; Rx, therapy; tx, treatment; U/S, ultrasound.

<sup>a</sup> Measuring joint-related adverse events.

<sup>b</sup> Duration of fluoroquinolone treatment and follow up (months of observation).

**Table 2. Studies reporting adverse events associated with fluoroquinolone use among adolescents and children.**

Reference	Study design	Subjects			Drug	Adverse events	Outcomes	Length of follow-up
		No.	Age (range)	Diagnosis				
[29]	P	18	(6–24 years)	CF	C	Photosensitivity (11.1%), diarrhea (5.5%), arthralgia (5.5%)	All resolved	4–6 months
[34]	P	41	Mean 11.7 (5–17) years	CF	C	Abn LFTs (25%), rash (15%), vomit (16%), CNS sx (1%), respiratory (10%), musculoskeletal (22%), injection complications (54%)	NA	14–30 days
[35]	P	18	(5–17 years)	CF	C	Abn LFTs (44.4%), arthralgia (11.1%)	All resolved	None
[36]	P	44	Mean 13.4 (4–25) years	CF	C	GI (4.8%), CNS (4.8%), knee arthralgia (4.8%), dry mouth (4.8%), photosensitivity (4.8%), abn LFTs (4.8%)	All resolved	6 weeks and 3 months
[27]	P	55	Mean 10.2 (5–17) years	CF	C	GI (14.5%), musculoskeletal (7.2%), rash (1.8%), nervousness (1.8%), abnormal LFTs (9.1%)	NA	20–30 days
[22]	P	24 pts, 39 courses	Mean 11.5 (2.5–17) years	CF	C	GI (12.5%), photosensitivity (4.2%), arthralgias (4.2%)	All resolved	None
[25]	P	26	(6–16 years)	CF	C	None reported	NA	14 days
[26]	P	58	Mean 11.7 (8 months–13 years) years	<i>Salmonella typhi</i>	C	GI (8.6%), abn LFTs (3.4%), abn DTRs (1.7%)	All resolved; growth NL in 53 with f/u	Mean 22.5 (19–37) months
[37]	P	8	(2.5–13 years)	<i>S. typhi</i>	C	None reported	NA	2 months
[38]	P	60	Median 6 (3.1–8.8) years	Dysentery	C	Arthralgias (18.3%), abn LFTs (5.2%), "other not felt related to tx" (27%)	All arthralgias resolved	7, 30, and 180 days
[28]	P	219	(5 days–14 years)	Multiple	C	Arthropathy (0.9%)	All resolved	6 months
[39]	P	8	(8–14 years)	UTI	C	None reported; growth normal	NA	3 and 6 months
[40]	P	21	Mean 4.25 (1–14) years	CSOM	C	Neutropenia (4.8%)	All resolved	11 months
[41]	P	100	Mean 8.2 (1–14) years	<i>S. typhi</i>	O	Delirium (1%), urticaria (1%)	All resolved	1 and 3 months
[42]	R	8	(3–16 years)	CF	C	None reported	NA	None
[43]	R	1733	<17 years	Multiple	C	Possible HUS exacerbation (0.06%)	Recovery	45 days
[44]	R	1795 pts, 2030 courses	<17 years	Multiple	C	GI (5.3%), metabolic (0.8%), CNS 1.4%, dermatologic (2.3%), hematologic (0.4%), photosensitivity (0.6%), cardiovascular (0.5%), respiratory (1.1%), arthralgias 1.7% (90% with CF)	92.5% resolved	None
[45]	R	634	(3 days–17 years)	Multiple	C	GI (4.9%), dermatologic (3.3%), CNS (2.2%), arthralgias (1.3%), GU (1.4%), metabolic (2.7%), fever (0.6%), flu symptoms (0.9%)	All resolved	None
[46]	R	21	Median 7 years	<i>S. typhi/S. paratyphi</i>	C	Limb ataxia (4.8%), confusion (4.8%)	All resolved	1 month
[47]	R	63	Mean 12 (1–21) years	CF	O	None reported	NA	None
[48]	R	40	(2–15 years)	<i>S. typhi</i>	O	Bilateral knee arthralgias (10%), hair loss (5%)	All resolved	3 and 6 months
[49]	R	5	(9–12 years)	Leukemia	N	None reported	NA	Mean 42.7 (24–62) months

**NOTE.** Abn, abnormal; C, ciprofloxacin; CF, cystic fibrosis; CSOM, chronic suppurative otitis media; DTR, deep tendon reflexes; GI, gastroenteric; HUS, hemolytic uremic syndrome; LFT, liver function test; N, norfloxacin; NA, not available; NL, normal; O, ofloxacin; P, prospective; pts, patients; R, retrospective; UTI, urinary tract infection.

**Table 3. Adverse events associated with fluoroquinolone use among adolescents and children as reported in the literature and by the Physicians Desk Reference (PDR) [10].**

Adverse event	Occurrence (%)		References
	PDR	Literature	
Cardiovascular	<1	0.5	[44]
CNS changes	<1–1.2	1–4.8	[26], [27], [34], [36], [41], [45], [46]
Constitutional symptoms <sup>a</sup>	<1	0.6–4.8	[36], [45]
Dermatologic <sup>b</sup>	1.1	1.0–15	[27], [34], [41], [45]
Gastrointestinal <sup>c</sup>	1.7–5.2	4.8–16	[22], [26], [27], [29], [34], [36], [44], [45]
Hematologic	0.1–0.6	0.4–4.8	[40], [44]
Metabolic abnormalities <sup>d</sup>	0.3–1.9	0.8–44.4	[26], [27], [34–36], [38], [44], [45]
Musculoskeletal <sup>e</sup>	<1	1.3–22	[22], [27–29], [34–36], [38], [44], [45], [48]
Photosensitivity	<1	0.6–11.1	[22], [29], [36], [44]
Possible HUS exacerbation	Normal	0.06	[43]
Respiratory	<1	1.1–10	[34], [44]

**NOTE.** HUS, hemolytic uremic syndrome; LFTs, liver function tests.

<sup>a</sup> Including fever, flulike symptoms, and dry mouth.

<sup>b</sup> Excluding photosensitivity.

<sup>c</sup> Including nausea, vomit, diarrhea, and abdominal pain.

<sup>d</sup> Including abnormal LFTs.

<sup>e</sup> Including arthralgias.

used extensively in children with pulmonary exacerbations due to cystic fibrosis, recommendations for fluoroquinolone use in patients aged <18 years have been limited [10, 11] because of documented irreversible articular cartilage damage in the large, weight-bearing joints of young animals [12–18].

Quinolone-induced arthropathy has been demonstrated in all immature animal species tested, including dogs, rabbits, rats, and guinea pigs [13, 15]. The effect on cartilage varies by animal species, age, quinolone type, and dose. Dogs are more susceptible to cartilage damage than other animal species, such as the rat [13, 15–18]. Young, skeletally immature animals primarily develop quinolone arthropathy [13, 15, 16, 19]. In juvenile beagle dogs, the period of maximal susceptibility corresponds to the period of maximal growth [16]. Most data have not demonstrated damage to older dogs. Although a study demonstrated microscopic adult cartilage changes after 12 months of continuous treatment with perfloxacin, a more arthropathic quinolone [17], we found no data that have attempted to demonstrate ciprofloxacin-induced cartilage toxicity in an adult animal. Ofloxacin produces damage at lower doses than ciprofloxacin [16, 17]. The minimum canine arthropathic dose of ciprofloxacin has been reported as 30 mg/kg/day, whereas the minimum dose for ofloxacin is reported as 10 mg/kg/day [16, 17]. Higher fluoroquinolone doses produce more extensive articular damage. For example, young beagles treated with ciprofloxacin 200 mg/kg/day were more likely to exhibit articular cartilage lesions than those treated with 100 mg/kg/day [18].

Clinically, the fluoroquinolone-associated cartilage toxicity in animal models has mainly been seen in large, weight-bearing joints. Affected dogs become lame, with sporadic synovial ef-

fusion after 1–7 days of quinolone treatment [16]. In addition, affected dogs exhibit an altered standing posture characterized by hyperextension of weight-bearing joints [16]. Histopathologic damage, such as blisters, fissures, and erosions accompanied by joint effusions, and MRI abnormalities are correlated with clinical findings [13, 15, 16, 18, 19].

Adolescents aged <18 years are at great risk for gonorrhea. This population would clearly benefit from greater availability of an inexpensive, effective gonorrhea treatment but are restricted from the use of fluoroquinolones because of a theoretical risk of associated cartilage toxicity observed in animals. In the present article, we review empirical evidence from the medical literature to assess whether (1) the theoretical barrier to the use of fluoroquinolones in patients aged <18 years is justified and (2) changes in fluoroquinolone treatment recommendations for uncomplicated gonorrhea infection should be made in future guidelines for treatment of sexually transmitted diseases (STDs).

## MATERIALS AND METHODS

We conducted a search of the literature from 1966 to 2000, using the MEDLINE 2000 database of the US National Library of Medicine. The terms “anti-infective agents,” “fluoroquinolones,” “ciprofloxacin,” and “ofloxacin” (as subjects) and “adverse effects,” “toxicity,” and “contraindications” (as key words) were searched in titles and abstracts. We found 69 references. We limited the search to articles concerning human subjects in English, French, or German. We excluded articles if data were not provided for at least one of the recommended gon-

orrhoea treatment regimens [6], if the age of the subjects was either undefined or if the majority of subjects were aged <1 or ≥18 years, or if subjects were taking additional antimicrobials during the study period. This reduced the number of citations to 14. We obtained an additional 17 citations from article references that had not been identified by the original search.

We included studies that provided data on the adverse effects of fluoroquinolone use in adolescents through their mid-20s. We summarized articles and recorded information on evaluation methodology, subject age, diagnoses, results, and study conclusions. Length of fluoroquinolone exposure and duration of follow-up were presented in months.

To estimate cost of the drugs included in the CDC-recommended gonorrhoea treatment regimens, the Department of Health and Human Services Supply Service Center catalogue [20] was used for “low-end” drug-cost estimates, such as those experienced by public-sector purchasers or managed care organizations; the Henry Schein Medical catalogue [21] was used for estimates of “high-end” drug costs, such as those incurred for purchase from a private-sector pharmacy. We drew conclusions on the basis of evidence from the literature for future changes in recommendations of adolescent fluoroquinolone use for the treatment of gonorrhoea infection.

## RESULTS

**Studies with histopathologic or radiological end points.** We reviewed 10 studies that, radiographically or pathologically by autopsy, evaluated pediatric and adolescent patients aged 5 days–24 years who were treated with ciprofloxacin or ofloxacin for 7 days–10 months [22–31]. These studies found no evidence of the cartilaginous pathology described in the original fluoroquinolone animal studies (table 1) [12–19]. Schaad et al. [31] performed autopsies of the left knee on 2 children aged 7 and 13 years with cystic fibrosis treated with 9–10 months of ciprofloxacin. He found no histopathologic cartilage lesions.

Of the 9 radiographic studies that evaluated large joints, 5 used X-ray and 5 used MRI [22–30]. None reported pathologic changes detected as a direct effect of therapy. One prospective study followed 29 pediatric patients with cystic fibrosis who had received 7–10 days of antibiotic treatment; 14 were treated with ciprofloxacin or ofloxacin, and 15 were treated with other standard cystic fibrosis antibiotic regimens [30]. The authors found similar proportions of abnormal knee X-ray and MRI findings in both treatment groups after completion of therapy (cases, 43% abnormal X-rays and 50% abnormal MRI; controls, 33% abnormal X-rays and 70% abnormal MRI.) Because children with cystic fibrosis are predisposed to joint abnormalities, this study failed to demonstrate that fluoroquinolone was associated with any additional risk of joint damage [32, 33].

The fluoroquinolone-induced irreversible articular cartilage

damage observed in large weight-bearing joints of juvenile animals evolves rapidly, within days [12, 15, 16]. However, irreversible fluoroquinolone-induced cartilage toxicity was not demonstrated during treatment and follow-up time (range, 0.3–10 months) among the 201 youth reported in the aforementioned studies (table 1). Such a finding should indicate the problems with extrapolating from animal data to humans and provide evidence, at the very least, that if fluoroquinolones do have adverse effects on the cartilage of children and adolescents, those effects are minimal compared with those found among animals.

**Clinical research studies with adverse events as end points.** A variety of adverse events associated with fluoroquinolone use have been described among pediatric and adolescent patients (table 2) [22, 25–29, 34–49]. The most common complaints were gastrointestinal (e.g., diarrhea and vomiting), musculoskeletal (e.g., arthralgias), dermatologic (e.g., photosensitivity rash), and hepatic enzyme elevation. Many of these studies were conducted among patients whose underlying diseases, such as cystic fibrosis or typhoid fever, may have caused the reported adverse events. All of the adverse events were self-limited. Six of 22 studies failed to detect any fluoroquinolone-associated adverse events among 118 pediatric and adolescent subjects [25, 37, 39, 42, 47, 49].

The spectrum and frequency of adverse events associated with fluoroquinolone use among pediatric and adolescent patients are compared with reports of adverse events among individuals aged ≥18 years as listed in the Physicians Desk Reference (PDR) in table 3. The most frequently reported fluoroquinolone-associated events listed in PDR include gastrointestinal complaints (nausea, diarrhea, vomiting, and abdominal pain/discomfort), CNS symptoms (headache and restlessness), dermatologic changes (rash), and elevated hepatic enzymes [10]. Although the spectrum of adverse events reported in adults is similar to those found among patients aged <18 years, the frequency of these events is greater among pediatric age groups. This may be due to reporting bias, because most pediatric patients in these studies had diagnoses that would render them more susceptible to gastrointestinal, dermatologic, and CNS symptoms and musculoskeletal complaints, such as typhoid fever and cystic fibrosis. Musculoskeletal complaints occurred more frequently among pediatric and adolescent patients than among adults. It is important to note that permanent arthropathy, the theoretical adverse event that restricts fluoroquinolone use among patients aged <18 years, was not reported in any of the scientific studies or the PDR.

**Case reports of adverse events.** Various reported pediatric and adolescent fluoroquinolone-associated adverse events, such as anaphylactic reaction, dystonic reaction, sleep disturbance, arthralgias, and hallucinations, have also been reported to occur

in fluoroquinolone-treated adults (table 4) [10, 23, 24, 50–53]. Benign intracranial hypertension, reported by Winrow et al. [54] in a 14-year-old girl treated with ciprofloxacin for a pulmonary exacerbation of cystic fibrosis, was not listed in the PDR [10]. However, intracranial hypertension has been reported in infants and children using nalidixic acid, a quinolone antibiotic [55].

**Published recommendations.** The American Academy of Pediatrics recommends fluoroquinolone regimens for the treatment of gonorrhea genital infections only for patients aged  $\geq 18$  years who weigh  $>100$  lbs (45 kg) [11, 56]. Other professional medical organizations, such as the American College of Obstetricians and Gynecologists and the American Academy of Family Physicians, have not published gonorrhea treatment recommendations.

**Costs of gonorrhea treatment regimens.** The costs for a course of ciprofloxacin range between \$1.05 and \$4.66 per curative dose (table 5) [20, 21]. Treatment costs are substantially greater with other recommended therapies, such as ofloxacin (\$2.39–\$6.01) and cefixime (\$4.78–\$6.44). Listed ceftriaxone prices (\$2.60–\$10.25) do not include the costs incurred with dispensing an intramuscular medication.

## DISCUSSION

Adolescents have the highest reported rates of gonorrhea; the reported 1999 rates were 738.1 out of 100,000 among females aged 15–19 years [1]. Ciprofloxacin, a fluoroquinolone antibiotic, is an effective single-dose treatment for uncomplicated

gonorrhea genital infections [57]. However, the theoretical risks of clinically and histopathologically apparent irreversible juvenile animal cartilage damage, evident within a few days of treatment, have restricted the use of this drug among adolescents aged  $<18$  years [12, 14–16, 18, 19]. Because gonorrhea rates are high in this population and STD control resources are limited, it is appropriate to consider whether the theoretical risks outweigh the therapeutic and economic benefits of ciprofloxacin use for treatment of gonorrhea infections in adolescents.

The 10 identified studies that have evaluated children and adolescents exposed to multiple-day doses of fluoroquinolones through objective radiological or histological methods demonstrated no evidence of irreversible cartilage damage [22–31]. Other studies that have assessed for fluoroquinolone-induced cartilage damage by more passive means did not report any evidence of clinically apparent irreversible damage among 4999 children and adolescents [34–49].

Age and quantity of drug exposure influenced the risk of animal joint damage. In beagle dogs, the period of maximal susceptibility corresponds to the period of maximal growth [16]. The vast majority of sexually active adolescents treated for gonorrhea will have passed their period of maximal growth. The recommended ciprofloxacin gonorrhea treatment regimen is a single 500-mg dose [6]. This dose calculates to 10 mg/kg in an individual who weighs 50 kg. The minimum ciprofloxacin dose associated with juvenile dog cartilage damage is 30 mg/kg/day over multiple days. The risk of a single  $\leq 10$ -mg/kg ciprofloxacin dose causing an adverse event in a skeletally ma-

**Table 4. Case reports of adverse events associated with quinolone use among adolescents and children.**

Reference	Patient characteristics		Abx	Adverse event	Outcome
	Age, years	Diagnosis			
	16	CF	C	Anaphylactic reaction	Resolved
[50]	15	CF	C	Anaphylactic reaction	Resolved
[23]	15	CF	C	Bilat hip and knee arthralgias with edema, effusion, bilat knees decreased ROM	Hip and knee X-rays NL; resolved
[51]	14	CF	C	Benign ICH	Electrolytes and CSF studies NL; resolved
[24]	16	CF	C	Bilat knee and left wrist arthralgia	X-rays, no articular cartilage/periostitis or erosion; lab tests, serum chemistries, PT, and U/A NL; resolved
[52]	5	<i>S. typhi</i>	C	Dystonic reaction	CSF, CBC, urine, stool, and chest X-ray NL; resolved
	6	CF	O	Sleep disturbances	Resolved
	6	CF	O	Sleep disturbances	Resolved
[53]	10	CF	O	Sleep disturbances	Resolved
[54]	17	Dysentery	N	Hallucinations	Resolved

**NOTE.** Abx, antibiotics; bilat, bilateral; C, ciprofloxacin; CBC, complete blood count; CF, cystic fibrosis; ICH, intracranial hypertension; N, norfloxacin; NL, normal; O, ofloxacin; PT, prothrombin time; ROM, range of motion; U/A, urinalysis.

**Table 5. Costs per curative dose for Centers for Disease Control–recommended treatment of *N. gonorrhoeae*.**

Medication	Curative dose, g	Cost <sup>a</sup> per curative dose (\$)	
		DHHS SSC catalogue	Henry Schein catalogue
Ceftriaxone sodium for injection	0.125	2.60–3.42	4.79–10.25
Cefixime tablets	0.4	4.78	6.44
Ciprofloxacin tablets	0.5	1.05–2.78	4.66
Ofloxacin tablets	0.4	2.39	6.01

**NOTE.** DHHS SSC, Department of Health and Human Services Supply Service Center

<sup>a</sup> Obtained from the DHHS SSC and Henry Schein Pharmaceutical catalogues. *C. trachomatis* cotreatment regimens not included.

ture adolescent should be much lower than the risk associated with multiple dose regimens dispensed to skeletally immature animals.

Our MEDLINE 2000 database literature search on this topic proved to be an insensitive method for identifying relevant journal articles. Although we may have missed other published studies that described pediatric fluoroquinolone-associated adverse events, it is unlikely that both our original search results and supplemental sources missed a study with significantly different findings.

Conclusions based on a literature review of fluoroquinolone-associated adverse events are also limited by the reality that a clinical trial is unlikely to have adequate power to detect a rare and serious adverse event. However, neither studies that followed 201 fluoroquinolone-exposed youth from 0.3 to 10 months nor case reports have described serious or irreversible cartilage damage associated with pediatric fluoroquinolone use. In light of the fact that the concerns of fluoroquinolone use and joint damage are well known, one might expect that if such a case had come to medical attention, its existence would have been reported [14, 15].

Limitations of the studies reviewed include sensitivity of methods used to detect cartilage damage. Three of the studies used X-ray to objectively measure joint-related adverse events [22–24]. X-ray may not be the most sensitive test to detect cartilage damage. However, more sensitive objective methods, MRI and autopsy, also failed to demonstrate evidence of irreversible fluoroquinolone-related cartilage damage [25–31].

These data are also limited by the specificity of the criteria used to assess for fluoroquinolone-related adverse events. Most of these studies involved subjects with an underlying disease known to cause joint pain, such as cystic fibrosis, typhoid fever, sepsis, and cancer. Therefore, it may have been difficult to differentiate drug-related events from disease-related events. However, Church et al. [34] were able to demonstrate that patients with cystic fibrosis experienced the same rate of joint-related events regardless of fluoroquinolone exposure. In this randomized controlled trial of patients aged <18 years treated

for pulmonary exacerbations of cystic fibrosis, subjects who received ciprofloxacin did not differ in treatment-associated musculoskeletal adverse events from the control group, which received standard therapy (21% vs. 22%).

The cost data we used may not be generalizable to all clinical settings. However, these quotes are representative estimates derived from major pharmaceutical suppliers that service the public [20] and private sectors [21]. Ciprofloxacin, a fluoroquinolone antibiotic, is the least expensive among the recommended oral regimens. Although the lower-end costs of ceftriaxone overlap with higher-end costs of ciprofloxacin, an intramuscular regimen incurs other dispensing costs, such as cost of syringes, needles, and nursing time. In addition, painful treatment may deter the adolescent from seeking future STD treatment services. Even though the absolute price per dose between recommended ciprofloxacin and the cefixime regimen differs by only a few dollars, the proportional difference is half. Because gonorrhea prevalence is relatively higher among adolescents, clinics that provide STD treatment services would expect to dispense a significant proportion of gonorrhea treatment to patients aged <18 years. Therefore, total programmatic costs for gonorrhea control would be reduced if fluoroquinolone use were not limited by age.

In light of the failure to demonstrate associated cartilage toxicity in fluoroquinolone-exposed children, the Food and Drug Administration is reassessing its restrictions on pediatric ciprofloxacin use. Ciprofloxacin has recently been approved for postexposure prophylaxis for pediatric inhalational anthrax, and the drug is currently being studied in phase 3 and 4 clinical trials for treatment of pediatric otitis media (C. Skowronski, personal communication).

In conclusion, the benefits of a single 500-mg dose of ciprofloxacin for the treatment of uncomplicated adolescent gonorrhea infection appear to outweigh the theoretical risks. Gonorrhea is a significant health problem among adolescents. Ciprofloxacin is an effective and inexpensive treatment option for uncomplicated genital gonorrhea infections. The cost of a single dose of ciprofloxacin is approximately half the cost of

the other oral nonfluoroquinolone, CDC-recommended single-dose gonorrhea treatment regimens. Irreversible cartilage toxicity, the theoretical risk that limits its use among the age group with the highest reported gonorrhea prevalence, has not been demonstrated in 5236 growing children or skeletally mature adolescents (aged 5 days–24 years) treated with 5486 courses of fluoroquinolones. Providers should consider these risks and benefits when managing uncomplicated gonorrhea infections in adolescents.

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