Fluoroquinolones and Musculoskeletal Toxicity in Pediatrics:

Is The Fear Real?

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Learning ojectives:

1) Provide a brief overview of fluoroquinolone antibiotic class
2) Discuss the pathophysiology of musculoskeletal toxicity associated with fluoroquinolones
3) Review the primary literature analyzing the safety profile of fluoroquinolones in pediatrics
4) Formulate a clinical recommendation regarding the use of fluoroquinolones in pediatric infections

Background on Fluoroquinolones

I) History [1,3,4]

A) 1962: Lesher discovers nalidixic acid as by-product of chloroquine synthesis
B) 1964: Nalidixic acid became first quinolone approved by the FDA, but limited utility due to its narrow spectrum of activity and toxicity
C) 1980s: Addition of fluorine to the six position of the basic quinolones structure resulted in norfloxacin and ciprofloxacin
D) 2014: Currently marketed fluoroquinolones (FQ) for systemic use include norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin and gemifloxacin

II) Mechanism of action [1,2]

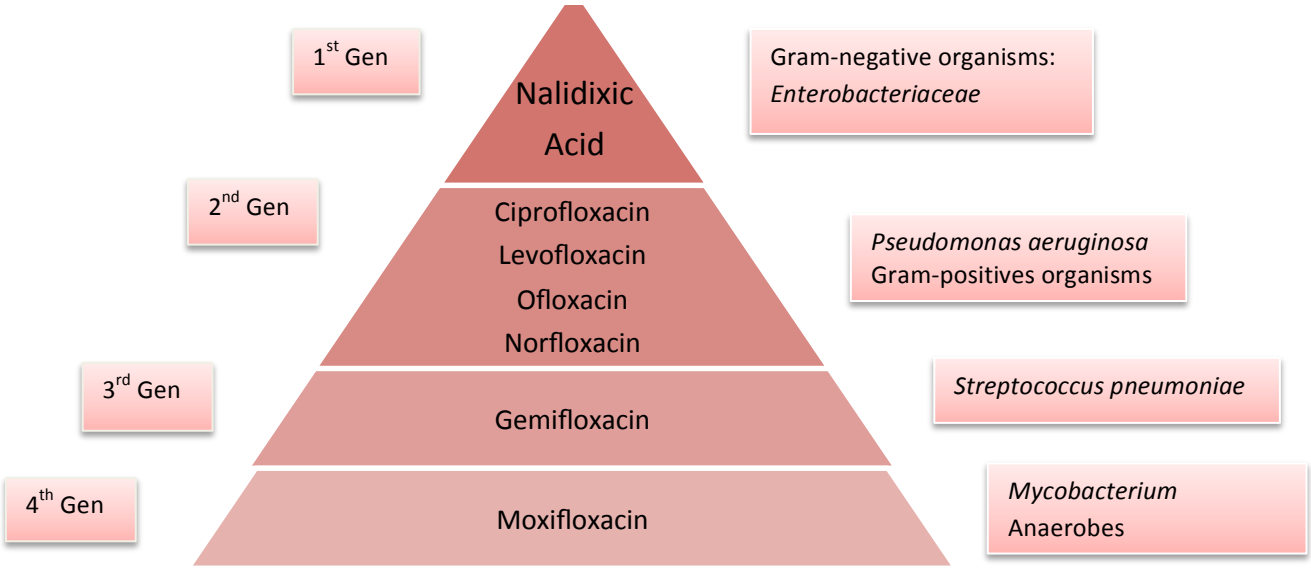
A) Bactericidal agents
B) Inhibit bacterial deoxyribonucleic acid (DNA) synthesis by interfering with:
    1) DNA gyrase: main target of quinolones in gram negative bacteria
    2) Topoisomerase IV: main target of quinolones in gram positive bacteria

III) Pharmacodynamics & pharmacokinetics [1,5,8]

A) Rapid absorption and great bioavailability for oral administration (75-100%)
B) Volume of distribution
    1) Excellent tissue penetration
    2) Good intracellular diffusion
C) Concentration dependent killing
D) Metabolism/Elimination
    1) Hepatic metabolism: no dose adjustment needed
    2) Renal elimination: dose adjustment required for all except moxifloxacin

IV) Spectrum of activity [1,2]

Figure 1: Classification and antimicrobial activity of fluoroquinolones



Korean J pediatr. 2013 May; 56 (5): 196-201[2]

V) Indications [1,9]

Table 1: FDA labeled indications for systemic fluoroquinolones in adults[1]

Ciprofloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Anthrax	Anthrax	LRTI/ URTI *	Cervicitis
Bone/Joint infections	Chlamydia	SSTI **	Bronchitis
Intra-abdominal infections	Intra-abdominal infections	Complicated intra-abdominal infections	Pelvic inflammatory disease
Febrile neutropenia	LRTI/ URTI *	Tuberculosis (MDR±)	Prostatitis
Gonoccoccal infections	Prostatitis		UTI ¥
Endocarditis	SSTI **		Urethritis
Infectious diarrhea	Surgical prophylaxis		
LRTI/ URTI *	Tuberculosis		
SSTI **	UTI ¥		
Surgical prophylaxis			
UTI ¥			

*LRTI: lower respiratory tract infection; URTI: upper respiratory tract infection; **SSTI: skin and soft tissue infection; ¥ UTI: urinary tract infection; ± MDR: multi-drug resistant

Table 2: FDA labeled indications for systemic fluoroquinolones in pediatrics[2,3,5]

Ciprofloxacin	Levofloxacin	Moxifloxacin
Anthrax	Anthrax	
Complicated UTI/pyelonephritis	Community acquired pneumonia (CAP)	CAP
Cystic Fibrosis	Cystic fibrosis	
	Tuberculosis (MDR)	

In 2006, American Academy of Pediatrics (AAP) stated FQ that use in children allowed if: [4]

1) Multi-drug resistant (MDR) bacteria and intravenous FQ therapy is the only viable treatment option
2) Oral FQ required for use in outpatient setting and all other therapeutic options are intravenous

VI) Mechanism of resistance [4,5]

A) Change in target enzymes
   1) DNA gyrase and topoisomerase IV
   2) Cross resistance to entire class
B) Increase in efflux pumps
C) Alternations in membrane porins

VII) Adverse effects and toxicity [2, 7]

A) Gastrointestinal (most common)
B) Central nervous system
C) Dermatological
D) QT interval prolongation and arrhythmia

1) Moxifloxacin > levofloxacin > gemifloxacin > ciprofloxacin [5]
2) Risk factors: elderly, female, pre-existing QT prolonging conditions or arrhythmias

E) Musculoskeletal[2, 6]
1) Arthropathy: disease of the joint
2) Arthritis: inflammation of the joint evidenced by redness or swelling of area
3) Arthralgia: pain in the joint as evidenced by complaint
4) Chondrotoxicity: injury to the cells of the connective tissue cartilage
5) Gait abnormality: limping or refusal to walk
6) Tendinopathy: disease or injury of a tendon

Musculoskeletal Toxicity Associated with Fluoroquinolones

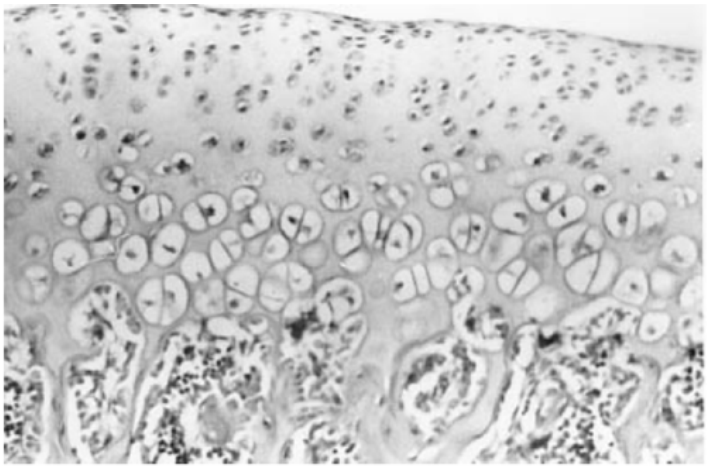
I) Chondrotoxity in animals

Table 3: Summary of animal studies indicating musculoskeletal toxicity with quinolones

Study Title	Quinolone/ Study animal	Dose	Musculoskeletal Toxicity
Ingham et al.(1977) [11]	Nalidixic acid oxolinic acid pipemidic acid on Immature dogs	200- 1000 mg/kg for 1 to 15 days	1. Stiffness of gait and lameness of limbs observed 2. Higher incidence in younger animals 3. Signs of arthropathy only in weight-bearing joints 4. Clinical signs of toxicity resolved within 14–21 days even with continued medication but the blisters and erosions not resolved in animals autopsied up to 87 days after withdrawal of drug
Linseman et al. (1995)[12]	Pipemidic acid on neonatal mice (1.5-2 grams)	SQ 50, 400, or 3150 mg/kg/day for 7 or 14 days	1. Lameness observed only after higher doses 2. Mice treated for 14 days had lower incidence of lesions than mice treated for 7 days (suggests potential for reversibility during ongoing treatment) 3. Histopathological assessment of weight bearing joints revealed lesions characterized by chondrocyte loss, matrix degeneration, erosion of articular cartilage
	Ciprofloxacin on neonatal mice (1.5-2 grams)	50 or 200 mg/kg/day) for 5, 7, 14 days	
Keutz et al. (2004)[13]	Ciprofloxacin on young beagle dogs	0, 10, 30, 90 mg/kg/day for 2 weeks (5 month observation follow-up)	1. Only 30 mg/kg and 90 mg/kg doses had histopathological evidence of cartilage injury after 14 days of treatment 2. histopathological evidence of skeletal toxicity 3. Clinical signs of injury resolved in 2 months but histopathological evidence was present at 5 month follow-up
Kato et al. (1995)[14]	Perfloxacin on 4 week old rats (95.7 g weight)	300 and 900 mg/kg as single dose or once daily for 2 week	1. Mild edema, dilation of blood vessels, lesions and mononuclear cell infiltration seen along the affected tendon sheath of Achilles tendon; cavitations seen in the middle zone of the articular cartilage 2. Ofloxacin induced tendon lesions on articular cartilage at 900 mg/kg dose only; 70% incidence of tendon lesions seen with ofloxacin 3. Observation after 2 week treatment, edema had resolved, lesions were replaced by fibrotic foci and chondrocyte clusters were observed around lesions. This was thought to be representative of regenerative process. Lesions were able to recover even during the course of continued administration (for 2 weeks)
	Ofloxacin on 4 week old rats (95.7 g weight)	300 mg/kg and 900 mg/kg) as single dose or once daily for 2 week duration	

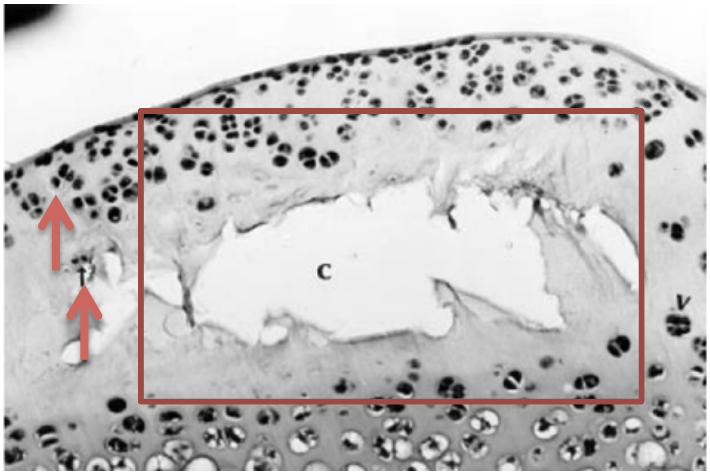
Figure 2: Comparison of articular cartilage after ofloxacin administration[16]

A)



Normal histology of the articular cartilage of a five week old rat

B)



Histology of articular cartilage at two weeks following 900 mg/kg/ day ofloxacin for 7 days

- Cavitations can be seen
- Shrunken chondrocytes with pyknotic nuclei (articular surface over the cavity is irregular and slightly elevated)

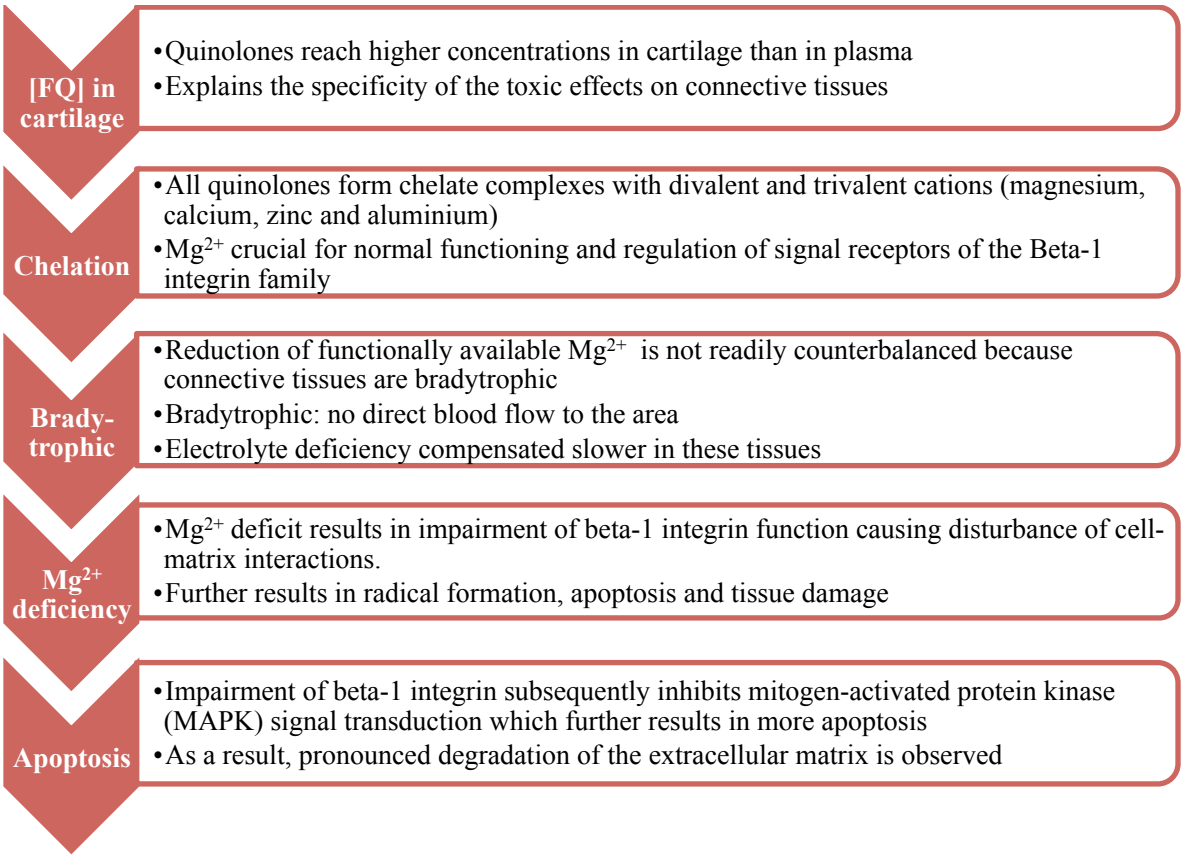
Turk J Med Sci. (2000) 30: 441-44

II) Mechanism behind condrotoxicity [17-19]

A) Theories based on in-vitro studies of cartilage tissues
   1) Inhibition of collagen or glycosaminoglycan synthesis
   2) Oxidative injury to chondrocytes
   3) Inhibition of chondrocyte DNA synthesis
   4) Compromised mitochondrial integrity
   5) Chelation of magnesium ions (Mg^{2+}) [19-20]

B) The most recent and plausible postulation is chelation of Mg^{2+}

Figure 3: Quinolone chondrotoxicity due to chelation of magnesium ions[17-18]



III) Animal studies support theory of chondrotoxicity due to Mg^{2+} deficiency

A) Stahlmann R et al. (1995)[19]

1) Group 1: Mg^{2+} deficiency induced by feeding juvenile rats a Mg^{2+} deficient diet for 9 days and treated the rats with single oral doses of ofloxacin (0, 100, 300, 600, or 1,200 mg/kg of body weight) during this period
2) Group 2: Group of juvenile rats on a normal diet treated with ofloxacin (0, 100, 300, 600, or 1200 mg/kg)
3) Lesions in rats treated with ofloxacin plus Mg^{2+} deficiency were more pronounced than those in rats with normal Mg^{2+} concentrations
4) The similarity of the findings in both groups of animals (ofloxacin treatment and Mg^{2+} deficiency) gives proof that a lack of functionally available Mg^{2+} is the primary event in the development of quinolone-induced arthropathy

B) Forster C et al. (1996) [20]

1) Joint cartilage lesions were detected in ofloxacin-treated and Mg^{2+}deficient rats
2) Expression of several integrins was reduced in the vicinity of lesions after oral treatment with 2 x 600 mg ofloxacin/kg for one day
3) Changes in cartilage matrix composition showed similar alterations in ofloxacin-treated and Mg^{2+} deficient rats.

Literature Review

<table>
<tr><td colspan="3">Yee C et al. Tendon or joint disorders in children after treatment with fluoroquinolones or azithromycin. Pediatr Infec Dis J. 2002;21:525-529 [22]</td></tr>
<tr><td>Objectives</td><td colspan="2">• Primary: Assess incidence and relative risk of tendon or joint disorders (TJD) associated with FQ compared to azithromycin
• Secondary: characterization of TJD cases based on age and gender, the anatomic location of TJDs and the time to onset of TJD</td></tr>
<tr><td>Design</td><td colspan="2">Retrospective, cohort, observational study (1992 to 1998)</td></tr>
<tr><td>Patients</td><td colspan="2">• Age < 19 years of age
• At least 90 days of continuous enrollment in their United Health Care plan</td></tr>
<tr><td>Method</td><td colspan="2">• Automated search of United Health Care Research database to identify patients prescribed ofloxacin, levofloxacin, ciprofloxacin or azithromycin (1992 -1998)
• ICD-9 coding to identify patient complaints, concomitant disease and indications
• TJD identified as joint, cartilage, tendon or gait related
• Phase 1: potential TJD cases identified by screening the research database
• Phase II: potential cases verified by a blinded independent reviewer</td></tr>
<tr><td>Results</td><td colspan="2">• 7897 children prescribed a FQ; 20,283 children prescribed azithromycin
• 576 potential cases of TJD identified; 168 confirmed TJD diagnosis
<table>
<tr><th>Antimicrobial</th><th>Exposure</th><th>Potential TJD</th><th>Verified TJD</th></tr>
<tr><td>Azithromycin</td><td>20,283</td><td>413 (2%)</td><td>118 (0.78%)</td></tr>
<tr><td>Ofloxacin</td><td>1905</td><td>34 (1.7%)</td><td>13 (0.82%)</td></tr>
<tr><td>Levofloxacin</td><td>38</td><td>1 (2.6%)</td><td>0 (0%)</td></tr>
<tr><td>Ciprofloxacin</td><td>5904</td><td>128 (2.2%)</td><td>37 (0.82%)</td></tr>
</table>
• Predominance of lower extremity involvement in all cohorts
• No difference in age or gender regarding risk for potential TJD cases and verified TJD cases
• Time to event onset evenly distributed over the 60 day observation period
• Joint related TJD predominated: 70%, 76% and 69% incidence in azithromycin, ciprofloxacin, ofloxacin respectively
• Relative risk for TJDs was 1.04 (95% CI 0.72-1.51) for ciprofloxacin and 1.04 (95% CI 0.55 to 1.84) for ofloxacin compared to azithromycin
• Azithromycin has no known effect on cartilage or joints therefore the incidence of TJD estimated in this study for azithromycin is likely due to background incidence of these disorders</td></tr>
<tr><td>Author's Conclusion</td><td colspan="2">Verified incidence of TJD in each individual agent was < 1%. Levofloxacin not used frequently enough to draw conclusion about this agent. TJD occurs rarely in children given FQ and the incidence of these disorders occurring within 60 days of prescription of FQ is not different from that which occurs after azithromycin use.</td></tr>
<tr><td>Critique</td><td>Strengths:
• Large sample size
• Multiple fluoroquinolones included
• Active comparator group
• Blinded evaluation of potential TJDs by specialists</td><td>Weakness:
• No specific diagnostic criteria for TJD
• No of events per TJD type not studied
• No mention of underlying joint diseases in children
• Duration and dose of FQ therapy not mentioned (authors mentioned that several off label indications that could have used low doses)
• A broad range of ICD-9 claim codes used to identify potential TJD episodes (overestimation of TJD)</td></tr>
</table>

<table>
<tr><td colspan="2">Chalumeau et al. Fluoroquinolone Safety in Pediatric Patients: A Prospective, Multicenter, Comparative Cohort Study in France. Am. Academy of Peds.2003;111(6): 714-719 [24]</td></tr>
<tr><td>Objective</td><td>Evaluate the safety of fluoroquinolones in comparison with other antibiotics</td></tr>
<tr><td>Design</td><td>Multicenter, observational, comparative, cohort study from (1998 to 2000)</td></tr>
<tr><td>Patients</td><td>Patients exposed to FQ use regardless of the regimen prescribed</td></tr>
<tr><td>Method</td><td>• All French pediatric departments and CF centers invited to participate: 145 centers accepted
• Data on baseline characteristics, prior FQ therapy, current regimen and potential adverse events (PAE) prospectively collected
• Exposed patients matched to a control (on another antibiotic and not received FQ during 15 days prior to inclusion) based on age and medical history of cystic fibrosis (CF)
• Patients observed for potential adverse events (PAEs) starting day 1 of therapy until 15 days post last dose
• All PAEs recorded but special emphasis on musculoskeletal events</td></tr>
<tr><td>Results</td><td>• FQ group: n= 276; comparator group: n= 249
• Patients: general pediatric wards or CF centers (62%); cancer units (18%); ICU (9%)
• Age: 23% < 2 years; 16% 2 - 6 years; 31% 6 yrs. - puberty onset; 29% started puberty
• Underlying conditions: 33% CF, 27% malignancy, 9% immunosuppression
• Indications:
<table>
<tr><th>Indications</th><th>% of Patients Treated</th></tr>
<tr><td>CF</td><td>33%</td></tr>
<tr><td>Bronchopulmonary infections</td><td>22%</td></tr>
<tr><td>Urinary tract infections</td><td>18%</td></tr>
<tr><td>Febrile neutropenia</td><td>13%</td></tr>
<tr><td>Septicemia</td><td>12%</td></tr>
<tr><td>GI infections</td><td>12%</td></tr>
<tr><td>Ear, nose, throat</td><td>6%</td></tr>
<tr><td>Bone and joint</td><td>6%</td></tr>
<tr><td>Meningitis</td><td>5%</td></tr>
</table>
• 51% had bacterial resistance to other antibiotics
• FQ used: ciprofloxacin (87%), ofloxacin (9%), perfloxacin (4%)
• PAEs:
o 264 in FQ group and 237 in control group included in analysis for side effects
o 52 (19.7%) and 13 (5%) incidence of potential adverse events (PAEs) in FQ and comparator group respectively
o OR for PAE in FQ group was 3.7 (95% CI: 1.9-7.5%)
o 15 GI events, 7 skin events, 5 kidney events, 3 CNS events in FQ group
o Musculoskeletal incidence: 10 vs 1 in FQ group vs control group respectively; OR= 9.3 (95% CI: 1.2-195, P= 0.02)
o OR for musculoskeletal events in CF patients treated with FQ = 1.2 (95% CI: 0.1-35, P= 0.99)
o Musculoskeletal events: all patients ≥ 6 years of age (P= 0.01), 80% female (P <0.05); 8 ciprofloxacin and 2 perfloxacin; all events were arthralgia or myalgia of large joints
o Number of concomitantly administered drugs significantly associated with higher PAE (OR: 2.6, P= 0.004)
o All musculoskeletal events were transient and occurred within first (n=8) or second (n=2) week of treatment introduction
o 7 events of moderate intensive but 3 serious events led to FQ discontinuation
o FQ dose and duration similar between subjects with and without musculoskeletal events</td></tr>
<tr><td>Author’s</td><td>FQ use in centers that participated in the study was in good agreement with the current</td></tr>
</table>

Conclusion	recommendations. Short- term PAEs and musculoskeletal PAEs occurred more frequently in FQ than in other antibiotics. Incidence of muscle toxicity low in children but much higher than in adults (3.8% vs 0.2%). Author supports the AAP's recommendation on restricting FQ use to specific groups of patients.	
Critique	Strengths: • Active comparator group with multiple antibiotics • Large sample size • Three FQ antibiotics used • Indicated doses and durations of therapy	Weaknesses: • Centers with appropriate FQ use more likely to participate • Hawthorne effect possible • Short 15 day observation period • Non-randomized study • Open label (overestimation of musculoskeletal toxicity possible with FQ group)

Noel G et al. Comparative Safety Profile of Levofloxacin in 2523 Children With a Focus on Four Specific Musculoskeletal Disorders. *Pediatr Infect Dis J*.2007;26(10):879-891[21]	
Objectives	Assess safety and tolerability of levofloxacin therapy in children for 1 year post therapy
Design	Longitudinal observational study (2002 to 2006)
Patients	Patients included in the efficacy trials (listed below) who took at least 1 dose of the study drug and provided safety information after the first dose
Method	• Safety data collected from children who participated in 1 of 3 efficacy trials and who participated the long term 1 year surveillance study (LTSS-001) • Analyzed 4 musculoskeletal disorders: arthritis, arthralgia, gait abnormality, tendinopathy • PCAP-003: 43 centers across 7 countries; pediatric patients with CAP treated with levofloxacin, amoxicillin/ clavulanic acid, clarithromycin or ceftriaxone • OTMD-002: 66 centers across 6 countries; pediatric patients with recurrent acute otitis media treated with levofloxacin or amoxicillin/ clavulanic acid • OTMD-001: 9 centers across 4 countries; pediatric patients with persistent recurrent acute otitis media were treat with levofloxacin • Safety evaluation: o Musculoskeletal events reported by patient or caregiver o Incidents evaluated by a blinded specialist within 72 hours of presentation o Appropriate examinations (MRI, ultrasound, X-ray etc.) of the joint performed o Need for linear growth assessment beyond 1 year determined by a child's failure to achieve at least 80% of expected increment in height o Incidence of musculoskeletal events evaluated at 1 month, 2 months and 12 months
Results	• Baseline characteristics similar between levofloxacin and comparator group • 2233 of 2535 (88.5%) children enrolled in the efficacy trials included in the 1 year follow-up • 2003 of 2523 (79.3%) children competed the 1 year follow-up assessment • Safety analysis: o 2 deaths in the levofloxacin group (not related to study drug) o 4 severe adverse events: 2 rash, 1 diarrhea and vomiting, 1 bloody diarrhea o Majority of levofloxacin discontinuation due to gastrointestinal side effects

<table>
<tr>
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Adverse events reported in the phase 3 trials:

<table>
<tr><th>Adverse Drug Reaction</th><th>Levofloxacin</th><th>Comparator</th></tr>
<tr><td>Gastrointestinal</td><td>360 (23%)</td><td>260 (36%)</td></tr>
<tr><td>Skin</td><td>232 (15%)</td><td>181 (18%)</td></tr>
<tr><td>Respiratory</td><td>202 (13%)</td><td>136 (14%)</td></tr>
<tr><td>Musculoskeletal</td><td>50 (3%)</td><td>26 (3%)</td></tr>
<tr><td>Nervous system</td><td>47 (3%)</td><td>29 (3%)</td></tr>
</table>

Most common musculoskeletal events:

<table>
<tr><th>Musculoskeletal Event</th><th>Levofloxacin (N = 1534)</th><th>Comparator (N = 989)</th></tr>
<tr><td>Myalgia</td><td>15</td><td>9</td></tr>
<tr><td>Arthralgia</td><td>22</td><td>7</td></tr>
<tr><td>Pathologic fractures</td><td>1</td><td>4</td></tr>
<tr><td>Arthropathy</td><td>2</td><td>2</td></tr>
<tr><td>Pain in extremities</td><td>7</td><td>2</td></tr>
</table>

Incidence of musculoskeletal disorders in LTSS-001 over time

<table>
<tr><th>Time Period (post therapy)</th><th>Levofloxacin (N =1340)</th><th>Comparator (N= 893)</th><th>P Value</th></tr>
<tr><td>1 month</td><td>23 (1.7, 1.1-2.6)</td><td>7 (0.8, 0.3-1.6)</td><td>0.063</td></tr>
<tr><td>2 months</td><td>28 (2.1, 1.4-3.0)</td><td>8 (0.9, 0.4-1.8)</td><td>0.038</td></tr>
<tr><td>12 months</td><td>46 (3.4, 2.5-4.6)</td><td>16 (1.8, 1.0-2.9)</td><td>0.025</td></tr>
</table>

Incidence of musculoskeletal disorders increase over time (independent of levofloxacin exposure)
Significant difference in events involving weight bearing joints at 2 month (P = 0.03) and 1 year (P = 0.047) post treatment
Higher incidence of arthralgia: 84% and 86% incidence in levofloxacin and comparator group respectively at 1 month (not statistically significant)
Musculoskeletal incidence transient and resolved without apparent sequelae
Five levofloxacin children underwent MRI or CT examination: no abnormalities found
Linear growth: children with at least 3 height measurements prior to drug exposure included.

Similarly percentage of children in levofloxacin (8.8%) and comparator (8.5%) were found to require additional growth evaluation

</td>
</tr>
<tr>
<td>Author's Conclusion</td>
<td colspan="2">Fluoroquinolones have been proven to be a very effective class of antibiotics. Gastrointestinal side effects are the most common issue associated with levofloxacin tolerability. The study does not establish a clinical correlation between quinolone associated lesion in animals and humans. However, higher incidence of joint disease is possible in children treated with fluoroquinolones.</td>
</tr>
<tr>
<td>Critique</td>
<td>Strength:

Defined musculoskeletal events
Included percentage of incidence in each musculoskeletal category
Included multiple large, multicenter studies

</td>
<td>Weakness:

Potential bias due to parental reporting of subjective incidences (ex: arthralgia)
Radiographic imaging not used frequently to help diagnoses musculoskeletal incidences

</td>
</tr>
</table>

<table>
<tr><td colspan="2">Adefurin et al. Ciprofloxacin safety in pediatrics: a systemic review. Arch Dis Child.2011;96:874-880 [23]</td></tr>
<tr><td>Objective</td><td>Determine the safety of ciprofloxacin in pediatrics in relation to arthropathy, any other adverse events and drug interactions</td></tr>
<tr><td>Design</td><td>Systematic review of ciprofloxacin use between 1950 to 2009</td></tr>
<tr><td>Patients</td><td>• Children < 17 years of age
• At least one dose of ciprofloxacin administered through any route for any infection</td></tr>
<tr><td>Method</td><td>A systematic search of MEDLINE, EMBASE, CINAHL, CENTRAL and bibliographies of relevant articles using ciprofloxacin. Only articles reporting safety was included.</td></tr>
<tr><td>Outcomes</td><td>• Occurrence of arthropathy specified as pain, swelling or reduced movement of joint or radiographic evidence of joint damage
• Occurrence of any other adverse events from ciprofloxacin use
• Occurrence of drug-drug interactions due to ciprofloxacin use
• Death due to adverse drug reactions from ciprofloxacin use</td></tr>
<tr><td>Results</td><td>• 105 studies included; 68 reported adverse events; 32 ((11,977 patients) reported incidence of arthropathy
• Types of studies included:
<table>
<tr><th>Study Type</th><th>Frequency (N = 105)</th><th>No. of Patients (N =16,184)</th></tr>
<tr><td>Case series</td><td>46</td><td>8876</td></tr>
<tr><td>Case report</td><td>24</td><td>24</td></tr>
<tr><td>RCT</td><td>15</td><td>1787</td></tr>
<tr><td>Cohort Study</td><td>12</td><td>5368</td></tr>
<tr><td>Pharmacokinetic</td><td>5</td><td>79</td></tr>
<tr><td>Non-RCT</td><td>3</td><td>50</td></tr>
</table>
• Dose: 10-30 mg/kg/day in 2 divided doses (3.1 to 93.8 mg/kg/day)
• Median duration of therapy: 14 days (range: one dose to 880 days)
• Drug interaction: aminophylline (n=4) and methotrexate (n =2)
• Safety analysis
o 1065 of 6184 patients reported adverse events (7%; 95% CI 3.2% to 14%)
o No dose/ duration dependent risk of toxicity (unlike animal studies)
o No neonatal patients experienced an adverse events
o 23 patients discontinued ciprofloxacin due to serious adverse events
o 57% increased risk of arthropathy in patients who received ciprofloxacin compared to comparator (OR=1.57, 95% CI: 1.26 to 1.97)67% increased risk of arthropathy (OR 1.67, 95% CI 1.13 to 2.45) in cystic fibrosis patients
o Majority of musculoskeletal events (86%) classified as possibly related to ciprofloxacin
<table>
<tr><th>Musculoskeletal events</th><th>Frequency (%)</th></tr>
<tr><td>Arthralgia</td><td>130 (50.0)</td></tr>
<tr><td>Tendon or joint disorder</td><td>48 (19.0)</td></tr>
<tr><td>Reduced movement/stiffness</td><td>39 (15.0)</td></tr>
<tr><td>Joint swelling</td><td>8 (3.0)</td></tr>
<tr><td>Radiological confirmed arthropathy</td><td>6 (2.3)</td></tr>
<tr><td>Myalgia</td><td>4 (1.6)</td></tr>
<tr><td>Arthritis</td><td>3 (1.2)</td></tr>
<tr><td>Pain in extremity</td><td>1 (0.4)</td></tr>
<tr><td>Osteitis</td><td>1 (0.4)</td></tr>
<tr><td>Unknown</td><td>18 (7.0)</td></tr>
<tr><td>Total</td><td>258* (100)</td></tr>
</table>
*258 musculoskeletal events occurred in 232 patients.
<table>
<tr><th>Common Adverse Events</th><th>Frequency</th></tr>
<tr><td>Musculoskeletal</td><td>232</td></tr>
<tr><td>Abnormal liver function tests</td><td>139</td></tr>
<tr><td>Nausea, vomiting, abdominal pain</td><td>75, 56, 38</td></tr>
<tr><td>Blood cell count derangements</td><td>57</td></tr>
<tr><td>Rash</td><td>51</td></tr>
</table></td></tr>
<tr><td>Author's Conclusion</td><td>Musculoskeletal toxicity is the most frequently reported adverse event following ciprofloxacin use. Unlike animal studies, muscle toxicity was not related to age, dose or duration. Arthropathy due to</td></tr>
</table>

	ciprofloxacin is transient reversible so patient should be analyzed for risk vs benefits	
Critique	Strength: • Systematic review • Large sample size • Can generalize to public • Patients categorized by age group	Weakness: • Vast variation in dose and duration • Side effects possibly due to co-administered drugs • No information on re-challenge of FQ • No quantitative data on management of arthropathy

Analyzing the Primary Literature

I) Comparison of animal and human studies

A) Evidence of arthropathy appears primarily in weight bearing joints in animals and humans
B) Clinical signs of injury resolved within several days from onset in animals and humans
C) Unlike animals, no direct relation to age seen with FQ induced chondrotoxicity in humans
D) Unlike animals, no dose or duration related effects seen with FQ induced chondrotoxicity in humans
E) Unlike animals, the prevelance of musculoskeletal events were considerably low in humans

II) Difference and animal and human studies

A) Velocity of growth

1) Animals that are used in the toxicological studies (beagle dogs, rats etc.) grow rapidly
2) Human growth extends over a much longer period and is not a continuous process.
3) One day in the life of a beagle pup equals 18 days in the life of a child

B) Saltatory growth[17,34]

1) Human growth in length occurs by discontinuous, aperiodic, saltatory spurts
2) These bursts are 0.5 to 2.5 centimeters in amplitude during intervals separated by no measurable growth (2 to 63 days duration)
3) 90-95% of normal development during infancy is growth-free
4) It is possible that the extremely rapid growth rates and nutritional requirements of the skeletons of animals causes higher sensitivity to musculoskeletal toxicity of quinolones

C) Differences in medication doses[3-4, 11-14]

Study FQ	Study Dose	Recommended Human dosing
Nalidixic acid	200- 1000 mg/kg	33 mg/kg/day to 55 mg/kg/day
Ciprofloxacin	30-90 mg/kg/day	20 to 30 mg/kg/day
Ofloxacin	300-900 mg/kg	15 mg/kg/day (max adult: 800 mg/day)

Resistance

I) The increased use of FQ in all age groups have resulted in a corresponding increase in bacterial resistance within the United States and globally[1,3-4]

II) Various studies have shown resistance to FQ among S*treptococcus pneumonia*, *Pseudomonas aeruginosa* and enterobacteriaceae like *Escherichia coli, Neisseria gonorrhea, Neisseria meningitis, Shigella and Salmonella*[3-4,31]

III) Resistance more commonly seen in adults than in children because restricted pediatric use [3-4]

IV) Prevention of resistance can be improved by better defining the optimal selected quinolone, dosage, duration of treatment for particular infections and infection control to prevent spread of resistant organisms

Clinical Recommendation

I) FQ are effective antimicrobial agents for use in pediatrics

II) While use of established, first-line agents is highly encouraged, potential consideration for FQ should also take place in the pediatric population

III) Providers should not be reluctant to use FQ in the pediatric setting solely because of musculoskeletal toxicity, especially if the FQ is a viable clinical option

IV) Nonetheless, cautious use of these agents is crucial due to potential emergence of resistance

Conclusion

I) Although animal studies have shown significant risk of musculoskeletal toxicity associated with FQ, there is no comparable documentation of FQ induced arthropathy in humans

II) Several human studies have shown that musculoskeletal toxicity associated with FQ are relatively infrequent and transient

III) The benefits of appropriate FQ use outweighs what appears to be a small short term risk of joint toxicity and pediatric patients should not be deprived of the therapeutic advantages that these agents have to offer

IV) It is crucial to keep in mind the emergence of resistance with antibiotics including FQ

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