The change of antibiotic susceptibility in febrile urinary tract infection in childhood and adolescence during the last decade

Useok Choi, Eunjae Kim, Don Hee Lyu, Kang Seob Kim, Bong Hee Park, Hong Chung, Chang Hee Han, Sangrak Bae

Department of Urology, Uijeongbu St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Uijeongbu, Korea

Purpose: The purpose of this study was to clarify the pattern of antibiotic resistance in pediatric urinary tract infections (UTIs).

Materials and Methods: We analyzed the data of entire urine culture tests and antibiotic susceptibility tests performed on hospitalized patients for febrile UTI at the Uijeongbu St. Mary’s Hospital during 2010–2020. A retrospective analysis was performed using medical records of urine culture results and antibiotic susceptibility results in patients with UTIs.

Results: We performed urine cultures from 2,491 patients, and identified bacterial types in 1,651 cases. We found that the resistance rates to ampicillin, ampicillin/sulbactam, cefazolin, gentamicin, piperacillin, tobramycin, and trimethoprim/sulfamethoxazole were already over 20% in 2010. The resistance rates to many other antibiotics also steadily increased over time. Among the antibiotics tested in 2020, only amikacin, cefoxitin, imipenem, piperacillin/tazobactam, and tigecycline showed the resistance rates below 20%. Noticeably, ciprofloxacin also showed an increase in the resistance rate from 7.3% in 2010 (S 139 vs. R 11) to 27.78% in 2019 (S 104 vs. R 40) and even over 30% (33.96%) in 2020 (S 35 vs. R 18).

Conclusions: Antibiotic resistance is a serious problem in pediatric UTIs. In the treatment of pediatric UTIs, more caution is needed in the use of antibiotics. It may be necessary to apply appropriate antibiotic management programs such as antibiotics steward program for pediatric patients. Failure of a proper response strategy coping with antibiotic resistance may accelerate the resistance crisis.

Keywords: Antibiotic resistance; Antibiotics; Ciprofloxacin; Urinary tract infections

INTRODUCTION

Febrile urinary tract infection (UTI) is one of the most common conditions in febrile illness in infants and children [1]. In addition, 30% of newborns with urinary tract malformations may have a UTI as the first sign or symptom of abnormality [2]. UTIs in children, if not properly treated, may cause a variety of severe consequences of recurrent UTI and subsequent hospitalization, permanent decline in renal function due to the formation of inflammatory scars in the pediatric kidney in pyelonephritis, sepsis or bacteremia due to severe infection, and death. In addition to such clinical
consequences, it may also lead to antibiotic resistance. In
general, according to the clinical guidelines of the American
Academy of Pediatrics, the diagnostic criteria for UTI are
positive dipstick test, pyuria or bacteriuria in microscopic
examination, and 50,000 cfu/mL pathogens in clean voided
urine or suprapubic aspirated specimen.

For pediatric patients, prophylactic antibiotics, which
prevent renal damage [3] are used to treat the diseases such
as vesicoureteral reflux, ureteropelvic junction obstruction,
primary megaureter, and ureterocele. UTIs accompanied
by fever and leukocytosis, in particular, require patients to
be hospitalized and treated with therapeutic antibiotics. A
patient treated with antibiotics at an early stage may ex-
perience various adverse events at later times [4,5]. Recent
studies have shown that the early exposure to antibiotics
may alarm microbiota, and cause dysbiosis [6] and antibiotic
resistance [7]. Therefore, exposure to antibiotics at a rela-
tively early age and for a long period of time enhances the
likelihood of developing antibiotic resistance.

While the emergence of expanded-spectrum beta-lacta-
mase positive pathogens as well as carbapenem-resistant
pathogens has been already a serious problem in adult UTIs
[8], the similar antibiotic resistance is also being raised as a
clinical challenge in pediatric UTIs [9]. Antibiotic resistance
has become a global problem beyond the national level. In
this regard, long-term studies on antibiotic resistance in pe-
diatric UTIs in Korea are urgent.

In this study, in order to further understand the recent
situation of antibiotic resistance for UTIs, we have investi-
gated the pattern of antibiotic resistance in pediatric UTI
patients.

MATERIALS AND METHODS

Institutional ethics review was sought and the study was
approved by the Catholic University of Korea, Institutional
Review Board (approval number: UC16RCMI0120). Because
only medical records were used, informed consent was not
obtained. We analyzed the entire urine culture tests and
antibiotic susceptibility tests performed on patients who
received inpatient treatment for febrile UTI at the pediat-
ric department of the Uijeongbu St. Mary’s Hospital dur-
ing the past decade (1 January, 2010–31 December, 2020). A
retrospective analysis was performed using medical records
of urine culture data and accompanying antibiotic suscepti-
ibility data in patients who had been diagnosed with UTIs
such as UTI, cystitis, and acute pyelonephritis (APN) as the
primary or secondary diagnosis. Based on the patient’s urine
culture results, the causative strains of infected pathogens
were identified and the extended-spectrum beta-lactamase
(ESBL) positivity and antibiotic susceptibility data were
analyzed every year during the period of this study.

In the antibiotic susceptibility test, the tested antibiotics
were not the same every year. However, if the antibiotics ad-
ministered at the time of the examination were confirmed,
they were compared. In this study, pathogens being defined
to be intermediate and resistance in the susceptibility test
were classified as antibiotic-resistant strains. Antibiotics
studied were amikacin, ampicillin, ampicillin/sulbactam,
astreonam, cefazolin, cefepime, cefotaxime, cefoxitin, cefazid-
dime, cefuroxime, ciprofloxacin, colistin, doripenem, gentami-
cin, imipenem, levofloxacin, meropenem, piperacillin, piper-
acillin/tazobactam, ticarcillin/clavulanic acid, tigecycline,
tobramycin, and trimethoprim/sulfamethoxazole. Regarding
to the resistance rate, antibiotic resistance rate under 20%
wash set as the green zone, 20%–30% as the yellow zone, and
the ratio over 30% as the red zone.

Urine culture for antimicrobial susceptibility test was
performed by MicroScan (Beckman Coulter, Brea, CA, USA),
VITEK2 (BioMerieux, Marcy-l’Etoile, France), and Microflex
LT (Bruker Daltonics, Bremen, Germany).

RESULTS

1. General characteristics of pediatric urinary
tract infection patients

A total of 2,498 pediatric patients including 1,141 males
and 1,357 females were hospitalized for UTI, indicating that
the male to female ratio was 1:1.9. The average number of
UTI occurrence episodes was found to be significantly high-
er in female with 1.1 vs. 1.13 episodes (p=0.014). The primary
diagnosis indicated APN (1,001 cases), UTI (847 cases), and
acute cystitis (358 cases), and various other accompanying
diseases could be identified. For imaging tests, KUB ultraso-

nography was performed in 2,153 patients and dimercapto-
succinic acid (DMSA) scan was performed in 1,581 cases. The
general characteristics of pediatric febrile UTI patients are
shown in Table 1.

To identify the infected bacterial strains, we tested
2,498 patients, and performed the urine cultures from 2,491
patients (Table 2). Among the 2,491 cases, bacteria were
identified in 1,651 cases, while other 225 cases showed con-
tamination. Among the total of 1,651 bacterial identification,
Escherichia coli was found the most at 74.2%, non-specific
strains including gram-positive cocci (GPC) accounted for the
second most at 9.6%, and Enterococcus faecalis was the third
at 6.8%. The distribution of the identified bacterial strains
is shown in Fig. 1. Our results revealed that there were 126
cases with multiple types of pathogens: 122 cases with two types of strains, 3 cases with three types of bacteria, and 1 case with four types of bacteria.

2. Extended-spectrum beta-lactamase pathogens

The ESBL positivity test data demonstrated that 1,137 cases (83.5%) were ESBL(-) and 225 cases (16.5%) were ESBL(+). Intriguingly, ESBL(+) cases were gradually increased from 5.3% in 2010 to 9.2% in 2013, and almost doubled between 2013 and 2014 (Fig. 2).

3. Antibiotic susceptibility tests

During 2010–2020, we investigated the susceptibility to 23 antibiotics. Of note, there was a limitation in the continuous observation of certain antibiotics because the list of the antibiotics to be tested for antibiotic susceptibility was different every year. We compared the susceptibility to all antibiotics tested during 2010–2020, and observed a change of antibiotic susceptibility patterns.

In a 2010 survey, ampicillin, ampicillin/sulbactam, cefazolin, gentamicin, piperacillin, tobramycin, trimethoprim/sulfamethoxazole had already shown a resistance rate of over 20%. Most of other antibiotics also showed a steady increase in the resistance over time. Only amikacin, cefoxitin, imipenem, piperacillin/tazobactam, and tigecycline showed the resistance rate below 20% in 2020. Although it is restrictively used for pediatric patients, ciprofloxacin also showed an increase in its resistance rate from 7.3% in 2010 (S 139 vs. R 11) to 27.78% in 2019 (S 104 vs. R 40) and 33.96% in 2020 (S 35 vs. R 18). In the case of ampicillin, ampicillin/sulbactam, and piperacillin, the resistance rates of those antibiotics consistently showed more than 60% during the past 10 years of this study. During the period of this study, amikacin and carbapenem, including imipenem, doripenem, and meropenem, kept less than 10%, while cefoxitin kept less than 20% in most years tested in our study. Aztreonam, cefepime, ticarcillin/clavulanic acid, and trimethoprim/sulfamethoxa-
Table 2. The uropathogen patterns in pediatric febrile UTIs during 2010–2020

| Variable                | 2010  | 2011  | 2012  | 2013  | 2014  | 2015  | 2016  | 2017  | 2018  | 2019  | 2020  |
|-------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Number of patients      | 222   | 226   | 208   | 244   | 267   | 200   | 254   | 322   | 250   | 232   | 73    |
| Male                    | 110   | 97    | 119   | 112   | 140   | 96    | 109   | 128   | 86    | 101   | 43    |
| Female                  | 112   | 129   | 89    | 132   | 127   | 104   | 145   | 194   | 164   | 131   | 30    |
| Pathogen                |       |       |       |       |       |       |       |       |       |       |       |
| Escherichia coli        | 110   | 106   | 119   | 117   | 110   | 124   | 145   | 112   | 120   | 47    |
| Klebsiella pneumoniae   | 11    | 9     | 6     | 6     | 21    | 3     | 7     | 13    | 3     | 10    | 3     |
| Klebsiella oxytoca      | 1     | 4     | 0     | 1     | 1     | 2     | 4     | 2     | 4     | 2     |
| Pseudomonas aeruginosa  | 1     | 0     | 1     | 2     | 1     | 4     | 3     | 0     | 0     | 0     |
| Proteus mirabilis       | 5     | 3     | 2     | 2     | 4     | 1     | 3     | 3     | 0     | 1     |
| Enterococcus faecalis   | 8     | 8     | 11    | 7     | 12    | 6     | 7     | 13    | 23    | 15    | 3     |
| Enterococcus faecium    | 2     | 6     | 6     | 9     | 6     | 2     | 2     | 2     | 7     | 0     | 0     |
| Other (GPC and etc.)    | 13    | 12    | 17    | 26    | 16    | 13    | 11    | 5     | 26    | 19    | 0     |

Values are presented as number only. UTI, urinary tract infection; GPC, gram-positive cocci.

Fig. 1. Annual numbers of the cases of infection caused by each pathogen in pediatric UTI patients. Urine cultures derived from pediatric patients who received inpatient treatment for febrile UTI during 2010–2020 were examined for the identification of pathogenic bacteria, as described in the MATERIALS AND METHODS. UTI, urinary tract infection; GPC, gram-positive cocci.

Fig. 2. Annual numbers of the cases of ESBL-negative or ESBL-positive infection. Urine cultures derived from pediatric patients who received inpatient treatment for febrile UTI during 2010–2020 were examined by ESBL test. The testing data were quantified for ESBL-negative (blue) or ESBL-positive (orange) infection. The percentages of the ESBL-positive infection among total infection were also shown (black line). ESBL, extended-spectrum beta-lactamase; UTI, urinary tract infection.
zole might have been considered as selectable and available antibiotic options in 2010; however, they showed a high resistance rate in 2020 (Fig. 3).

Given the antibiotic resistance rates in the green/yellow/red zones shown in Fig. 3, there were 12 antibiotics in the green zone and 3 antibiotics in the red zone in 2010. In comparison, in 2020 there were only 5 antibiotics in the green zone. The numbers of available antibiotics with relatively low antibiotic resistance dramatically decreased during the last decade.

**DISCUSSION**

Pediatric UTI is a disease with a prevalence of about 7%, which shows some variations according to gender and age [10]. Although only few studies on pediatric UTI have been reported in Korea, a recent domestic study suggests that pediatric UTIs in children younger than 1 year are more common in boys, whereas those in children older than 1 year are more in girls [11].

Infections cause not only medical problems but also various social and economic problems worldwide. In recent years, the continued use of antibiotics has brought serious problems in various ways, including dysbiosis resulting from the antibiotics-induced breakdown of microbiota homeostasis, which can also cause other diseases [12]. Furthermore, antibiotic resistance is one of the most common problems experienced and encountered in clinical practice. With generating a number of clinical problems in the treatment of infectious diseases, an increase in antibiotic resistance narrows the position of antibiotics as a therapeutic strategy against infectious diseases [13].

In adult patients, infections caused by ESBL-positive pathogens have already brought various problems in the therapeutic use of antibiotics in the medical field, given that the causative microorganisms of the first infection may acquire antibiotic resistance. In particular, Asia is a major region exhibiting high levels of resistance to quinolone in adults [13]. Korea is classified as a country with high antibiotic resistance, with being considered to reach a seriously high level of quinolone resistance. It is difficult to use quinolone for practical application to pediatric patients. We, however, have found in this study that the resistance rates of other antibiotics have already reached serious levels. Furthermore, the resistance rates of ESBL-positive pathogens are also increasing significantly.

Pediatric UTIs are often associated with urinary tract malformations. If these malformations are not severe, prophylactic antibiotics are administered to prevent the renal parenchymal damage caused by UTI [1,7,14]. The therapeutic
and preventive goal of the treatment of UTI in children is to reduce morbidity and mortality as well as to prevent renal scarring [15]. It has been suggested that certain factors such as age, gender, race, and circumcision status in males affect resistance and clinical features in pediatric UTI [10]. In one study, clinical features associated with relapse in UTI caused by ESBL-positive pathogens did not show a significant difference from those of ESBL-negative pathogens, implicating that general antibiotics should be used for the treatment of pediatric UTI [16].

Foreign studies on *E. coli*, one of the main causative bacteria of UTI in children, showed somewhat different results from this study. European studies have reported that the third-generation cephalosporin would be more effective because of the high levels of ampicillin resistance across European countries [17]. In comparison, in the studies in North America, amoxicillin as well as the second- or third-generation cephalosporins have been suggested as drugs of choice [1]. Thus, recommendations for antibiotics vary from region to region, depending on the antibiotic resistance rates and available antibiotics. Although other antibiotics can still be used clinically, amikacin and piperacillin/tazobactam showed superior sensitivity in this study if the antibiotic resistance rates are taken into account even though they have hepatotoxicity and nephrotoxicity. In case of antimicrobial therapy for infections caused by ESBL-positive pathogens, amikacin, and piperacillin/tazobactam may be considered first to minimize the use of carbapenem.

We have shown in this study that the percentages of ESBL-positive pathogens in children, newborns, and adolescents increased every year. Moreover, the resistance rates of the antibiotics belonging to the broad-spectrum antibiotic class have rapidly increased, while the antibiotics applied to the antibiotic stewardship program have maintained sensitivity. These findings are in good agreement with previous foreign studies suggesting that urologists are needed to be cautious to use drugs because of an increase in antibiotic resistance [7]. It is also noteworthy that there is a meta-analysis study suggesting a careful use of antibiotics for the treatment of pediatric UTI in primary medical institutions [18].

One of the emerging problems in pediatric patients is the infection of carbapenem-resistant pathogens [19], as in adults. In adult patients, carbapenem resistance, with already being spread rapidly, has been a major public health problem globally [20,21]. In fact, various attempts have been made to prevent the emergence of carbapenem-resistant pathogens. One study has implicated aminoglycoside as an alternative to carbapenem in the antibiotic therapy for children infected with ESBL-positive pathogens [22], while other studies have suggested the effectiveness of piperacillin/tazobactam [23], or ceftazidime-avibactam in a phase 3 RECAPTURE program [24]. Thus, diverse efforts are made for minimizing the use of carbapenem or the use of it along with other antibiotic classes. Our results in this study revealed that amikacin consistently exhibits less than 10% antibiotic resistance, suggesting that it might be used for retarding the emergence of CRE strains and for restricting the use of carbapenem in the treatment of pediatric UTI.

There are some caveats regarding our findings in this study. Firstly, this study was carried out with the patients from a single institution; therefore, our data in this study would not be representative of the national values of antibiotic sensitivity and resistance rate in Korea. In this respect, it is urgently needed to conduct nationwide and multicenter studies on the antibiotic susceptibility and resistance in Korea. Secondly, our study is a retrospective study, therefore, it is difficult to clarify the correlation between antibiotic sensitivity and actual clinical features. Future studies analyzing the characteristics as well as antibiotic efficacy and susceptibility of ESBL-positive strains would shed more insight into the better treatment of pediatric UTIs. Given that a variety of UTIs in children may cause various sequelae including deterioration of renal function, it is necessary to establish well-planned strategy for conducting long-term and systematic clinical research for pediatric UTI and its related fields.

**CONCLUSIONS**

Antibiotic resistance in pediatric UTI is under a serious status, with its rate rising steeply. In pediatric UTIs, therefore, more caution is needed in the therapeutic use of antibiotics. It may be necessary to apply appropriate antibiotic control and management programs such as antibiotics steward program for pediatric patients. Failure of a proper response strategy coping with antibiotic resistance may accelerate the resistance crisis, which might be predicted to come in the not-too-distant future.

**CONFLICTS OF INTEREST**

The authors have nothing to disclose.

**ACKNOWLEDGMENTS**

This work was supported financially by The Korean Society of Pediatric Urology.
AUTHORS’ CONTRIBUTIONS

Research conception and design: Useok Choi, Kang Seob Kim, Bong Hee Park, Hong Chung, Chang Hee Han, and Sangrak Bae. Data acquisition: Useok Choi, Eunjae Kim, and Don Hee Lyu. Statistical analysis: Useok Choi and Sangrak Bae. Data analysis and interpretation: Useok Choi and Sangrak Bae. Drafting of the manuscript: Useok Choi. Critical revision of the manuscript: Useok Choi. Obtaining funding: Sangrak Bae. Administrative, technical, or material support: Kang Seob Kim, Bong Hee Park, Hong Chung, Chang Hee Han, and Sangrak Bae. Supervision: Sangrak Bae. Approval of the final manuscript: Sangrak Bae.

REFERENCES

1. Leung AKC, Wong AHC, Leung AAM, Hon KL. Urinary tract infection in children. Recent Pat Inflamm Allergy Drug Discov 2019;13:2-18.
2. Sastre JB, Aparicio AR, Cotallo GD, Colomer BF, Hernández MC. Urinary tract infection in the newborn: clinical and radio imaging studies. Pediatr Nephrol 2007;22:1735-41.
3. Brandström P, Neveus T, Sixt R, Stokland E, Jodal U, Hansson S. The Swedish reflux trial in children: IV. Renal damage. J Urol 2010;184:292-7.
4. Slykerman RF, Thompson J, Waldie KE, Murphy R, Wall C, Mitchell EA. Antibiotics in the first year of life and subsequent neurocognitive outcomes. Acta Paediatr 2017;106:87-94.
5. Clausen TD, Bergholt T, bouaziz O, Arpi M, Eriksson F, Rasmussen S, et al. Broad-spectrum antibiotic treatment and subsequent childhood type 1 diabetes: a nationwide Danish cohort study. PLoS One 2016;11:e0161654.
6. Vangay P, Ward T, Gerber JS, Knights D. Antibiotics, pediatric dysbiosis, and disease. Cell Host Microbe 2015;17:553-64.
7. Kutasy B, Coyle D, Fossum M. Urinary tract infection in children: management in the era of antibiotic resistance-a pediatric urologist’s view. Eur Urol Focus 2017;3:207-11.
8. Zilberberg MD, Nathanson BH, Sulham K, Fan W, Shorr AF. Carbapenem resistance, inappropriate empiric treatment and outcomes among patients hospitalized with Enterobacteriaceae urinary tract infection, pneumonia and sepsis. BMC Infect Dis 2017;17:279.
9. Albaramki JH, Abdelghani T, Dalaen A, Khdhair Ahmad F, Allassaf A, Odeh R, et al. Urinary tract infection caused by extended-spectrum β-lactamase-producing bacteria: risk factors and antibiotic resistance. Pediatr Int 2019;61:1127-32.
10. Shaikh N, Morone NE, Bost JE, Farrell MH. Prevalence of urinary tract infection in childhood: a meta-analysis. Pediatr Infect Dis J 2008;27:302-8.
11. Suh W, Kim BN, Kang HM, Yang EA, Rhim JW, Lee KY. Febrile urinary tract infection in children: changes in epidemiology, etiology, and antibiotic resistance patterns over a decade. Clin Exp Pediatr 2021;64:293-300.
12. Konstantinidis T, Tsigalou C, Karvelas A, Stavropoulou E, Voidarou C, Bezirtzoglou E. Effects of antibiotics upon the gut microbiome: a review of the literature. Biomedicines 2020;8:502.
13. Choe HS, Lee SJ, Cho YH, Çek M, Tandoğdu Z, Wagenlehner F, et al. Aspects of urinary tract infections and antimicrobial resistance in hospitalized urology patients in Asia: 10-year results of the Global Prevalence Study of Infections in Urology (GPIU). J Infect Chemother 2018;24:278-83.
14. Yang SS, Tsai JD, Kanematsu A, Han CH. Asian guidelines for urinary tract infection in children. J Infect Chemother 2021;27:1543-54.
15. Mattoo TK, Shaikh N, Nelson CP. Contemporary management of urinary tract infection in children. Pediatrics 2021;147:e2020012138.
16. Hyun HS, Kim JH, Cho MH, Park E, Ha IS, Cheong HI, et al. Low relapse rate of urinary tract infections from extended-spectrum beta-lactamase-producing bacteria in young children. Pediatr Nephrol 2019;34:2399-407.
17. Vazouras K, Velali K, Tassiou I, Anastasiou-Katsiaridani A, Athanasopoulou K, Barbouni A, et al. Antibiotic treatment and antimicrobial resistance in children with urinary tract infections. J Glob Antimicrob Resist 2020;20:4-10.
18. Bryce A, Hay AD, Lane IF, Thornton HV, Wootton M, Costelloe C. Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by Escherichia coli and association with routine use of antibiotics in primary care: systematic review and meta-analysis. BMJ 2016;352:i939.
19. Vergadi E, Bitsori M, Maraki S, Galanakis E. Community-onset carbapenem-resistant Klebsiella pneumoniae urinary tract infections in infancy following NICU hospitalisation. J Pediatr Urol 2017;13:495.e1-6.
20. Cantón R, Akóva M, Carmeli Y, Giske CG, Glupczynski Y, Gniadkowski M, et al. Rapid evolution and spread of carbapenemases among Enterobacteriaceae in Europe. Clin Microbiol Infect 2012;18:413-31.
21. Samuelsen Ø, Naseer U, Tofteland S, Skutlaberg DH, Onken A, Hjetland R, et al. Emergence of clonally related Klebsiella pneumoniae isolates of sequence type 258 producing plasmid-mediated KPC carbapenemase in Norway and Sweden. J Antimicrob Chemother 2009;63:654-8.
22. Han SB, Lee SC, Lee SY, Jeong DC, Kang JH. Aminoglycoside therapy for childhood urinary tract infection due to extended-spectrum β-lactamase-producing Escherichia coli or Klebsiella pneumoniae. BMC Infect Dis 2015;15:414.
23. Sharara SL, Amoah J, Pana ZD, Simner PJ, Cosgrove SE, Tam-ma PD. Is piperacillin-tazobactam effective for the treatment of pyelonephritis caused by extended-spectrum β-lactamase-producing organisms? Clin Infect Dis 2020;71:e331-7.
24. Wagenlehner FM, Sobel JD, Newell P, Armstrong J, Huang X, Stone GG, et al. Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program. Clin Infect Dis 2016;63:754-62.