

The Use and Safety of Ciprofloxacin in Korean Children: A Retrospective Multicenter Study

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ABSTRACT

BACKGROUND: Ciprofloxacin is not approved in children under 18 years old due to its potential musculoskeletal adverse effects. However, it is widely prescribed in the pediatric patients. We conducted a retrospective multicenter study to evaluate the prescription pattern of ciprofloxacin and to review any reported adverse events in Korean children. **METHOD:** A retrospective review was performed in patients younger than 18 years old who received ciprofloxacin in 7 university hospitals in Korea from January 2006 to December 2011. **RESULT :** A total of 729 patients were identified. The median age was 15.9 years (range, 0.1-17.9); 18 patients (2.5%) were under 2 years old, 77 (10.6%) 2-9 years, 143 (19.6%) 10-14 years, and 491 (67.4%) 15-17 years. Two-hundred sixty-nine (36.9%) patients had comorbid medical conditions. Ciprofloxacin was given as the first-line antimicrobial agent in 480 (65.8%) patients. Clinical diagnoses at the time of ciprofloxacin prescription were gastroenteritis (325, 44.6%), urinary tract infections (159, 21.8%), abscess or skin and soft tissue infections (65, 8.9%) and pneumonia (55, 7.5%). There were 22 bacteremia cases (3.0%). Ciprofloxacin was prescribed mostly by emergency care physicians (207, 28.4%), internal medicine physicians (187, 25.7%) and pediatricians (153, 21.0%). The use of ciprofloxacin based on culture results was observed in only 26.1% of patients (190/729): 43.8% by pediatricians vs. 21.4% by non-pediatric physicians (P<0.0001). Adverse events after use of ciprofloxacin were observed in 15 patients (2.1%): four with hypersensitivity, six with gastrointestinal complaints, one with headache, one with EKG abnormality and three others. There was no musculoskeletal complication reported. **CONCLUSION :** This is the first multicenter study to evaluate the prescription pattern and safety of ciprofloxacin in Korean children. We found that ciprofloxacin was frequently prescribed in children as an empiric antibiotic choice in many unapproved indications and musculoskeletal adverse event was not reported in any of these patients. There is a need for systematic monitoring for the appropriate use of ciprofloxacin and development of musculoskeletal complication in Korean children.

INTRODUCTION

• Fluoroquinolones in pediatric patients

- **Not approved in children under 18 years old** due to its **potential musculoskeletal adverse effects**

Approved Pediatric Indications of Fluoroquinolones

US FDA	European Medicines Agency	In Korea
<ul style="list-style-type: none"> Inhalational anthrax Complicated urinary tract infection and pyelonephritis 	<ul style="list-style-type: none"> Bronchopulmonary infections in cystic fibrosis caused by <i>Pseudomonas aeruginosa</i> Inhalational anthrax Complicated urinary tract infections and pyelonephritis 	<ul style="list-style-type: none"> None

- **However, widely prescribed in the pediatric patients**

• Drug utilization review (DUR)

- **A system of ongoing, systematic, criteria-based evaluation of drug use**
- **Can help ensure that medicines are used appropriately at the individual patient**
- **In Korea, nationwide DUR has been performing since 2010.**

• Aims of this study

- To investigate prescription pattern of ciprofloxacin in Korean children
- To analyze the safety of ciprofloxacin in Korean children

METHODS

- Study period: January 1, 2006 ~ December 31, 2011
- Patients: Pediatric patients less than 18 years of age who received ciprofloxacin
- Exclusion: patients who received ciprofloxacin for prophylaxis (prior to surgeries, interventions or hematopoietic cell transplantation)
- Participating hospitals – 7 university hospitals in Korea
 - : Samsung Medical Center, Seoul National University Children's Hospital, Severance Children's Hospital, Gacheon Gil Hospital, St. Vincent's Hospital, Chonbuk National University Hospital, Pusan National University Children's Hospital
- Clinical information: Retrospective review of medical records
- Statistic analysis: Mann-Whitney test, Fisher's Exact test

RESULTS

Table 1 . Characteristics of patients

	N=729
Sex , Male (%)	419 (57.5)
Age, median (years, range)	15.9 (0.1-17.9)
Patients with underlying diseases (%)	269 (36.9)

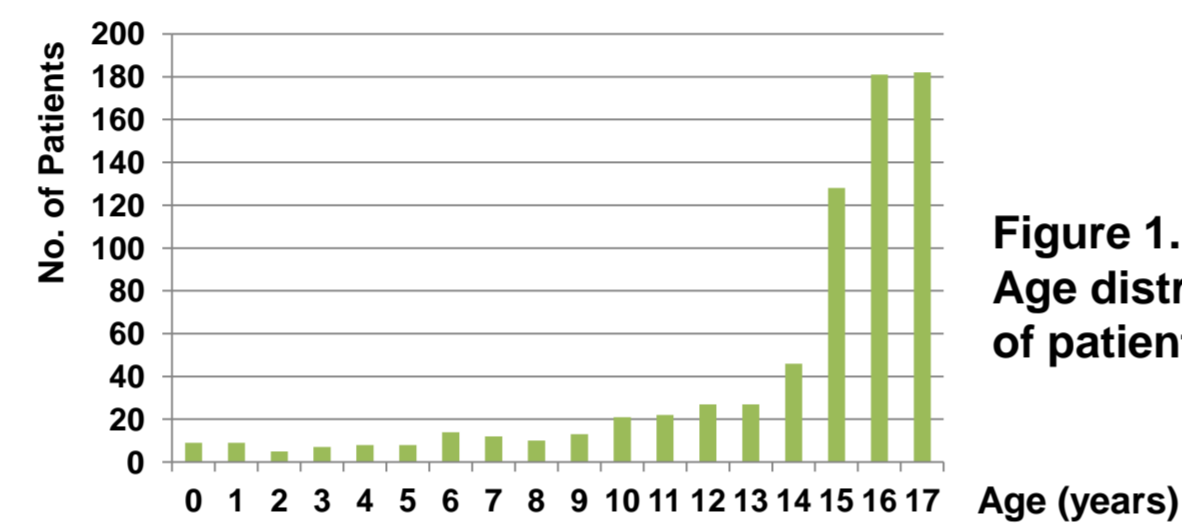


Figure 1. Age distribution of patients

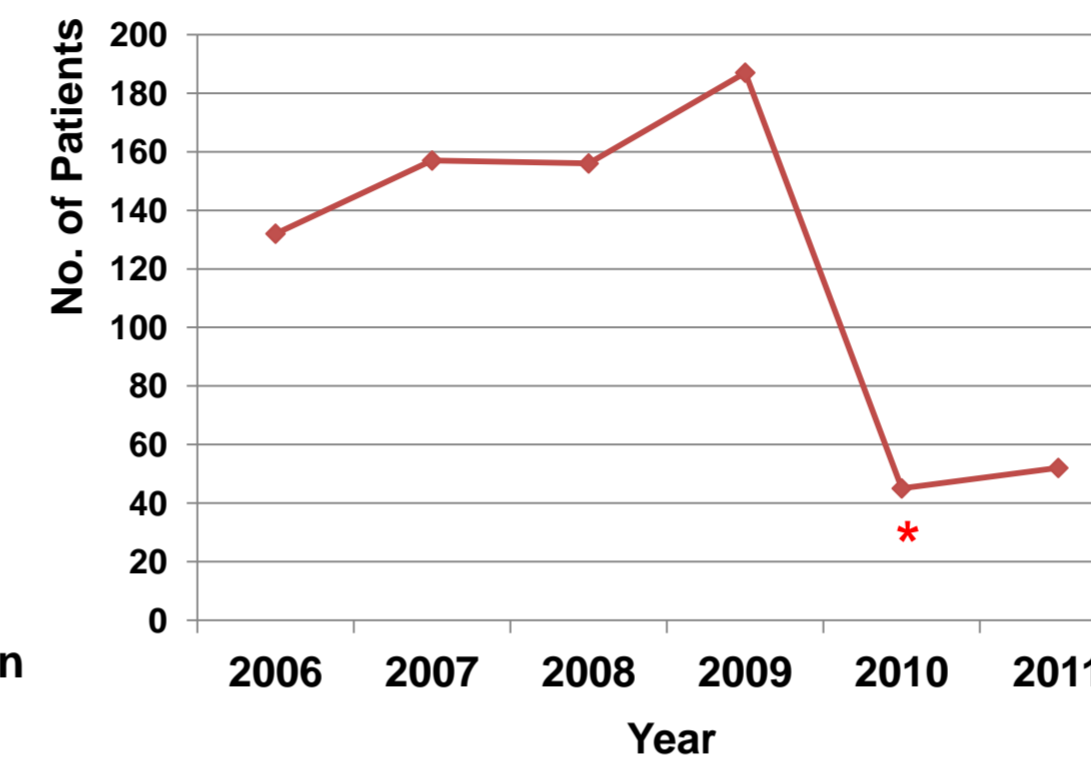


Figure 2. Yearly distribution of patients

* Nationwide introduction of DUR in 2010

Table 2 . Reasons for use of ciprofloxacin

Clinical diagnosis	n (%)
Bacteremia	22 (3.0)
Meningitis	5 (0.7)
Pneumonia	55 (7.5)
Urinary tract infections	159 (21.8)
Arthritis/Osteomyelitis	10 (1.5)
Deep abscess	21 (2.9)
Gastroenteritis	325 (44.6)
Otitis media or externa/Sinusitis	11 (1.5)
Others	152 (20.9)

Table 4. Prescribing physicians

Specialty	n (%)
Pediatrics	153 (21.0)
Internal medicine	187 (25.7)
Emergency medicine	207 (28.4)
General surgery	44 (6.0)
Neurosurgery	19 (2.6)
Otolaryngology	12 (1.6)
Orthopedic surgery	22 (3.0)
Urology	37 (5.1)
Others	48 (6.6)

Table 3. Results of culture studies in patients

	n (%)
Any culture studies performed	417 (61.3)
Positive culture results	190 (26.1)
Isolated pathogens	
<i>Pseudomonas aeruginosa</i>	55 (28.9)
<i>Pseudomonas</i> species	6 (3.2)
<i>Burkholderia</i> species	3 (1.6)
<i>Acinetobacter</i> species	10 (5.3)
<i>Klebsiella pneumoniae</i> spp.	8 (4.2)
<i>Escherichia coli</i>	39 (20.5)
<i>Salmonella</i> species	9 (4.7)
<i>Mycoplasma pneumoniae</i>	3 (1.6)
Others	79 (41.6)

Table 5. Differences in prescribing patterns between pediatricians and non-pediatricians

	PED	Non-PED	P-value
No. of patients	135	576	
Age, median (range)	11.3 (0.1-17.9)	16.3 (0.1-17.9)	<0.0001
Based on culture results (%)	67 (46.8)	123 (21.4)	<0.0001
Clinical diagnosis (%)			
Bacteremia	12 (7.8)	10 (1.7)	0.0004
Meningitis	2 (1.3)	3 (0.5)	0.2828
Pneumonia	32 (20.9)	23 (4.0)	<0.0001
UTIs	22 (14.4)	137 (23.8)	0.0114
Gastroenteritis	47 (30.7)	278 (48.3)	0.0001

PED, pediatricians; Non-PED, non-pediatricians

Table 6. Differences in prescribing patterns according to Drug Utilization Review

	Pre-DUR (2006-2009)	Post-DUR (2010-2011)	P-value
No. of patients	632	97	
Age, median (range)	16.1 (0.1-17.9)	15.0 (0.1-17.9)	<0.0001
Based on culture results (%)	150 (23.7)	40 (41.2)	0.0005
Clinical diagnosis (%)			
Bacteremia	14 (2.2)	8 (8.2)	0.0048
Meningitis	2 (0.3)	3 (3.1)	0.0187
Pneumonia	40 (6.3)	15 (15.5)	0.0034
UTIs	140 (22.2)	19 (19.6)	0.6920
Gastroenteritis	291 (46.0)	34 (35.1)	0.0482
Prescribing physicians (%)			
Pediatrician	98 (15.5)	55 (56.7)	<0.0001
Internal medicine	175 (27.7)	12 (12.4)	0.0011
Emergency department	199 (31.5)	8 (8.2)	<0.0001

Table 7. Reported adverse events after use of ciprofloxacin

Any adverse events (AEs)	N = 15 (2.1%)
Hypersensitivity	4
Gastrointestinal troubles	6
Headache	1
Abnormal EKG (QT prolongation)	1
Others	3
Musculoskeletal AE	0
Ciprofloxacin-related AEs*	9/15 (60.0%)
Unknown causality	6/15 (40.0%)

* Improvement of AEs after discontinuation of ciprofloxacin

SUMMARY

- The most common clinical diagnosis at the time of ciprofloxacin prescription were gastroenteritis (325/729, 44.6%).
- Most of ciprofloxacin was prescribed by non-pediatric physicians (576/729, 79.0%).
- The use of ciprofloxacin based on culture results was observed in only 26.1% of patients: 43.8% by pediatricians vs. 21.4% by non-pediatric physicians (P<0.0001).
- **The decline in prescription of ciprofloxacin by non-pediatric physicians was observed since the introduction of nationwide DUR.**
- Adverse events after use of ciprofloxacin were reported in 15 patients (2.1%).
- There was **no musculoskeletal complication reported.**

CONCLUSION

- This is the first multicenter study to evaluate the prescription pattern and safety of ciprofloxacin in Korean children.
- Ciprofloxacin was frequently prescribed in children as an empiric antibiotic choice in many unapproved and inappropriate indications.
- **There is a need for systematic monitoring for the appropriate use of ciprofloxacin and development of musculoskeletal complication in children.**