## **Review article**

Korean J Pediatr 2013;56(5):196-201 http://dx.doi.org/10.3345/kjp.2013.56.5.196 pISSN 1738-1061 • eISSN 2092-7258



# Systemic use of fluoroquinolone in children

Soo-Han Choi, MD<sup>1</sup>, Eun Young Kim, Pharm D<sup>2</sup>, Yae-Jean Kim, MD, PhD<sup>3</sup>

<sup>1</sup>Department of Pediatrics, KEPCO Medical Foundation KEPCO Medical Center, Seoul,

Fluoroquinolones are an important class of antibiotics that are widely used in adult patients because of their broad spectrum of activity, good tissue penetration, and oral bioavailability. However, fluoroquinolone use in children is limited because juvenile animals developed arthropathy in previous experiments on fluoroquinolone use. Indications for fluoroquinolone use in patients younger than 18 years, as stated by the U.S. Food and Drug Administration, include treatment of complicated urinary tract infections and postexposure treatment for inhalation anthrax. In Korea, the systemic use of fluoroquinolones has not been approved in children younger than 18 years. Although concerns remain regarding the adverse musculoskeletal effects of fluoroquinolones in children, their use in the pediatric population has increased in many circumstances. While pediatricians should be aware of the indications and adverse effects of fluoroquinolones, recent studies have shown that the risk for musculoskeletal complications in children did not significantly increase following fluoroquinolone treatment. In addition, fluoroquinolones may be particularly helpful in treating multidrug-resistant infections that have not responded to standard antibiotic therapy in immunocompromised patients. In the present article, we provide an updated review on the safety and current recommendations for using fluoroquinolones in children.

Key words: Fluoroguinolones, Adverse effects, Joint diseases, Child

Corresponding author: Yae-Jean Kim, MD, PhD Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea Tel: +82-2-3410-3539, Fax: +82-2-3410-0043 E-mail: yaejeankim@skku.edu

Received: 18 December, 2012 Accepted: 13 March, 2013

#### Introduction

Fluoroquinolones (FQs) are important antibiotics that are widely utilized in adult patients because of their excellent spectrum of activity, good tissue penetration, and oral bioavailability. FQ use in children remains limited because of arthropathy observed in juvenile animals<sup>1-5)</sup>. However, several reports have described using FQs to treat serious infections in children despite their few approved indications<sup>6-12)</sup>. In the present article, we reviewed the data, particularly from the last ten years, focusing on the current recommendations for the use and safety profile of FQs in children.

## **Overview of FQs**

## 1. Classification

Nalidixic acid, a first generation FQ, was initially introduced in 1964 for the treatment of urinary tract infections, and for more than 2 decades, it was used in children 3 months and older without restriction<sup>2-4</sup>. Nalidixic acid was discovered accidentally by Lesher and coworkers as a by-product of the synthesis of the antimalarial compound

Copyright © 2013 by The Korean Pediatric Society

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

<sup>&</sup>lt;sup>2</sup>Department of Clinical Pharmacy, College of Pharmacy, Chung-Ang University, Seoul,

<sup>&</sup>lt;sup>3</sup>Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

chloroquine<sup>4)</sup>. This discovery led to the development of quinolone compounds, and fluorination of quinolone led to the introduction of second-generation of FQs like norfloxacin in 1986 and ciprofloxacin in 1987. Other second-generation FQs, like levofloxacin, followed soon thereafter. The addition of the fluorine atom improves potency, enhances antimicrobial activity, and alters pharmacokinetic properties. Incorporating different substituents to various positions on the quinolone nucleus varies antimicrobial activity and alters FQ side-effect profiles<sup>3,4,13)</sup>. Currently, there are 4 generations of FQ antibiotics; among these, ciprofloxacin, levofloxacin, and moxifloxacin represent the most widely used systemic FQs (Fig. 1).

#### 2. Clinical pharmacology

FQs are bactericidal and inhibit bacterial DNA synthesis by interfering with DNA gyrase and topoisomerase IV, both of

which are necessary for DNA replication. FQs have advantageous pharmacokinetic properties such as gastrointestinal absorption (bioavailability of 70–95%), excellent penetration into many tissues, and good intracellular diffusion. Peak plasma concentrations of levofloxacin and moxifloxacin are generally attained within 1 to 2 hours after oral administration, and bioavailability is usually unaffected by concurrent food ingestion. Levofloxacin has nearly 100% bioavailability<sup>5,14)</sup>. FQs penetrate well into cerebrospinal fluid, where concentrations can exceed 50% of the corresponding plasma drug concentration<sup>10)</sup>.

FQs have extended antimicrobial activity against gram-negative organisms, gram-positive organisms, and atypical bacteria (Fig. 1). 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*. New-

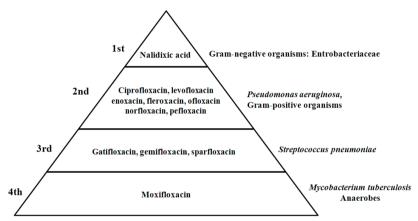


Fig. 1. Classification and antimicrobial activity of fluoroquinolones.

Table 1. Effective fluoroguinolones according to common infections

	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		
Oose			
Oral	20-40 mg/kg/day, every 12 hours	6 months to 5 years old: 16-20 mg/kg/day, every 12 hours	Adolescents: 400 mg once daily
	(maximum 750 mg/dose)	5 years of age and older: 10 mg/kg/day, once daily	
		(maximum 750 mg/dose)	
Intravenous	20-30 mg/kg/day, every 8 to 12 hours (maximum 400 mg/dose)	Same as oral dose	Adolescents: same as oral dose

generation FQs have enhanced activity against staphylococci, streptococci, and anaerobes. Moxifloxacin, a fourth-generation FQ, has excellent activity against many mycobacteria, including *Mycobacterium tuberculosis*<sup>15-18)</sup> (Table 1).

# Safety data regarding FQ use in children with a focus on adverse musculoskeletal events

The most common adverse effects of FQs are gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain. Skin rashes, allergies, and photosensitivity are also frequent. Infrequently, patients develop neutropenia, eosinophilia, and elevated liver enzymes (1–4%). All of these adverse effects are typically transient and reversible with conservative management <sup>16,17)</sup>.

Preclinical studies of quinolones in juvenile beagle dogs revealed articular cartilage damage in weight-bearing joints 19-21). This finding restricted the general use of FQs in pediatric patients, given concern for the occurrence of similar adverse effects in growing children. Case reports of 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 19,22). The tendon symptoms generally develop during the first 1-2 weeks following initiation of FQ treatment, while tendon rupture typically occurs 2–3 weeks after FQ initiation 19). In a case-control study, Achilles tendon disorders associated with FQ exposure were found to be relatively rare, with an overall risk estimated at 3.2 cases per 1,000 patient-years. Concomitant corticosteroid use appears to increase that risk substantially<sup>22)</sup>. To date, there have been no reports of Achilles tendon rupture in children following FO administration.

Chalumeau et al.<sup>23</sup> reported results from a prospective, multicenter, observational, 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 odds ratio (OR) and adjusted OR for potential adverse events in the FQ group were 3.7 (95% confidence interval [CI], 1.9 to 7.5) and 3.0 (95% CI, 1.5 to 5.9), respectively. 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. Adverse musculoskeletal events occurred more frequently in the FQ group than in the controls (3.8% vs. 0.4%); the crude OR for musculoskeletal potential adverse events in the FQ group was 9.3 (95% CI, 1.2 to 195). 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.

A large, prospective safety study conducted by Bayer compared (1) intravenous ceftazidime with intravenous ciprofloxacin, permitting oral step-down therapy, and (2) oral ciprofloxacin with oral cefixime or trimethoprim-sulfamethoxazole for the treatment of complicated urinary tract infections in children aged 1–17 years <sup>18,24)</sup>. One of the primary objectives of the study was to evaluate musculoskeletal safety with ciprofloxacin therapy. At 6 weeks follow-up, the arthropathy rate was 9.3% (31/335) in the ciprofloxacin-treated group and 6.0% (21/349) in the control group (95% CI, –0.8 to 7.2), and cumulative arthropathy rate at 1 year follow-up was 13.7% and 9.5%, respectively (95% CI, –0.6 to 9.1).

In a systematic review of ciprofloxacin safety in 16,184 children from 105 studies, 258 musculoskeletal adverse events occurred in 232 pediatric patients (estimated risk, 1.6; 95% CI, 0.9 to 2.6), approximately 1 musculoskeletal adverse event for every 62.5 patients. Arthralgia was the most commonly reported adverse musculoskeletal event (50%), most frequently affecting the knee joint. Patient age at occurrence of arthropathy ranged from 7 months to 17 years (median age, 10 years). Musculoskeletal events were reversible through conservative management, which included cessation of antibiotics. Analysis of the pooled safety data from 23 controlled trials in this review showed that there was a 57% increased risk of arthropathy in the patients receiving ciprofloxacin compared to that in patients in the control arm (0R, 1.57; 95% CI, 1.26 to 1.97)<sup>25)</sup>.

Kaguelidou et al.<sup>26)</sup> performed a systematic literature search from 1966 to July of 2009 to evaluate the efficacy, safety, and pharmacokinetics of ciprofloxacin in neonates. The study population for this review included 308 ciprofloxacin-treated patients and 692 controls from 5 cohort studies, as well as 143 ciprofloxacin-treated neonates from 27 case reports or series. Ciprofloxacin was used in neonates as a salvage therapy for sepsis caused by multidrug-resistant pathogens or for clinical exacerbation after first-line antibiotic therapy. 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. Using multipleregression modeling and adjusting for weight and gestational age at birth, 2 of the studies showed no significant relationship between ciprofloxacin use and the cartilage size of the right knee, as measured by ultrasound<sup>27)</sup>, and no height differences at 12 months corrected age<sup>28)</sup>.

Noel et al.<sup>29)</sup> investigated the safety profile of levofloxacin in 2,523 children using data from 3 multicenter efficacy trials. Spontaneous reports of 1 or more musculoskeletal adverse events (arthritis, arthralgias, tendinopathy, or gait abnormality) were higher in levofloxacin-treated children than in those treated with non-FQ antibiotics at both 2-month (2.1% vs. 0.9%, P=0.04)

and 12-month follow-ups (3.4% vs. 1.8%, P=0.03). However, long-term outcomes of children with musculoskeletal adverse events during the 5-year safety study were slightly higher in the control group (2.0% vs. 4.0%)<sup>18)</sup>. Of note, current studies are investigating moxifloxacin safety in the pediatric population<sup>30,31)</sup>.

## Use of systemic FQs in children

Despite the limited indications for the use of FQs in the pediatric population and concerns for adverse events, approximately 520,000 FQ prescriptions were written for patients younger than 18 years in the United States (US) in 2002. An estimated 13,800 of those prescriptions were for children 2–6 years of age, and 2,750 were written for those 2 years and younger<sup>15</sup>. Although there have been no systemic data on FQ use in children in Korea, 1 study, which analyzed the antibiotic prescription patterns of pediatricians and ENT (ear, nose, and throat) physicians, reported that the proportion of quinolones prescribed was 3.5% (539/15,396) during an 1-year period. These data should be interpreted with caution, as they were collected from prescription sheets in 7 community pharmacies within Ulsan City, Korea<sup>32</sup>. More data are clearly needed to assess FQ use in Korean children.

## 1. Approved indications of FQs in children

Currently, FQs that are approved by the U.S. Food and Drug Administration (FDA) for use in children include ciprofloxacin for the treatment of inhalation anthrax, complicated urinary tract infections, and pyelonephritis along with levofloxacin for inhalational anthrax<sup>15,18)</sup>. Ciprofloxacin is the only FO approved by the European Medicines Agency for use in the following pediatric conditions: bronchopulmonary infections in cystic fibrosis caused by Pseudomonas aeruginosa, complicated urinary tract infections, pyelonephritis, and inhalation anthrax (both for postexposure prophylaxis and curative treatment)<sup>33)</sup>. Ciprofloxacin and levofloxacin are available as oral suspensions in many countries. An oral suspension of ciprofloxacin is available in the US, Canada, and 15 European countries<sup>34</sup>, but systemic FQ use is not approved in Korea for any indication in children younger than 18 years. Additionally, oral suspensions are not available in Korea.

## 2. Organizational guidelines for FQ use in children

The World Health Organization (WHO) has provided guidelines for the management of common illnesses in hospitals with limited resources. In the WHO Pocket Book of Hospital Care for Children, ciprofloxacin is recommended as a suitable first-line agent for the treatment of dysentery (oral 10–15 mg/kg per dose given twice per day for 5 days, maximum 500 mg per dose), but its use in children is only warranted if the benefits outweigh

the risk of arthropathy<sup>35)</sup>. In the 18th WHO Expert Committee meeting for "The Selection and Use of Essential Medicines," the committee concluded that the effectiveness and safety of FQs in the treatment of life-threatening bacterial infections, such as resistant tuberculosis, dysentery, and cholera, in children have been sufficiently established<sup>36)</sup>.

In 2006, the American Academy of Pediatrics (AAP) published a policy statement summarizing the assessment of risks and benefits of FQs in pediatric patients<sup>15)</sup>. According to the AAP, situations in which FQs may be useful include multidrugresistant infections for which there is no safe and effective alternative, and 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:

- Exposure to aerosolized *Bacillus anthracis* to decrease the incidence or progression of the disease (FDA licensed)
- Urinary tract infections caused by *P. aeruginosa* or other multidrug-resistant, gram-negative bacteria (FDA licensed for complicated *Escherichia coli* urinary tract infections and pyelonephritis attributable to *E. coli* in patients 1–17 years old)
- Chronic suppurative otitis media or malignant otitis externa caused by *P. aeruginosa*
- Chronic or acute osteomyelitis or osteochondritis caused by *P. aeruginosa* (but not for prophylaxis of nail puncture wounds to the foot)
- Exacerbation of pulmonary disease in patients with cystic fibrosis who are colonized with *P. aeruginosa* and can be treated in an ambulatory care setting
- Mycobacterial infections caused by isolates known to be susceptible to FQs
- Gram-negative bacterial infections in immunocompromised hosts in which oral therapy is desired or resistance to alternative agents is present
- Gastrointestinal tract infections caused by multidrug-resistant Shigella species, Salmonella species, Vibrio cholerae, or Campylobacter jejuni
- 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
- Serious infections attributable to FQ-susceptible pathogen(s) in children with a life-threatening allergy to alternative agents

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 community-acquired pneumonia (CAP) in infants and children by the

Pediatric Infectious Diseases Society and the Infectious Diseases Society of America (IDSA)<sup>37)</sup>, 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. Levofloxacin is preferred in oral therapy (step-down therapy or mild infection) for CAP caused by penicillin-resistant S. pneumoniae in skeletally mature adolescents. Moxifloxacin is recommended as an alternative oral agent for CAP caused by M. pneumoniae and Chlamydia species in skeletally mature adolescents. In addition, levofloxacin is now recommended in children as a treatment option for acute bacterial rhinosinusitis according to the IDSA clinical practice guideline (2012) for acute bacterial rhinosinusitis in children and adults<sup>38)</sup>: 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. Updated WHO guideline from 2011 for drug-resistant tuberculosis recommended that second-line antituberculosis regimens should include a later-generation FQ such as levofloxacin, moxifloxacin, or gatifloxacin<sup>39</sup>.

### **Conclusions**

Although concerns about potential musculoskeletal adverse effects in young children treated with FQs remain, many previous studies have repeatedly shown no significant increase in musculoskeletal complications in these children. In a review article, Schaad<sup>40</sup> commented that the triad of feared arthrotoxicity, potential explosion in bacterial resistance, and enormous requirements regarding adequate study and postmarketing control would make it unlikely that FQs will ever be recommended for treating common infections in children.

However, 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.

In conclusion, 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 lifethreatening and difficult-to-treat infections when alternative agents cannot be used.

## **Conflict of interest**

No potential conflict of interest relevant to this article was reported.

## **Acknowledgments**

This research was supported by a grant (11172KFDA294) from Korea Food and Drug Administration in 2011–2012.

## References

- Karande SC, Kshirsagar NA. Adverse drug reaction monitoring of ciprofloxacin in pediatric practice. Indian Pediatr 1992;29:181-8.
- Lietman PS. Fluoroquinolone toxicities. An update. Drugs 1995;49
  Suppl 2:159-63.
- Lipsky BA, Baker CA. Fluoroquinolone toxicity profiles: a review focusing on newer agents. Clin Infect Dis 1999;28:352-64.
- 4. Andriole VT. The quinolones: past, present, and future. Clin Infect Dis 2005;41 Suppl 2:S113-9.
- 5. Grady RW. Systemic quinolone antibiotics in children: a review of the use and safety. Expert Opin Drug Saf 2005;4:623–30.
- Bonafede ME, Blumer JL. Role of newer broad-spectrum betalactam and fluoroquinolone antibiotics in children. Adv Pediatr Infect Dis 1996;12:71-108.
- White NJ, Dung NM, Vinh H, Bethell D, Hien TT. Fluoroquinolone antibiotics in children with multidrug resistant typhoid. Lancet 1996;348:547.
- Freifeld A, Pizzo P. Use of fluoroquinolones for empirical management of febrile neutropenia in pediatric cancer patients. Pediatr Infect Dis J 1997;16:140-5.
- Redmond AO. Risk-benefit experience of ciprofloxacin use in pediatric patients in the United Kingdom. Pediatr Infect Dis J 1997;16:147-9.
- Saez-Llorens X, McCoig C, Feris JM, Vargas SL, Klugman KP, Hussey GD, et al. Quinolone treatment for pediatric bacterial meningitis: a comparative study of trovafloxacin and ceftriaxone with or without vancomycin. Pediatr Infect Dis J 2002;21:14-22.
- Sideri G, Kafetzis DA, Vouloumanou EK, Papadatos JH, Papadimitriou M, Falagas ME. Ciprofloxacin in critically ill children. Anaesth Intensive Care 2011;39:635-9.
- 12. Sung L, Manji A, Beyene J, Dupuis LL, Alexander S, Phillips R, et al. Fluoroquinolones in children with fever and neutropenia: a systematic review of prospective trials. Pediatr Infect Dis J 2012; 31:431-5.
- 13. Schaad UB. Fluoroquinolone antibiotics in infants and children. Infect Dis Clin North Am 2005;19:617-28.
- Chien S, Wells TG, Blumer JL, Kearns GL, Bradley JS, Bocchini JA Jr, et al. Levofloxacin pharmacokinetics in children. J Clin Pharmacol 2005;45:153-60.
- Committee on Infectious Diseases. The use of systemic fluoroquinolones. Pediatrics 2006;118:1287-92.
- Sabharwal V, Marchant CD. Fluoroquinolone use in children. Pediatr Infect Dis J 2006;25:257-8.
- 17. Velissariou IM. The use of fluoroquinolones in children: recent advances. Expert Rev Anti Infect Ther 2006;4:853-60.
- 18. Bradley JS, Jackson MA; Committee on Infectious Diseases;

- American Academy of Pediatrics. The use of systemic and topical fluoroquinolones. Pediatrics 2011;128:e1034-45.
- Melhus A. Fluoroquinolones and tendon disorders. Expert Opin Drug Saf 2005;4:299-309.
- 20. Forsythe CT, Ernst ME. Do fluoroquinolones commonly cause arthropathy in children? CJEM 2007;9:459-62.
- Sansone JM, Wilsman NJ, Leiferman EM, Conway J, Hutson P, Noonan KJ. The effect of fluoroquinolone antibiotics on growing cartilage in the lamb model. J Pediatr Orthop 2009;29:189-95.
- van der Linden PD, Sturkenboom MC, Herings RM, Leufkens HG, Stricker BH. Fluoroquinolones and risk of Achilles tendon disorders: case-control study. BMJ 2002;324:1306-7.
- 23. Chalumeau M, Tonnelier S, D'Athis P, Treluyer JM, Gendrel D, Breart G, et al. Fluoroquinolone safety in pediatric patients: a prospective, multicenter, comparative cohort study in France. Pediatrics 2003;111(6 Pt 1):e714-9.
- 24. U.S. Food and Drug Administration. Drug approval package: cipro (ciprofloxacin hydrochloride) tablets, cipro IV (ciprofloxacin) solution, cipro (ciprofloxacin) oral suspension [internet]. Silver Spring: U.S. Food and Drug Administration; [cited 2012 Nov 25]. Available from: http://www.accessdata.fda.gov/drugsatfda\_docs/nda/2004/019537s49\_19847s27\_19857s31\_20780s13TOC.cfm.
- Adefurin A, Sammons H, Jacqz-Aigrain E, Choonara I. Ciprofloxacin safety in paediatrics: a systematic review. Arch Dis Child 2011;96:874-80.
- Kaguelidou F, Turner MA, Choonara I, Jacqz-Aigrain E. Ciprofloxacin use in neonates: a systematic review of the literature. Pediatr Infect Dis J 2011;30:e29-37.
- Chaudhari S, Suryawanshi P, Ambardekar S, Chinchwadkar M, Kinare A. Safety profile of ciprofloxacin used for neonatal septicemia. Indian Pediatr 2004;41:1246-51.
- Dutta S, Chowdhary G, Kumar P, Mukhopadhay K, Narang A. Ciprofloxacin administration to very low birth weight babies has no effect on linear growth in infancy. J Trop Pediatr 2006;52:103-6.
- 29. Noel GJ, Bradley JS, Kauffman RE, Duffy CM, Gerbino PG, Arguedas A, et al. Comparative safety profile of levofloxacin in 2523 children with a focus on four specific musculoskeletal disorders. Pediatr Infect Dis J 2007;26:879-91.
- ClinicalTrials.gov. Moxifloxacin in pediatric subjects with complicated intra-abdominal infection (MOXIPEDIA) [Internet].
   Bethesda: National Institutes of Health; [cited 2012 Nov 25].
   Available from: http://clinicaltrials.gov/ct2/show/NCT01069900.
- 31. ClinicalTrials.gov. Safety, tolerability and pharmacokinetics

- of single dose intravenous moxifloxacin in pediatric patients [Internet]. Bethesda: National Institutes of Health; [cited 2012 Nov 25]. Available from: http://clinicaltrials.gov/ct2/show/NCT01049022.
- 32. Kim SC, Park YC, Kim BG, Nam DH. Outpatient antibiotic prescription by pediatric and ENT physicians in Ulsan city. Korean J Clin Pharm 2010;20:145–50.
- 33. European Medicines Agency. 5-year report to the European Commision. General report on the experience acquired as a result of the application of the paediatric regulation [Internet]. London: European Medicines Agency; c2012 [cited 2012 Nov 25]. Available from: http://ec.europa.eu/health/files/paediatrics/2012-09\_pediatric\_report-annex1-2\_en.pdf.
- 34. European Medicines Agency. Ciprofloxacin Bayer [Internet]. London: European Medicines Agency; c2012 [cited 2012 Nov 25]. Available from: http://www.emea.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Ciprofloxacin\_Bayer/human\_referral\_000024.jsp.
- 35. World Health Organization. Pocket book of hospital care for children [Internet]. Geneva: World Health Organization; c2013 [cited 2012 Nov 25]. Available from: http://www.who.int/maternal\_child\_adolescent/documents/9241546700/en/.
- 36. World Health Organization. The selection and use of essential medicines. Report of the WHO expert committee, 2011 [Internet]. Geneva: World Health Organization; c2013 [cited 2012 Nov 25]. Available from: http://apps.who.int/iris/bitstream/10665/44771/1/WHO\_TRS\_965\_eng.pdf.
- 37. Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis 2011;53:e25-76.
- 38. Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJ, Hicks LA, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis 2012; 54:e72-e112.
- World Health Organization. Guidelines for the programtic management of drug-resistant tuberculosis - 2011 update [Internet]. Geneva: World Health Organization; c2013 [cited 2012 Nov 25]. Available from: http://apps.who.int/iris/bitstre am/10665/44597/1/9789241501583\_eng.pdf.
- Schaad UB. Will fluoroquinolones ever be recommended for common infections in children? Pediatr Infect Dis J 2007;26:865-7.