Review Article:

Safety Profile of Using Ciprofloxacin in Paediatrics: A Systematic Review and Meta-Analysis

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ABSTRACT

Context: The use of ciprofloxacin is contraindicated in children due to safety concerns. Animal studies have revealed that ciprofloxacin can be associated with arthropathy (joint toxicity) in juvenile animals; however, this potential side effect has not been proven in children. Many clinicians still prescribe ciprofloxacin when there is no suitable alternative. In many developing countries, access to the newer generation of antibiotics is either limited or expensive. Therefore, ciprofloxacin is an available and cost-effective alternative that can save lives when necessary.

Objective: This study aimed to systemically review the published studies about the safety profile of using ciprofloxacin in children.

Data Sources: All relevant studies published from 1990 to 2018 in the Cochrane library, Trip database, ScienceDirect, PubMed, and Google Scholar were collected.

Study Selection: We have only considered clinical trials, which included the following keywords: "ciprofloxacin", "children under 18 years", and "arthropathy".

Data Extraction: The collected data were analyzed by Comprehensive Meta-Analysis software (CMA.2). We used random or fixed-effect methods based on the heterogeneity of the results. The heterogeneity was checked by I^2 index and tau-squared. The publication bias was evaluated by the Begg's test.

Results: The obtained data indicated no increased risk of arthropathy after ciprofloxacin use in children on a short-term basis, in comparison to placebo or other antibiotics.

Conclusions: Ciprofloxacin is potentially a safe alternative to be used in children under 18 years old when there is no better alternative.

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1. Context

Quinolones have been used for many years for treatment of various infectious diseases. Nalidixic acid is the first quinolone that was discovered in 1962 (1). However, due to its limitations, such as toxicity issues, the narrow spectrum of antibacterial activity and low serum bioavailability, it is no longer used in practice (1, 2). The fluorination of quinolones resulted in the production of fluoroquinolones. Ciprofloxacin is a second-generation fluoroquinolone, which was discovered in 1987 (1). Ciprofloxacin and other second-generation fluoroquinolones have superior properties compared to nalidixic acid, such as the broad-spectrum bactericidal activity, and appropriate tissue penetration (2). Considering the above-mentioned properties, these antibiotics are more suitable to be used in practice (1, 3).

1.1. Mechanism of action

Although the antimicrobial resistance is increasing, many bacteria are still sensitive to fluoroquinolones (4). Based on the evidence, ciprofloxacin is the safest and most effective antibiotic in children compared to other fluoroquinolones (3, 5). It is effective in a wide range of Gram-positive and Gram-negative pathogens and acts by interfering with DNA functioning and inhibiting DNA gyrase and topoisomerase IV in bacteria. These enzymes are essential for DNA replication, transcription, repair, and recombination (5, 6).

Fluoroquinolones have many favorable properties in the treatment of bacterial infections in adults and children (2, 4, 5). Despite their effectiveness, the use of these antibiotics in growing children were limited due to the debatable safety concerns over the risk of joint toxicity and other adverse side effects (2). In vitro study of juvenile animals of different species, such as dogs, mice, rats, and rabbits, have illustrated that the use of ciprofloxacin and other quinolones can cause arthropathy in weight-bearing joints (2, 3). No evidence has proved the definite joint injury induced by ciprofloxacin in children (5). Since adverse effects are inevitable, fluoroquinolones like ciprofloxacin are recommended when other options are not available or effective (5).

1.2. Pharmacokinetics

The pharmacological data available on the use of ciprofloxacin to treat hospitalized pediatric patients are scarce. The literature review suggests that the half-life of ciprofloxacin is significantly longer in infants (under 1 year old) than toddlers (1 to 5 years old) (3). However, there is a very slight difference in maximum serum concentration levels (3, 7). Therefore, it is important to consider the age of the child at prescription. Most research on ciprofloxacin pharmacology has been performed on children with Cystic Fibrosis (CF).

Aradottir et al. (1999) found the Mean±SD scores of peak serum concentration and peak time following oral administration as 3.7±1.4 mg/L and 2.5±1.8 hours, respectively. The same records after intravenous administration were 5.0±1.5 mg/L and 1.0±0.3 h (7). The mean oral bioavailability of ciprofloxacin was obtained 76% in the same study. Younger patients (about 68%) absorb ciprofloxacin less compared to older patients (95%). Due to the higher clearance of this drug in adults, smaller doses are recommended in children. Ciprofloxacin is eliminated through renal and hepatic pathways (2).

1.3. Indications

Some guidelines approve the use of fluoroquinolones in pediatrics when the first line of treatment is not effective and no alternative is available (8, 9). Normally, the fluoroquinolone of choice is ciprofloxacin, due to its higher safety profile in comparison with other fluoroquinolones. Ciprofloxacin is prescribed in children with serious infections when its benefit outweighs the risks (3). The potential indications in pediatrics that several European and American guidelines agreed on include respiratory infections with Pseudomonas (P) aeruginosa in cystic fibrosis, multidrug-resistant infections, particularly in immunocompromised patients and those under chemotherapy, multidrug-resistant Shigella and Salmonella infections, and complicated urinary tract infections (5, 8, 9).

The mentioned infections are the main indications of ciprofloxacin in pediatrics. Furthermore, in the model list of essential medicines for children by the World Health Organization (WHO) (2010), ciprofloxacin (250 mg tablets) is only indicated for Shigella infection treatment in children aged 1 to 17 years, but not neonates (5, 6). While there are newer generations of fluoroquinolones available in the first world countries and developing countries, the shortage of these antibiotics has remained an issue (10). However, ciprofloxacin is the most cost-effective, cost-benefit, and available antibiotic in fluoroquinolones that can be used in practice in such countries (3, 10). Furthermore, upon discharging the patients on intravenous antibiotics from the hospital, the regimen must change to an oral preparation

when appropriate, which is more convenient for the patients and their parents (11).

2. Objective

Ciprofloxacin is an appropriate oral antibiotic applicable in many serious infections when there is no available alternative. There is no recent systemic review available to confirm the safety of this antibiotic in children. The present review aimed to collect evidence from clinical trials to evaluate the safety of using ciprofloxacin, focusing on arthropathy in children on a short-term basis (2 to 3 weeks).

3. Data Sources

The reviewed databases were Cochrane library, Trip database, ScienceDirect, PubMed, and Google Scholar as well as hand searching.

4. Study Selection

We have only considered clinical trials and the applied keywords that have been used were "ciprofloxacin", "fluoroquinolones", "pediatrics", "arthropathy", and "children under 18 years".

5. Data Extraction

A pediatrician and a pharmacist screened the collected data. We only included the full text English clinical trials and those focusing on pediatrics. We have considered ciprofloxacin treatment, as well as prophylaxis for different conditions. The factors that were included in this study were patients' age, underlying conditions, administration route, treatment duration, and potential side effects, with a special focus on arthropathy or cartilage toxicity. The studies that only involved adults were excluded from our research. Inclusion criteria consisted of the studies with

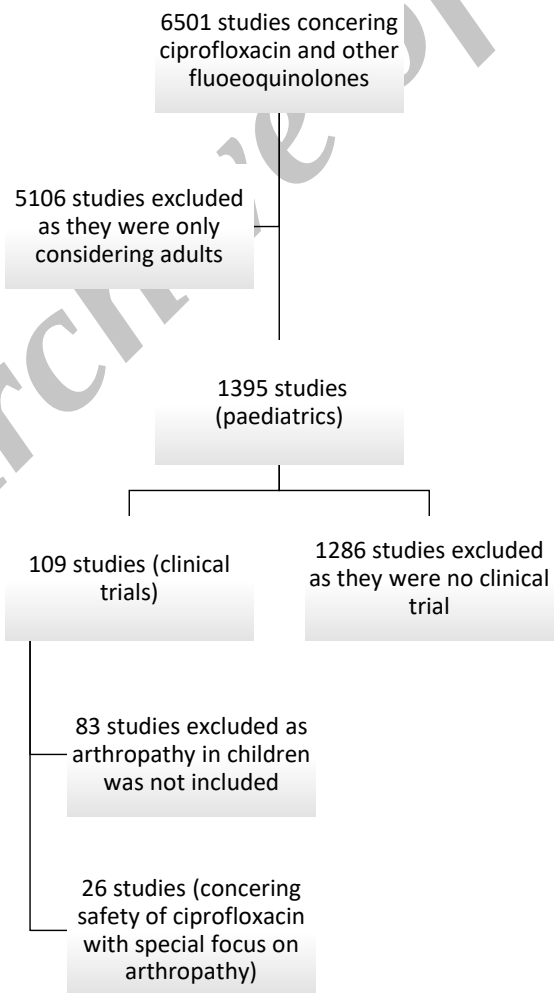

Figure 1. Consort diagram

the study patients aged ≥18 years and children with underlying conditions such as CF and malignancies.

5.1. Statistical analysis

The obtained data were analyzed by Comprehensive Meta-Analysis software (CMA.2). We used random or fixed-effect methods base on the heterogeneity of the results. Heterogeneity was checked by I^2 index and Tau-squared. The standard continuity correction of 0.5 was applied to zero events. Publication bias was evaluated by the Begg's test.

6. Results

We identified a total of 109 studies (Figure 1). From those, 26 studies investigated the safety of ciprofloxacin use in children and most of them were randomized clinical trials and observational studies. Appendix 1 presents the details of these 26 studies. We collected data from clinical trials published from 1990 to 2018. In total, there were 16155 pediatric study patients who were exposed to ciprofloxacin as a treatment for a range of indications. Among those, there were 82 reports of musculoskeletal adverse reactions.

Some studies suggest the risk of arthropathy associated with the use of ciprofloxacin equal to less than 1% (about 0.82%), and some stated that the odds could be as high as 3.3% (3, 5). Appendix 1 presents that the ciprofloxacin use in neonates (under 1 month old) is less likely to cause arthropathy; however, there exists a possibility of under-diagnosis in this age group. The obtained data suggest that the youngest age of the child's ciprofloxacin prescription was 3 days old (12, 13) (Tables 1 and 2).

7. Discussion

This systematic and meta-analysis review was conducted to evaluate the safety of using ciprofloxacin in children. We have pooled together and analyzed all the relevant articles, for drawing a conclusion in this regard. The studied reports in this review were clinical trials on the safety of ciprofloxacin and its suspected adverse events, especially arthropathy in children. Ciprofloxacin is not the first line recommended antibiotic in children (except for limited indications), based on joint toxicity reported by juvenile animal studies (1, 3). Ciprofloxacin is widely used in practice despite being contraindicated in this age category (3). We have investigated the arthropathy risk associated with ciprofloxacin and the effect of underlying conditions, treatment duration, age, and its dosage.

Fifteen out of 26 studies compared ciprofloxacin use to a control group; with 5 using a placebo in the con-

Table 1. The summary of musculoskeletal complications in children with cystic fibrosis

Results	No. of Musculoskeletal Complications	Drug Dose, mg/kg/day	Treatment Duration	Patients' Age	Study No. (Appendix 1, Table 1)
Treatment discontinued in 3 patients (2 of 3 had CF)	10	4-53	15 days	<19 years old	3
1 mild pain of knee (continued) 1 severe knee and ankle joints pain (discontinued)	Arthropathy n=2	10-20	-	5 days-14 years	6
All patients with arthropathy had CF	Arthropathy n=8	3.1-93.8	1-30 days	3 days-17 years	7
Ciprofloxacin is well-tolerated in CF	0	25-30	32 months	7-17 years	9
No arthropathy during or 2 weeks after the end of therapy	0	10-60	-	<18 years	12
Arthropathy not related to dose or duration	0	21.25±6.35	21 days (except 2 cases that received long-term Cipro)	2-18 years	13
No statistical differences between placebo and ciprofloxacin treated groups	0	15-20	18 months	1-12 years	15

Table 2. The summary of musculoskeletal events in children with cancer

Outcome	No. of Musculoskeletal Events	Dose (mg/kg/day)	Treatment Duration	Patients' Age	Study No. (Appendix 1, Table 1)
1 discontinuation due to maculopapular rash	0	10	18 days	3 months-18 years	2
Treatment discontinued in 3 patients (2 of 3 had CF)	10	4-53	15 days	<19 years	3
-	0	25	9 days	0-13 years	5
Ciprofloxacin use as prophylaxis in patients with Acute lymphoblastic leukemia	0	Depending on body weight	Long-term	0-15 years	20
No arthropathy	0	20 (to maximum of 500 mg)	No fixed duration	1-21 years	21
Treating patients with oral ciprofloxacin or IV ceftriaxone for fever and neutropenia is effective and safe	0	8-25	No fixed duration	3-20 years	23

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trol group. The rest were compared to other antibiotics (Figure 2). As shown in Figure 2, the decrease in arthropathy after treatment with fluoroquinolones compared to other antibiotic or placebo was 0.67 (95% CI: 0.5-0.89), which was statistically significant. The heterogeneity I^2 index and tau-squared were 32.2% and 0.36, respectively. Egger's test suggested no publication bias in the studies (P=0.729).

In conclusion, arthropathy has occurred either less frequently or equally in three studies with ciprofloxacin use, compared to placebo or other antibiotics (Figure 2). Laoprasopwattana et al. (2013) compared the use of ciprofloxacin to other antibiotics. They illustrated that arthropathy occurrence was the same in the ciprofloxacin-treated and control (placebo) groups (14).

Study number 17 reported that the incidence of joint dysfunction associated with the use of ciprofloxacin and

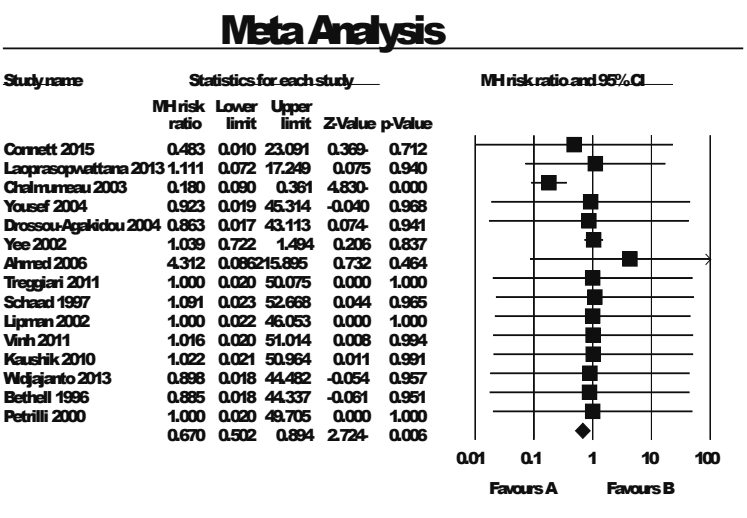

Figure 2. The forest plot for arthropathy risk following treatment with fluoroquinolones

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ofloxacin was 0.82% (13 of 1539), compared to 0.78% for azithromycin (118 of 15073) (15). However, azithromycin usually has no adverse effects on joint, tendon or cartilage; thus, the incidence of arthropathy could be related to the underlying conditions in the studied children rather than the antibiotics use (15, 16).

Underlying conditions, therefore, can be an important factor in the occurrence of arthropathy in children. Studies number 7, 14 and 26, listed in Appendix 1 revealed a higher number of children with joint-related side effects after ciprofloxacin exposure. However, all those children had CF and two studies have reported that arthropathy occurred in 7% to 8% of pediatric patients with CF even without ciprofloxacin exposure (17, 18). Consequently, having CF as an underlying condition can increase the risk of arthralgia development in children (17-19). Ciprofloxacin is often used in children with CF compared to other diseases. Therefore, a higher incidence of ciprofloxacin-related arthropathy is observed in this group of patients.

The follow-up time for investigating the arthropathy occurrence or any other joint toxicity after ciprofloxacin exposure in these studies ranged from two weeks to three years (2, 19). Arthralgia occurred in about 50% of the musculoskeletal complications and ranged from the mild pain of joints to inflammation and severe pain in patients. In total, only 9 children out of 82 who developed musculoskeletal problems discontinued their treatment with ciprofloxacin. All cases of arthralgia were reversible and patients remained asymptomatic on long-term follow-up (2, 8, 12, 20, 21).

We have also investigated the potential link between the treatment duration and arthropathy risk. In 7 studies ciprofloxacin has been used on a short-term (2 to 3 weeks) basis and the reported joint toxicity was either very small or none, which could indicate the possible effect of treatment duration on the risk of developing arthropathy (2, 14, 15, 21-23). In most studies, the short-term use of ciprofloxacin has not been associated with arthropathy even after a long-term follow-up of the patients (15, 16, 21, 24-31).

Only two studies have observed arthropathy occurrence in short-term ciprofloxacin usage. However, the incidence rate was either similar (study No. 2) or smaller (study No. 3) compared to the control groups. This could indicate that ciprofloxacin exposure was not the only factor causing arthropathy in those patients (2, 3). Contrary to these findings, which recognized the treatment duration as a risk factor in arthropathy occurrence, the finding of only one study was not compatible with the others. Faghihi (2017) study suggests that the risk of joint toxicity or arthropathy is not related to the dose or duration of treatment (32). However, this study had some limitations, including small sample size, no control group, and missing the effect of underlying conditions on arthropathy occurrence in pediatrics.

Furthermore, we have studied the potential relationship between the children's age and incidence of arthropathy. Of total 16155 children who studied in our dataset, 82 children developed joint problems after or during the ciprofloxacin treatment. The majority of these children were ≥6 years old. Only 7 of 82 affected children were under 6 years old, which indicates a much lower percentage compared to the older ones (8.5% vs. 91.5%) (8, 12, 15, 20). In addition, the use of ciprofloxacin in neonates up to one-year-old has not been associated with an increase in arthropathy incidence (16, 19). Therefore, ciprofloxacin use may be safe in younger ages, especially neonates.

In general, ciprofloxacin was administrated either orally or intravenously. The doses have been calculated according to the patient' weight and ranged from 3.1 to 93.8 mg/kg/day and were normally prescribed in two divided doses. We failed to find any relationship between the ciprofloxacin dose and arthropathy occurrence. This finding is similar to the review by Adefurin et al. (2011) where they could not confirm this relationship (1). We have considered ciprofloxacin treatment as well as prophylaxis use in this study. According to the collected data, the prophylactic use of ciprofloxacin has not been associated with an increased risk of arthropathy (9, 14). There were no major limitations associated with this study. However, we excluded some articles in this study from Embase due to the access limitations.

8. Conclusions

Our systemic review identified a relatively low and reversible risk of arthropathy associated with ciprofloxacin use in children compared to other fluoroquinolones. This adverse event is less likely to occur in short-term use and the incidence could also be related to other factors such as patients' underlying conditions and other medications used. Therefore, we suggest that when needed, this antibiotic can be prescribed safely in most children without the risk of joint toxicity. We suggest that future research is performed on patients with underlying conditions, especially those with CF to understand the effect of these conditions among children, with respect to arthropathy occurrence.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this article. The participants were informed about the purpose of the research and its implementation stages; they were also assured about the confidentiality of their information; Moreover, They were allowed to leave the study whenever they wish, and if desired, the results of the research would be available to them.

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Authors contributions

Conceptualization, Methodology, investigation and analysis: All authors; Writing-original draft: Baraneh Masoumi; and Supervision: Mohammad Sadegh Rezai, Gohar Eslami.

Conflict of interest

The authors declared no conflict of interest.

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Appendix 1. The summary of the clinical trial studies that reported the safety of ciprofloxacin in pediatrics

No.	Journal	Publication Year	First Author	Type of Study	P, CI	% or No.	Age of Study Groups	Healthy/ Underlying Conditions	Side Effects	Routes of Administration	Outcomes
1	Therapeutic Advances in Respiratory Disease	2015	Connett, G.	RCT	P<0.05	41	2-14 years	CF	N/A	Systemic (oral)	Recommendation of use of ciprofloxacin for 2 weeks as a second-line treatment Concern over the emergence of resistant by increasing the use of ciprofloxacin in children
2	The Pediatric Infectious Disease Journal	2013	Laoprasopwattana, K.	RCT	P=0.03	95	3 months -18 years	Acute Lymphoblastic Leukemia (ALL) Lymphoma	Maculopapular rash in 1 patient (discontinuation) Abdominal pain (2 vs. 5) Arthralgia/ arthritis (1 vs.1)	Systemic (oral)	Significantly lower (23%) development of fever in patients receiving ciprofloxacin in comparison to placebo users during the induction phase of chemotherapy Median treatment duration of 18 days, which could be a possible reason for the lower occurrence of arthropathy in patients
3	Pediatrics Journal	2003	Chalumeau, M.	Comparative cohort study	P<0.05 CI: 14.9-24.5	525	Neonates-18 years	Malignancies CF Immunosuppression	GI (n=15) Musculoskeletal system (n=10): arthralgia of large joints or myalgia-No observation of tendinopathy Skin (n=7) Kidney (n=5) CNS (n=3)	Systemic (IV and PO)	Higher incidence of musculoskeletal events compared to adults These events appeared within 2 weeks after the initiation of FQ, mainly observed as large joint arthralgia of knees, shoulders, and wrists. Much higher events of musculoskeletal events with pefloxacin (18.2%) compared to ciprofloxacin (3.3%)
4	BMC Infectious Diseases	2018	Meesters, K.	The retrospective drug utilization study	P<0.05	262	Neonates-18 years	Malignancies CF Other indication without an underlying condition	N/A	Systemic (Oral and IV) Topical	Most FQ use for the treatment of CNS infection (24.8%)- off-label use Then, prophylaxis of febrile neutropenia, RI, pneumonia and UTI
5	Pediatric Blood Cancer	2004	Yousef, A.	Pilot study	P<0.05	69	0-13 years	Acute Lymphoblastic Leukemia (ALL)	No bone or joint side effects were observed in the test and control groups	Systemic	Reduction of hospitalization (decreased to 58%) The use of prophylactic ciprofloxacin in children with ALL may reduce the incidence of bacteremia and associated hospitalization. Risk of antibiotic resistance
6	Indian Journal of Pediatrics	2000	Singh, U.K.	Observational study	-	219	5 days-14 years	No underlying conditions CF	Arthropathy (0.9%)	Systemic IV	Arthropathy only occurred in two patients (0.09%), both resolved after the discontinuation of treatment with ciprofloxacin, X-ray and MRI showed no abnormality during treatment and at 6 months follow-up. Ciprofloxacin is safe, cheap and a useful alternative antibiotic in children, thus, this study suggests the use of it when there is a case of multidrug-resistant infection or when the organism is sensitive to ciprofloxacin.

No.	Journal	Publication Year	First Author	Type of Study	P, CI	% or No.	Age of Study Groups	Healthy/ Underlying Conditions	Side Effects	Routes of Administration	Outcomes
7	Infection Journal	1991	Chysky, V.	Case report	-	634	0-17 years	CF	GI Skin CNS	Systemic	A total of 8 reports of arthralgia (1.3%). All of them were female and suffering from CF. All joints complain were transient and reversible upon discontinuation. Slight higher incidence of arthralgia in children compared to adults. This can be related to underlying conditions.
8	The Pediatric Infectious Disease Journal	2004	Drossou-Agakidou, V.	Observational prospective study	-	216	0-1 month		Thrombocytopenia Hyperbilirubinemia Elevated hepatic enzyme Elevated creatinine	Systemic	No clinical evidence of arthropathy was observed at either the initial hospitalization or follow up. No potential effect on growth, even though height maybe totally independent of cartilage damage. A similar growth rate in both control and test groups.
9	Clinical Pediatrics	1993	Orenstein, D.	RCT	-	39	7-17 years	CF	A slight increase of serum creatinine concentration A small increase in alkaline phosphatase concentration.	Systemic	During the two-week treatment with ciprofloxacin, no arthropathy episode has been observed. Overall, 7% to 8% of CF patients develop arthropathy without exposure to ciprofloxacin. This study was based on a short course of Ciprofloxacin, use in CF and long-term safety cannot be justified.
10	The Pediatric Infectious Disease Journal	2002	Yee, Ch.	Observational study	95% CI	21197	<19 years	More than 4000 children who were prescribed FQ, including children with underlying conditions such as CF	N/A	Systemic	This study suggests that the incidence of joint toxicity is likely to reflect the underlying conditions. The use of FQ compared to azithromycin does not increase the joint toxicity incidence.
11	The Paediatric Infectious Disease Journal	2006	Ahmed, N.	Prospective study	-	497	Preterm neonates <33 weeks gestation	N/A	Retinopathy (4:1 ratio between the test and control groups)	Systemic (IV)	No differences were observed in the development of children in the ciprofloxacin group compared to the control group in terms of first walking, and other aspects of motor, language or cognitive development. No evidence of acute or subclinical joint toxicity was observed in the neonates who were treated with ciprofloxacin.
12	BMC Infectious Diseases	2013	Yang, Zh.T.	Observational mono-center study	-	98	<18 years	Patients with and without CF have been included in this study	-	Systemic	No notice of any bone/joint when ciprofloxacin was used in short term.

No.	Journal	Publication Year	First Author	Type of Study	P, CI	% or No.	Age of Study Groups	Healthy/ Underlying Conditions	Side Effects	Routes of Administration	Outcomes
13	Journal of Research in Pharmacy Practice	2017	Faghihi, T.	Observational study		32	2-18 years	Most patients were non-CF children In total, 9% of children had CF	No other side effect has been discussed in this study.	Systemic	No case of arthropathy was observed. However, it has been illustrated that the risk of arthropathy is not dependent on dose or duration of treatment. The study emphasizes on the importance of using ciprofloxacin when no other safe alternatives are available.
14	Journal of Antimicrobial Chemotherapy	1990	Black, A.	Observational study		202	2-17 years		GI Arthralgia Skin Renal Thrombophlebitis Dizziness Hallucinations	Systemic	Very few adverse reactions have been noted during this study, with only one case of arthralgia. None of the cases with arthralgia were severe in nature, also patients suffered from CF and 7-8% of arthropathy cases were present in this patient group.
15	Archives of Paediatrics and Adolescent Medicine Journal	2011	Treggiari, M.	RCT	95% CI	304	1-12 years	CF	-	Systemic	The occurrence of adverse events was not significantly different between groups except for the higher frequency of cough in patients.
16	The Paediatric Infectious Disease Journal	1997	Schaad, U. B.	RCT	-	44	4-15 (23 patients)	CF	Abdominal pain CNS Dry mouth Knee pain	Systemic	The study concludes that the use of ciprofloxacin in CF patients can improve the clinical, bacteriologic and pulmonary functions. Ciprofloxacin is well tolerated and no sign of ciprofloxacin-related skeletal toxicity has been observed.
17	Intensive Care Medicine Journal	2002	Lipman, J.	Clinical trial	-	20	3 months-5 years	Severe sepsis	Seizure N=1 (inappropriately high dose)	Systemic	No arthropathy has been identified in this study.
18	Neglected Tropical Diseases Journal	2011	Vinh, H.	RCT	95%CI, P=0.83	494	2 months-12 years	Shigellosis	Night sweating Vomiting	Systemic	Both ciprofloxacin and gatifloxacin showed similar efficacy in the treatment of dysentery. No evidence of and ciprofloxacin-related arthropathy has been identified in this study with a two-year follow-up of ciprofloxacin-treated children. This study confirms the safety of fluoroquinolones in pediatrics.
19	Indian Paediatrics Journal	2010	Kaushik, J.	RCT	95% CI	470	2-12 years	Cholera	-	Systemic (single dose)	Single dose azithromycin is superior compared to single dose ciprofloxacin in the treatment of cholera in children.
20	Journal of Blood Medicine	2013	Widjajanto, P.	RCT	P=0.07-0.01	110	1-14 years	Acute Lymphoblastic Leukemia (ALL)	Diarrhea Nausea Vomiting Neuritis	Systemic	Using ciprofloxacin as prophylaxis during the induction treatment has shown a lower neutrophil count and a higher rate of mortality.

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21	American Cancer Society	2000	Aquino, V.	CT	-	32	1-21 years	Cancer	In total, 2/45 severe vomiting and required hospitalization	Systemic	A total of 89% of patients were treated successfully in outpatient settings with oral ciprofloxacin for febrile neutropenia. A study with larger sample size is required to confirm the safety of this approach.
22	Archives of Disease in Childhood	1996	Bethell, D.	Prospective cohort study	95% CI	326	1-14 years	N/A	-	Systemic	No evidence of acute or subclinical joint toxicity was observed during the treatment and after two years of follow-up. No reason to withhold FQ antibiotics in pediatrics when no safe alternative was available.
23	Medical and Paediatric Oncology	2000	Petrilli, A. S.	Randomized prospective trial	P<0.05	186	3-20 years	Cancer	GI side effects (nausea, vomiting, diarrhea and epigastric pain)	Systemic	In low-risk febrile neutropenia, patients were treated successfully as an outpatient for fever due to infection. Both oral ciprofloxacin and IV ceftriaxone have yielded therapeutic success. Treating children in outpatient settings have a number of benefits, including better patient satisfaction, low cost, and low nosocomial infection risk.
24	Journal of Antimicrobial Chemotherapy	1992	Schaad U.B.	CT	-	18	6-24 years	CF (n=5)	N/A	Systemic	No evidence of arthropathogenicity was observed during this comprehensive monitoring.
25	Diagnosis of Microbiol Infection Disease	1999	Krcmery, V.	CRT	-	12	3 weeks-6 months	-		Systemic	Despite the occurrence of arthropathy in animals, the ciprofloxacin-induced joint toxicity in neonates has not been confirmed. However, due to the risk, the duration of the therapy should be limited.
26	Indian Paediatrics Journal	1996	Karande, S.	CT		3341 (n=582, long-term follow-up)	2-12 years	-	N/A	Systemic	During the therapy with ciprofloxacin no joint-related ADR in 581 children as observed. A total of 20 cases of ciprofloxacin-related acute arthropathy, which all have been reversible on follow up (within 2 weeks)

Abbreviations: RCT: Randomized Clinical Trial; CT: Clinical Trial; CF: Cystic Fibrosis; IV: Intravenous