Fluoroquinolone use in children

Introduction

- **Fluoroquinolones (FQs) are important antibiotics that are widely utilized in adult patients because of good:**

✓**spectrum of activity**

✓**tissue penetration**

✓**oral bioavailability**

Introduction

- FQ use in children remains limited because of arthropathy observed in juvenile animals
- This presentation focuses on the current recommendations for the use and safety profile of FQs in children.

Classification

- Nalidixic acid, a first generation FQ, was initially introduced in 1964 for the treatment of UTI
- Nalidixic acid was discovered accidentally as a by-product of the synthesis of the antimalarial compound chloroquine.
- This discovery led to the development of quinolone compounds, and fluorination of quinolone led to the introduction of second-generation of FQs like norfloxacin, ciprofloxacin and levofloxacin
- Currently, there are 4 generations of FQ antibiotics

Mechanism of action

- FQs are bactericidal and inhibit bacterial DNA synthesis by interfering with DNA gyrase and topoisomerase IV, both of which are necessary for DNA replication.

pharmacokinetic properties

- **FQs have advantageous pharmacokinetic properties such as:**

✓**gastrointestinal absorption (bioavailability of 70–95%)**

✓**excellent penetration into many tissues**

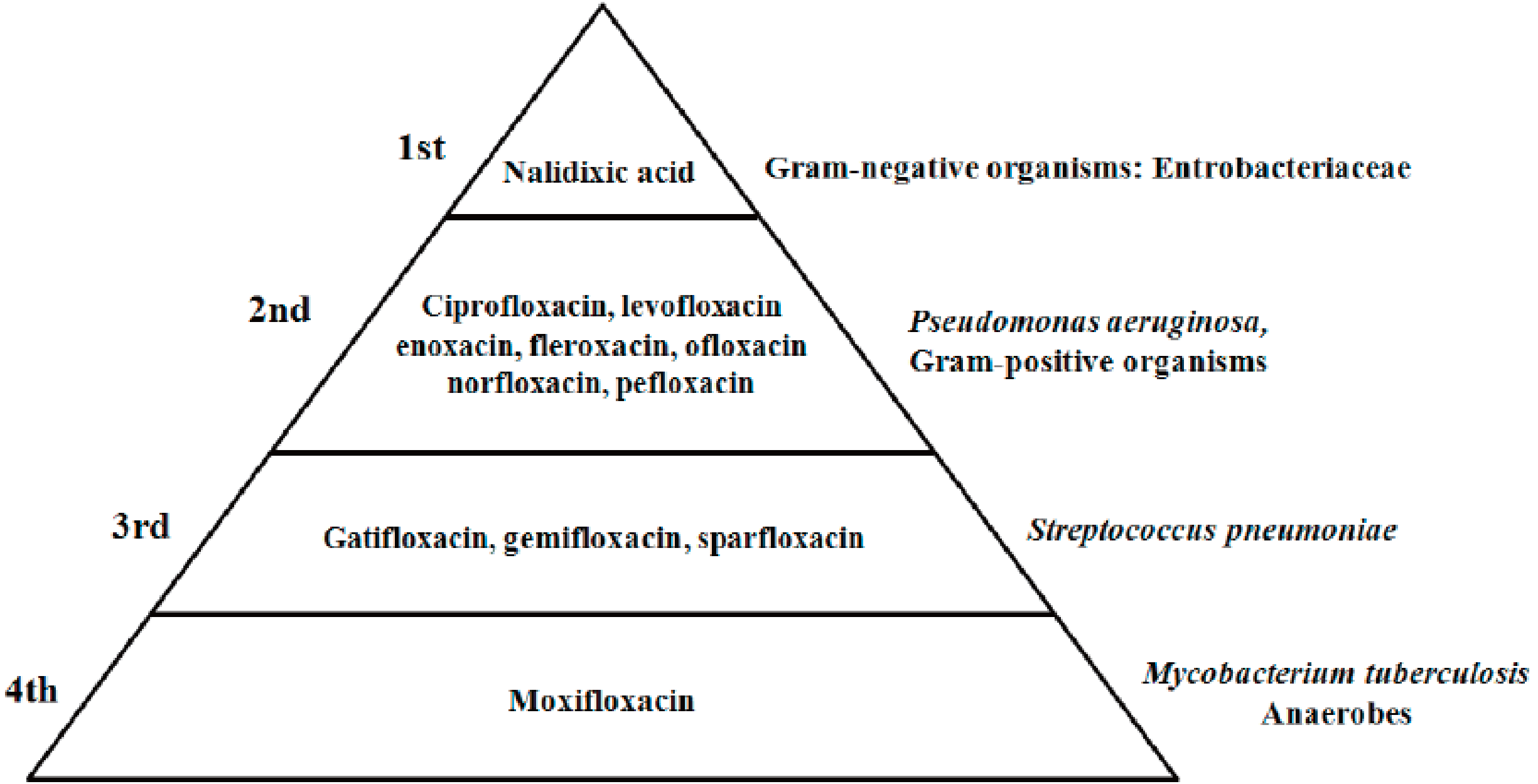
✓**FQs penetrate well into CSF where concentrations can exceed 50% of the corresponding plasma drug concentration**

The spectrum of activity

- FQs have extended antimicrobial activity against gram-negative organisms, gram-positive organisms, and atypical bacteria
- Early-generation FQs predominantly target gram-negative pathogens, especially the Enterobacteriaceae family.
- Second generation FQs have even greater gram-negative coverage, with additional activity against Pseudomonas aeruginosa.

The spectrum of activity

- New-generation FQs have enhanced activity against staphylococci, streptococci, and anaerobes.
- Moxifloxacin, a fourth-generation FQ, has excellent activity against many mycobacteria, including Mycobacterium tuberculosis



Classification and antimicrobial activity of fluoroquinolones

	Ciprofloxacin	Levofloxacin	Moxifloxacin
Infections	Urinary tract infections	Acute otitis media and sinusitis	Multidrug-resistant tuberculosis
	Escherichia coli	*Streptococcus pneumoniae*	*Mycobacterium tuberculosis*
	Pseudomonas aeruginosa	*Haemophilus influenzae*	
	Enterobacter species	Pneumonia	
	Citrobacter species	*Streptococcus pneumoniae*	
	Serratia species	*Mycoplasma pneumoniae*	
	Gastrointestinal infections	Multidrug-resistant tuberculosis	
	Salmonella species	*Mycobacterium tuberculosis*	
	Shigella species		
Dose			
Oral	20–40 mg/kg/day, every 12 hours (maximum 750 mg/dose)	6 months to 5 years old: 16–20 mg/kg/day, every 12 hours 5 years of age and older: 10 mg/kg/day, once daily (maximum 750 mg/dose)	Adolescents: 400 mg once daily
Intravenous	20–30 mg/kg/day, every 8 to 12 hours (maximum 400 mg/dose)	Same as oral dose	Adolescents: same as oral dose

Safety data in children with a focus on adverse musculoskeletal events

- ✓The most common adverse effects of FQs are GI symptoms such as nausea, vomiting, diarrhea, and abdominal pain.
- ✓Skin rashes, are also frequent.
- ✓Infrequently, neutropenia, eosinophilia, thrombocytopenia and elevated liver enzymes
- ✓Neurologic complications associated with fluoroquinolone use, very uncommon in children, include peripheral neuropathy, seizures, sleep disorders, hallucinations, dizziness, headaches
- All of these adverse effects are typically transient and reversible with conservative management.

adverse musculoskeletal events

- Preclinical studies of quinolones in juvenile beagle dogs revealed articular cartilage damage in weight-bearing joints
- FQ-associated tendon disorders, like tendinitis and tendon rupture, have demonstrated that these injuries tend to occur in elderly patients, with the Achilles tendon being the most commonly injured

Studies

- Results from a prospective, multicenter, cohort study that compared potential adverse events in 276 pediatric patients who received FQs and 249 matched controls who received an antibiotic agent other than FQ.
- The most commonly affected systems were the gastrointestinal followed by musculoskeletal (arthralgias of large joints or myalgias but no tendinopathy), skin, and central nervous systems.

Studies

- Adverse musculoskeletal events occurred more frequently in the FQ group than in the controls
- Although adverse events did occur more frequently with FQ treatment, all cases were transient, and no severe or persistent musculoskeletal injuries were observed at follow-up.

Studies

- In a systematic review of ciprofloxacin safety in 16,184 children 258 musculoskeletal adverse events occurred
- Arthralgia was the most commonly reported adverse musculoskeletal event (50%), most frequently affecting the knee joint.
- Musculoskeletal events were reversible

Studies

- a systematic literature search from 1966 to 2009 evaluated the efficacy, and safety of ciprofloxacin in neonates.
- The study population for this review included 308 ciprofloxacin-treated patients and 692 controls
- No serious adverse events were observed.
- Analysis of the short-term and long-term effects of ciprofloxacin on cartilage and growth indicated no significant differences between ciprofloxacin and control groups with respect to these factors.

Approved indications of FQs in children

- **Currently, FQs that are approved by the FDA for use in children include:**
- **ciprofloxacin for the treatment of**

✓**inhalation anthrax**

✓**complicated UTIs, and pyelonephritis**

- **levofloxacin for**

✓**inhalational anthrax**

Approved indications of FQs in children

- **Ciprofloxacin is the only FQ approved by the European Medicines Agency for use in the following pediatric conditions:**

✓**bronchopulmonary infections in cystic Fibrosis caused by Pseudomonas aeruginosa**

✓**complicated UTI, pyelonephritis**

✓**inhalation anthrax (both for post exposure prophylaxis and curative treatment)**

Organizational guidelines for FQ use in children

- **WHO Expert Committee concluded that the effectiveness and safety of FQs in the treatment of life-threatening bacterial infections, in children have been sufficiently established such as:**

✓**resistant tuberculosis**

✓**dysentery**

✓**cholera**

American Academy of Pediatrics

- **According to the AAP, situations in which FQs may be useful include:**

✓**multi drug resistant infections for which there is no safe and effective alternative**

✓**when parenteral therapy is not feasible and no other effective oral agent is available.**

The AAP recommendations for FQ use in children are as follows:

1. Exposure to aerosolized Bacillus anthracis to decrease the incidence or progression of the disease (FDA licensed)
2. UTIs caused by P. aeruginosa or other multidrug-resistant, gram-negative bacteria (FDA licensed for complicated E. coli UTIs and pyelonephritis attributable to E. coli in patients 1–17 years old)
3. Chronic suppurative otitis media or malignant otitis externa caused by P. aeruginosa

The AAP recommendations for FQ use in children are as follows:

4. Chronic or acute osteomyelitis or osteochondritis caused by P. aeruginosa

5. Exacerbation of pulmonary disease in patients with cystic fibrosis who are colonized with P. aeruginosa and can be treated in an ambulatory care setting

6. Mycobacterial infections caused by isolates known to be susceptible to FQs

7. Gram-negative bacterial infections in immunocompromised hosts in which oral therapy is desired or resistance to alternative agents is present

The AAP recommendations for FQ use in children are as follows:

8. GI tract infections caused by MDR Shigella species, Salmonella species, Vibrio cholerae, or Campylobacter jejuni

9. Documented bacterial septicemia or meningitis attributable to organisms with in vitro resistance to approved agents or in immunocompromised infants and children in whom parenteral therapy with other appropriate antimicrobial agents has failed

10. Serious infections attributable to FQ-susceptible pathogen(s) in children with a life-threatening allergy to alternative agents

clinical practice guidelines for CAP

- As data on the musculoskeletal safety of FQs in the pediatric population accumulate, more guidelines recommend FQ use in children.
- In the 2011 clinical practice guidelines for (CAP) in infants and children by the Pediatric Infectious Diseases Society and the IDSA, levofloxacin was recommended in certain situations as an alternative treatment option for Streptococcus pneumoniae , Haemophilus influenzae (typeable [A–F] or nontypeable), Mycoplasma pneumoniae, Chlamydia trachomatis , and Chlamydia pneumoniae .

clinical practice guidelines for (CAP)

- **In addition, levofloxacin is now recommended in children as a treatment option for acute bacterial rhinosinusitis according to the IDSA for acute bacterial rhinosinusitis in children and adults:**

✓**with a history of type I hypersensitivity to penicillin,**

✓**as a second-line agent for children with risk for antibiotic resistance, failed initial therapy, or severe infection requiring hospitalization.**

Conclusions

- clinicians today are facing more situations when the use of FQs should be considered in treating pediatric patients who have not responded to standard therapy and those who are infected with multidrug-resistant pathogens, including tuberculosis.
- In addition, in areas with restricted medical resources, FQs may be the only option for the treatment of serious infections, especially when parenteral drug administration is not available.

Take home message

- FQs should not be used in pediatric patients for routine infections when other safe and effective antimicrobials are available.
- However, FQs should be considered in life threatening and difficult-to-treat infections when alternative agents cannot be used.