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Original Research Article

Safety and tolerability of moxifloxacin in pediatric population: A systematic review of evidence-based practice

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Abstract

Purpose: *To evaluate the adverse events (AEs) associated with moxifloxacin (MFX) use in children below the age of 18 years.*
Methods: This review was performed in conformity with the preferred items for systematic reviews and meta-analysis (PRISMA) guidelines using different databases. Articles meeting the inclusion criteria were screened and the studies were selected for the qualitative synthesis.
Results: A total of 21 studies were included in the systematic review. Among these, 7 retrospective cohort studies, 6 case reports, 3 prospective cohort studies, 2 randomized clinical trials (RCT) and the remainder utilized other methodologies. The variability in studies allowed for an assessment of the safety and tolerability of both short-term and long-term MFX administration in pediatric patients.
Conclusion: Although MFX use is associated with AEs, the majority were mild and resolved on their own. The reason for QTc prolongation and elevated liver enzymes remain a question for clinicians in prescribing MFX in pediatric patients.

Keywords: Moxifloxacin (MFX), Community-acquired pneumonia (CAP), Adverse effects (AEs), Randomized clinical trials (RCT)

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INTRODUCTION

The use of antibiotics in children is challenging due to their unique pharmacokinetic and pharmacodynamic characteristics, which results in unpredictable drug reactions and adverse events [1]. Therefore, it is crucial to assess the safety and tolerability of antibiotics in pediatric population to ensure their rational use. Moxifloxacin (MFX) is a fourth-generation fluoroquinolone with broad-spectrum activity against most causative organisms involved in adult community-acquired pneumonia (CAP), complicated intraabdominal infections (cIAIs), urinary tract infections and complicated skin infections [2-5]. However, systemic use of MFX in children is not currently approved by the Food and Drug Administration (FDA) due to concerns regarding its potential adverse effects, including nervous system disorders, tendon disorders, and polyneuropathy [6]. Nevertheless, MFX holds a unique function among pediatric treatment options and is often used to treat various bacterial infections in children, such as multidrug-resistant tuberculosis [7-9] and neonatal *Mycoplasma hominis* meningitis [10], due to its high oral bioavailability, broad-spectrum of activity, and ability to penetrate the central nervous system.

Although the use of MFX has been established in pediatric population in certain conditions, clinical data on its safety and tolerability is scarce. In one of the early studies, Silver *et al* [11] examined the safety and efficacy of MFX when given as an ophthalmic solution to bacterial conjunctivitis patients. They found that several patients developed ocular and non-ocular adverse events following treatment. Similarly, in 2008, a case report highlighted the manifestation of severe migratory polyarthritis with tendon rupture and bursae effusions following treatment of mild upper respiratory infection with high dose MFX [12]. This study brought forward the atherogenic effects of MFX in children. A recent study of FDA adverse events reporting system (FAERS) found 375 AEs attributed to MFX. From these AEs, MFX was a primary agent in 37.9 %, with elevated liver enzymes being the most common [13]. Lack of clinical data on the use of moxifloxacin in children has resulted in cautious prescribing practices and limited use of this drug in pediatric patients. The goal remains to compile evidence regarding the safety and tolerability of MFX in patients under 18 years old, focusing on the frequency and types of AEs. This systematic review aimed to assist in strategizing treatment plans for pediatric populations who require MFX therapy.

METHODS

Study design

This review was performed in conformity with the preferred items for systematic reviews and meta-analysis (PRISMA) and the Cochrane Collaboration guidelines [14,15].

Data sources and searches

A primary literature search was performed from inception till 5th March 2023 using PubMed, Science Direct and Scopus electronic databases. Further, a supplementary search was done using Google Scholar. Additionally, bibliographies of retrieved studies were searched to identify potentially eligible studies. The search string used the following keywords: ‘moxifloxacin’, "pediatrics," ‘pediatric population’, ‘children’, ‘Avelox’, ‘vigamox’, "safety," and "tolerability".

Inclusion and exclusion criteria

All articles shortlisted from the literature search were exported to Endnote Reference Library (Version X7.5; Clarivate Analytics, Philadelphia, Pennsylvania) software where duplicates were removed. The two independent reviewers scrutinized the remaining articles according to the set eligibility criteria. No language restriction was placed in the literature search.

Original studies satisfying the following inclusion criteria were added to the systematic review: pediatric patients (age < 18 years) undergoing treatment for a particular disease with moxifloxacin and articles including adverse effects of moxifloxacin (MFX) or evaluating the safety profile of the drug. Discrepancies were resolved by discussion. Review articles, conference proceedings, abstracts, and commentaries were excluded.

Data extraction

Two independent reviewers carried out data extraction and verification. Any disagreement was resolved by discussion. Lastly, a snowball search was performed to ensure no articles were missed. Data was collected from Tables, Figures, and text of relevant articles and extracted in Google Sheets.

This data included general study characteristics (author’s name and year, design, sample size, and location of study) and patient demographics (age, sex, population type, race, treatment duration, and detailed list of adverse events).

Quality assessment

The Newcastle Ottawa Scale (NOS) was used to assess the quality of cohort studies, whereas the Risk of Bias 2 (RoB-2) tool of the Cochrane Collaboration was used for randomized controlled trials (RCTs). For case reports, the Joanna Briggs Institute (JBI) critical checklist was used to assess the quality. The NOS is a 9-star grading system comprising three domains: selection, comparability, and outcomes. Whereas, the RoB-2 tool includes generation of allocation sequence, randomization of participants to exposure, selective reporting of outcomes, and missing data. Two investigators performed quality assessment independently and disagreements were resolved by consensus.

Data synthesis and reporting

Data extracted from the included studies were summarized qualitatively. As this study is based on a systematic review of published literature, no ethical approval is required. The results of this study were reported following the PRISMA 2020 guidelines, ensuring transparency and completeness of the reporting process.

RESULTS

Study selection

A comprehensive search of all electronic databases returned a total of 2788 articles. After deduplication and removal of reports based on title and abstract, 1248 were shortlisted for eligibility assessment. Further 643 articles were excluded owing to incorrect patient population or study type (review articles, case reports, and commentaries). Finally, a total of 255 studies were given a full-text evaluation. From this, 59 studies were excluded as they included non-pediatric population, 84 were excluded due to incomplete information, and 91 were removed as they included other interventions alongside MFX. The PRISMA flowchart in Figure 1 highlights the study selection process.

General characteristics

The included studies (Table 1) present a wide range of populations and conditions in which moxifloxacin was administered to pediatric patients. A total of 21 original studies met the set inclusion criteria of this systematic review with a total of 1773 patients. From these 21 studies, 7 retrospective cohort studies, 6 case reports, 3 prospective cohort studies, 2 RCTs and the remaining with other methodologies. The sample sizes of the included studies vary significantly, ranging from single case reports to larger cohorts. While larger sample sizes provide more robust data, smaller studies provide valuable insights into specific conditions or rare adverse events associated with moxifloxacin use. The age range of the participants varied across the studies, with some studies including a wide age range from infants to adolescents, while others focused on specific age groups. The mean age of participants was 9.9 years and the mean male sex percentage of 52.4 %. The proportion of male participants varied across the studies, ranging from 33.33 to 100 %. The studies were conducted in multiple countries, including the USA, Venezuela, Italy, South Africa, Saudi Arabia, Germany, Canada, France, China, and multiple other countries through data from the FDA Adverse Event Reporting System (FAERS). The pediatric populations included in the studies varied widely, encompassing children with bacterial conjunctivitis, upper respiratory tract infection, pulmonary drug-resistant tuberculosis, multidrug-resistant tuberculosis, complicated intra-abdominal infections, disseminated BCGitis, underlying infections, lens-related surgery, severe refractory *M. pneumoniae* (pneumonia), *Stenotrophomonas maltophilia* (VP shunt infection), *Mycoplasma hominis* (meningitis), and rifampicin-resistant tuberculosis. These diverse populations highlight the breadth of conditions in which moxifloxacin is used and allow for a comprehensive understanding of its safety and tolerability across different indications. The duration of moxifloxacin treatment varied among the studies, ranging from a few days to several months. The variability in treatment duration allows for an assessment of the safety and tolerability of both short-term and long-term moxifloxacin administration in pediatric patients.

Adverse effects of moxifloxacin

Table 2 presents the most common adverse events reported in the included studies. The majority of the studies include a standard regimen of moxifloxacin, as recommended by the WHO, except for Torres and Bajares [12]. They reported a case from Venezuela of a 12-year-old male child who had been prescribed a high dose (50 mg/kg/day) of MFX for a mild upper respiratory tract infection. Five days after the prescription, the child presented with symptoms of severe migratory polyarthritis, including an inability to move, swelling of the large joints, and effusions of both knees. Microbiological cultures were negative, no trauma history was reported, and no autoimmune or rheumatic disease was noticed. Intravenous and oral steroids were given for the treatment of severe migratory polyarthritis

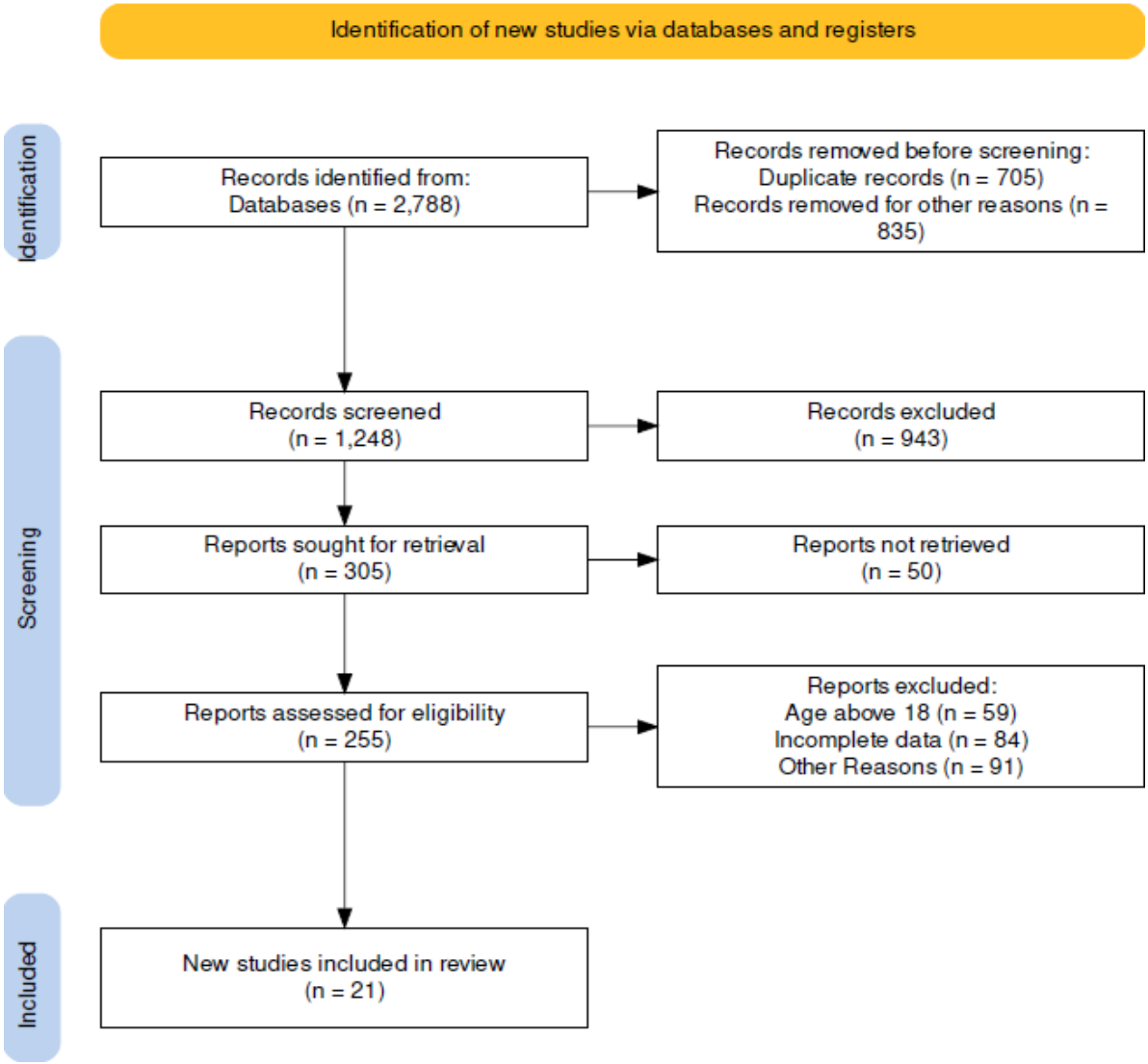

Figure 1: PRISMA flowchart

for one week. Two studies included overall side effects seen following treatment with an ophthalmic solution of 0.5 % MFX. Silver *et al* [11] used the solution for the treatment of bacterial conjunctivitis and reported AEs after a treatment duration of nine days whereas, Khalili *et al* administered it to those undergoing lens-related surgery [22]. Amongst the ocular side effects, ocular discomfort (1.9 %), conjunctivitis (1.1 %), and subconjunctival hemorrhage (0.9 %) were the most common. From the non-ocular AEs, the most common were: increased or development of cough (3.2 %), otitis media (3.0 %), and infection (2.6 %). In Khalili *et al,* [22] patients were followed for a total of 19 months following surgery and AEs were recorded. Corneal edema was reported in 7 eyes out of a total of 170 eyes, and acute inflammation was seen in 23.9 % of patients. However, both studies included overall adverse events which may not have been attributed to MFX. In both studies, MFX was considered safe as MFX group had comparable AEs as the comparator groups. Garazzino *et al* followed nine patients with pulmonary drug-resistant TB given a 10mg/kg/day dosage of MFX for an average of 6.8 months. At follow-up, from the nine patients, one developed arthritis of the ankle and the other showed a grade 3 elevation of liver enzymes. Thee *et al* [17] included 23 multidrug-resistant TB patients taking a 7.5-10mg/kg/day dosage of MFX for a mean of 10.2 months. The most common AE reported was nausea (39 %), followed by arthralgia, elevated liver enzymes, and headache, all in 21.7 % of the patients. Pruritis (17.4 %), vomiting (13.0 %), and increased bilirubin levels (4.3 %) were also observed. Dixit *et al* studied patients from a children's hospital in USA who underwent treatment with MFX for various illnesses. A total of 463 AEs were reported from 221 children. However, 46 of them were attributed to MFX.

Table 1: General characteristics of the included studies

Study, year	Design	Country	Sample size	Population	Treatment Duration	Age, years	Male (%)	Race
Silver 2005 [11]	RCT	USA	462	Bacterial conjunctivitis	3-4 days	3 days - 17 years	NA	Any
Torres & Bajares 2008 [12]	Case report	Venezuela	1	Healthy (Mild upper respiratory tract infection)	5 days	12	100	NA
Garazzino 2014 [16]	Retrospective	Italy	9	Pulmonary drug-resistant TB	207 ± 116 days	6 months – 13 years	33.33	NA
Thee 2014 [17]	Prospective study	South Africa	23	MDR TB	14 days	Median age 11.1 years	39.10	Blacks 56.5%
Dixit 2018 [18]	Retrospective	USA	221	Children's Hospital patients	22 days (average)	10.4 years	57	Whites 64.3% Blacks 7.2%
Wirth 2018 [19]	RCT	-	301	cIAI	Mean 8.7 days (1-24 days)	Median age 13 years	59.50	White 96%
Alsuhaibani 2019 [20]	Retrospective descriptive study	Saudia Arabia	10	Disseminated BCGitis	307 days	3.3 years	60	Asian 100%
Stass 2019 [21]	Retrospective cohort study	Germany	31	Underlying infections	Single IV infusion over 60 mins	Mean 5.3 ± 3.7 years	77	Whites 68% Blacks 16%
Khalili 2020 [22]	Retrospective cohort study	Canada	113	Undergoing lens-related surgery	Single dose intracamerally	Mean age 4.9 years	56	-
Kong 2023[13]	Retrospective	USA	375	FAERS	5 days	12-18 years	41.90	-
Pinon 2010 [24]	Case reports	Italy	2	MDR-TB	395 days in pt 1 60 days in pt 2	23 years & 11 years	50	White 100%
HE, 2023 [25]	Retrospective study	China	31	SRMPP	10 days	6.96 ± 3.72 years	64.52	Asian 100%
Chauny 2012 [26]	Case reports	France	6	TB	487 days	9 months-15 years	16.6	Asians 50%, Africans 33.3% French 1%
Radtke 2022 [27]	Observational prospective study	South Africa	85	RR-TB	274 – 548 days	Median age 4.6 years	43.5	Africans 100%
Granet 2007 [28]	Randomized placebo-controlled study	USA	10	Normal ocular health	Single visit	9 years and above	39	97% Caucasians

Note: RCT: Randomized controlled trials; MDR TB: Multidrug-resistant-tuberculosis; cIAI: Complicated Intra-abdominal Infections; FAERS: FDA adverse event reporting system; SRMPP: severe refractory *M. pneumoniae* pneumonia; TB: Tuberculosis; RR-TB: Rifampicin resistant tuberculosis; PK: Pharmacokinetic; LRTI: Lower respiratory tract infection; VP: Ventriculoperitoneal

Table 1: General characteristics of the included studies *(continued)*

Study, year	Design	Country	Sample size	Population	Treatment Duration	Age, years	Male (%)	Race
Greenberg 2022 [29]	Prospective population PK study	USA	14	LRTI, Fever, skin or soft tissue infection	Standard treatment	1-16 years	71	Caucasian 43%, Black 29%, Asians 7%, Multi-racial 7%,
Wagner 2004 [30]	Crossover designed	USA	50	Normal healthy	Single drop	7-17 years	NA	NA
Gregory 2019 [31]	Case report	USA	1	Stenotrophomonas Maltophilia	21 days	5 months	100	Caucasian
Watt 2012 [32]	Case report	USA	1	VP Shunt Infection Mycoplasma hominis Meningitis	3 days	6 days	100	NA
Winckler 2020 [33]	Cross-sectional study	South Africa	26	TB	273 days	Median age 6.9 years	NA	NA
Shen 2013 [34]	Case report	China	1	Mycoplasma pneumoniae infection	7 days	7 years	100	100 % Asian

Note: RCT: Randomized controlled trials; MDR TB: Multidrug-resistant-tuberculosis; cIAI: Complicated Intra-abdominal Infections; FAERS: FDA adverse event reporting system; SRMPP: severe refractory *M. pneumoniae* pneumonia; TB: Tuberculosis; RR-TB: Rifampicin resistant tuberculosis; PK: Pharmacokinetic; LRTI: Lower respiratory tract infection; VP: Ventriculoperitoneal

Table 2: Most common adverse events reported in all the studies

Study, year	OD	CI	IFM	Infection	H	IC	Vomiting	ELE	QTC p	IB	Diarrhea	Pruritus	SBMP	Arthritis	MI
Silver 2005 [11]	9/462 (1.95%)	NAR	NAR	12/462 (2.6)	3/462 (0.6)	15/462 (3.2)	6/462(1.3)	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR
Torres & Bajares 2008 [12]	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	1/1 (100)	NAR	NAR
Garazzino 2014 [16]	NAR	NAR	NAR	NAR	NAR	NAR	NAR	1/9 (11.1)	NAR	NAR	NAR	NAR	NAR	1/9 (11.1)	NAR
Thee 2014 [17]	NAR	NAR	NAR	NAR	5/23 (21.7)	NAR	3/23(13.0)	5/23 (21.7)	NAR	1/23 (4.3)	NAR	4/23 (17.4)	NAR	NAR	1/23 (4.3%)
Dixit 2018 [18]	NAR	NAR	NAR	NAR	NAR	NAR	NAR	8/300 (2.7)	18/300 (6.0)	3/300 (1.0)	1/300 (0.3)	1/300 (0.3)	NAR	NAR	NAR
Wirth 2018 [19]	NAR	NAR	NAR	NAR	NAR	NAR	1/301(0.3)	NAR	21/301 (7.0)	NAR	6/301 (2.0)	NAR	NAR	NAR	NAR
Alsuhaibani 2019 [20]	NAR	NAR	NAR	NAR	NAR	NAR	10.2 months	3/10 (30.0)	NAR	1/10 (10.0)	NAR	NAR	NAR	NAR	NAR
Stass 2019 [21]	NAR	NAR	NAR	NAR	NAR	NAR	2/31(6.5)	3/31 (9.7)	NAR	NAR	1/31 (3.2)	NAR	NAR	NAR	NAR
Khalili 2020 [22]	-	7/170 (4.1%)	27/113 (23.9)	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR
Kong 2023 [13]	NAR	NAR	NAR	NAR	NAR	NAR	NAR	19/375 (5.1)	10/375 (2.7)	NAR	NAR	NAR	NAR	NAR	NAR
He 2023 [25]	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	5 (16.13)
Chauny 2012 [26]	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	1(16.6)	NAR
Granet 2007 [28]	1(1%)	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR	NAR

Note: NAR: No ADR Reported; OD: Ocular discomfort; CI: Corneal edema; H: Headache; IC: increased cough; ELE: Elevated Liver Enzymes; IB: Increased bilirubin SBMP: Severe bilateral migratory polyarthritis; IFM: inflammation; QTC p: QTC prolongation; MI: Musculoskeletal injury

The most frequent AE was QTc prolongation making up 39.1 % of the AEs. Increased transaminase levels, rash, and increased bilirubin levels were also seen, forming 2.7, 1.0, and 1.0 % of the total AEs credited to MFX, respectively. An RCT, conducted by Wirth *et al,* [19] followed 301 complicated intraabdominal infections (IAIs) pediatric patients treated with MFX. A total of 175 patients developed some kind of adverse event. Reporting AEs occurring because of MFX, 7 % showed prolongation of the QTc interval. Similarly, diarrhea was seen in 2 % of the patients. No headache, fever, or elevated liver enzymes were reported. Additionally, when compared with ertapenem with co-amoxiclav, MFX was associated with an increased number of AEs. Similarly, a study conducted in Germany by Stass *et al* [21] highlighted side effects caused by MFX treatment of various underlying infections. The most common infection seen in the patients was respiratory tract infection. Elevated liver enzymes were reported in 9.7 % of the patients. 6.5 % of the patients developed vomiting, whereas 3.2 % had increased cough, rash, and diarrhea. No QTc prolongation was observed. Alsuhaibani *et al* [20] showed ten pediatric patients with a severe complication of the BCG vaccine (BCGitis) undergoing treatment with 10 mg/kg/day MFX orally. Followed for a mean of 10.2 months, three patients showed a marked increase in liver enzymes and one patient had an elevated bilirubin count. All these AEs were attributed to MFX. Kong *et al* [13] studied the FDA adverse events reporting system and shortlisted 375 patients who underwent treatment with MFX. Vomiting and cardiac arrest were significantly associated with the use of MFX. None of the studies reported valve regurgitation and arthralgia as adverse reactions while studies by Pinon *et al* [24], Radtke *et al* [27], Greenberg *et al* [29], Wagner *et al* [30], Gregory *et al* [31], Watt *et al* [32], Winckler *et al* [33] and Shen *et al* [34] did not report any adverse reactions.

Overall, the adverse events reported in the studies were generally low, with some studies reporting specific adverse events in certain patient populations. However, it is important to note that the absence of adverse events in a study does not necessarily indicate their absence in clinical practice, as reporting biases and limitations in data collection and documentation influence the reporting of adverse events.

Quality assessment of studies

The quality assessment of cohort studies showed that all were of good quality as per the NOS. From a total score of nine, all studies were seven or above, indicating the robust methodology of the included cohort studies. The RoB-2 tool showed a low overall risk of bias in the included RCTs. Similarly, JBI critical checklist highlighted the good quality of case report.

DISCUSSION

This systematic review of 21 studies including a total of 1546 pediatric patients (age < 18 years), establishes an association between adverse events and MFX use. The studies encompass various designs, including randomized controlled trials (RCTs), case reports, retrospective studies, prospective studies, cohort studies, and observational studies. This diversity in study design allows for a comprehensive evaluation of MFX's safety and tolerability across different research methodologies. In this study, adverse events were noted in patients with multidrug-resistant TB, complicated intraabdominal infection (cIAI), bacterial conjunctivitis, those undergoing lens-related surgery, disseminated BCGitis, and patients with some underlying infection.

This study reports that elevated liver enzymes, QTc prolongation, and gastrointestinal disturbances were amongst the most common AEs attributed to MFX. Several side effects were reported concerning pediatric patients undergoing treatment with an ophthalmic solution of 0.5 % MFX. Earlier *in vitro* ocular studies assessing the safety of the ophthalmic solution of MFX in animals reported no effect of the drug on corneal thickness, which is a sensitive predictor of corneal health [34]. However, Khalili *et al* reported corneal edema and acute inflammation as AEs credited to the treatment regimen of ophthalmic solution of MFX [22]. This could be due to pediatric patients being relatively more prone to an increased inflammatory response after cataract surgery [35]. In the study by Khalili *et al*, however, MFX treatment was not more likely to develop side effects when compared with the subconjunctival antibiotics group [22]. Although acute inflammation and corneal edema were observed, MFX was deemed equally safe as subconjunctival antibiotics after cataract surgery. Similarly, in Silver *et al* [11] MFX was determined safe and tolerable in children as it had comparable adverse events as the vehicle group. Although patients experienced ocular discomfort, it was generally mild and usually resolved on their own. Amongst non-ocular AEs, patients developed a cough, infection, rhinitis, and otitis media, all of which were flagged as unrelated to MFX treatment.

For pediatric patients with TB, gastrointestinal disturbances, liver enzyme elevation, and headaches were most commonly seen. However, Garazzino *et al* [16] added evidence of fluoroquinolones-induced arthralgia and arthritis as one patient developed arthritis of the ankle. This could be attributed to the fact that fluoroquinolones possess the ability to induce cartilage toxicity [36]. Similarly, Torres and Bajares showed a 12-year-old boy treated with high-dose MFX for a mild upper respiratory tract infection [12]. After five days, the boy developed severe migratory polyarthritis, thus, increasing evidence for the arthrogenic effects of MFX. In the study by Thee *et al*, five patients developed mild arthralgia following MFX therapy, which was reversed upon cessation of the drug [17]. Thee *et al* established the safety of MFX in long-term use with the recommended dosage [17]. In both the TB studies, MFX was well-tolerated and in Garazzino *et al* all children except those lost to follow-up were clinically cured [16]. Thus, cementing the use of MFX for aggressive forms of TB, drug-resistant and extensive forms. The liver toxicity caused by the elevation of transaminases may not be attributed to MFX as both studies contained concomitant hepatotoxic drugs. Similarly, in Alsuhaibani *et al* liver toxicity was documented in three of the ten patients with disseminated BCGitis [20]. These patients were undergoing treatment with MFX and concomitant hepatotoxic medications (ethambutol and clarithromycin). Thus, elevated liver enzymes could not be properly attributed to MFX.

Dixit *et al* studied patients admitted to a children's hospital who were treated with moxifloxacin [18]. Overall, MFX was considered safe and well-tolerated as a low rate of drug-related AEs was observed (14.3 %). In this study, QTc prolongation was the most common AE credited to MFX, followed by raised transaminase levels. QTc prolongation might be attributed to fluoroquinolones' interaction with cardiac K+ channels hERG [40]. However, moxifloxacin was administered concomitantly with other QTc prolongation drugs. As identified by the study, the number of concomitant medications was significantly associated with QTc prolongation. Regardless of this, electrocardiogram (ECG) monitoring is warranted upon admission and during MFX therapy to observe any changes to the QTc interval. The elevated transaminase levels could be associated with fluoroquinolone-associated liver injury. Although the pathophysiology is not fully understood, it is linked with hypersensitivity reactions [38]. In this study, MFX was associated with lower overall rate of AEs (16 %) as compared to other studies surveying children undergoing treatment with fluoroquinolones.

Wirth *et al* [19] compared the safety and efficacy of MFX with ertapenem followed by co-amoxiclav. Although there were more AEs reported in the MFX cohort, generally, both drugs were safe and tolerable. Fluoroquinolones-associated arthropathy was not observed in this study. Unsurprisingly, MFX was attributed to increases in QTc interval. No link between MFX-induced QTc prolongation and risk factors could be established as subjects with well-known risk factors (hypokalemia, bradycardia, hypocalcemia, hypomagnesemia, and history of cardiovascular disease) were excluded from the study [39]. Thus, QTc prolongation in this study again might be attributed to fluoroquinolones' modulation of cardiac potassium channels since increased serum MFX concentration has been significantly associated with increased QTc interval [40].

Kong *et al* [13] studied the Food and Drug Administration (FDA) adverse events reporting system (FAERS). Two AEs were significantly linked to the use of MFX. Vomiting was seen in 7.5 % and cardiac arrest in 2.7 % of the patients. Vomiting could be attributed to moxifloxacin-associated abdominal distension [41,42]. Cardiac arrest could be associated with QTc prolongation as increased QTc intervals, especially above 500ms, are associated with Torsade de Pointes arrhythmia.

Limitations of this study

The investigation successfully determined the frequency and types of numerous adverse events attributed to MFX. While this study adds evidence to the existing literature, there are some limitations. Firstly, the sample size of the included studies was not sufficient enough to come to a strong conclusion. Secondly, elevated liver enzymes and QTc prolongation AEs could be linked with concomitant medication use. Thirdly, the majority of the studies were retrospective cohorts, thus, more randomized controlled trials are warranted to study the safety and tolerability of MFX in children. Lastly, the studies did not divide the pediatric population into various subgroups based on age.

CONCLUSION

This review demonstrates that while there are certain side effects associated with the use of MFX in pediatric population, the AEs were generally mild and resolved spontaneously. MFX was well-tolerated in pediatric patients. The

findings provide valuable insights into the safety and tolerability profile of moxifloxacin in pediatric population, contributing to evidence-based decision-making in pediatric clinical practice. However, ECG readings and liver function tests must be performed at baseline and during treatment. Finally, large-scale studies are still needed to solidify safety of MFX in children.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All the authors significantly contributed to this systematic review.

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