Clinical Features of Febrile Urinary Tract Infection Caused by Extended-spectrum Beta-lactamase-producing *Escherichia Coli* in Children

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The global prevalence of infections caused by extended-spectrum beta-lactam (ESBL)-producing *Escherichia coli* has been increasing. In children, ESBL-producing *E. coli* manifest mostly as febrile urinary tract infections (fUTIs). This study aimed to elucidate the clinical features of fUTI resulting from ESBL-producing *E. coli* in Japanese patients. The clinical features of children with *E. coli*-related fUTI were retrospectively examined. These children underwent treatment at the National Hospital Organization Saitama Hospital, Japan, between May 2010 and April 2018. Urine specimens were obtained by either bladder catheterization or the clean-catch method. All children having positive urine cultures (≥10^4 colony-forming unit/mL for catheter specimens and ≥10^5 colony forming unit/mL for clean-catch specimens) and a fever of ≥38°C were considered to have fUTI. During the study period, 171 patients were diagnosed with *E. coli*-related fUTI. Among these, 17 (9.9%) fUTI cases were caused by ESBL-producing *E. coli*. A significant difference was noted in the median age of the populations having ESBL-producing *E. coli* and non-ESBL-producing *E. coli* infections (2 and 5 months, respectively); other characteristics were not significantly different between the two patient groups. ESBL-producing *E. coli* infections markedly increased in our hospital between 2013 and 2018. In the present study, young age was the only risk factor for fUTI caused by ESBL-producing *E. coli* identified in Japanese children. (DOI: 10.2302/kjm.2019-0005-OA; Keio J Med 69 (2) : 43–47, June 2020)

**Keywords:** extended-spectrum beta-lactamase-producing *Escherichia coli*, febrile urinary tract infection, risk factor

**Introduction**

The global prevalence of infections caused by extended-spectrum beta-lactam (ESBL)-producing Enterobacteriaceae, which are resistant to a wide spectrum of newer beta-lactam antibiotics, has increased.\(^1\,^2\) Moreover, the number of infections in children related to these pathogens has also increased worldwide. *Escherichia coli* and *Klebsiella* spp. are the most common Enterobacte-

riiaceae causing urinary tract infections (UTIs). However, in Japan, most cases of febrile UTI (fUTI) are caused by *E. coli*; indeed, *Klebsiella* is a rare pathogen in Japan.\(^3\,^4\) Therefore, this study focused only on *E. coli*.

Several reports have discussed the clinical significance and treatment of infections caused by ESBL-producing Enterobacteriaceae.\(^5\,^8\) However, the risk factors associated with fUTI caused by ESBL-producing pathogens, and their treatment, remain unclear. Previous reports
have suggested that the patient characteristics of pediatric urinary tract infection in Japan are different from those in The United States and European countries. However, no literature is available in English on the comparison of clinical characteristics between pediatric fUTI caused by ESBL-producing and non-ESBL-producing E. coli in Japan. The present study therefore aimed to elucidate the clinical features of fUTI caused by ESBL-producing E. coli in Japanese patients.

**Patients and Methods**

The clinical features of children having fUTI caused by E. coli were retrospectively reviewed. We included patients aged <18 years who had undergone treatment at the National Hospital Organization Saitama Hospital in Saitama, Japan, between May 2010 and April 2018. In the current study, we counted one patient per episode, even if the same patient had more than one episode of fUTI. Urine specimens were obtained either by bladder catheterization or by the midstream or clean-catch method. Patients were considered to have fUTI if they had a fever of ≥38 °C and if a single pathogen (≥10⁴ colony-forming unit/mL for catheter specimens or ≥10⁵ colony-forming unit/mL for clean-catch specimens) was identified on urine culture. These diagnostic criteria were based on Japanese guidelines. ESBL was identified using the BD Phoenix ESR test according to the 2010 Clinical and Laboratory Standards Institute guidelines. The data collected from the medical records database included patients’ gender, age, history of urinary tract infections, results of blood culture, findings on abdominal ultrasound and voiding cystourethrogram (VCUG), and recent antimicrobial use (within 1 month). In addition, details about the initial antimicrobial therapy, definitive therapy post-antimicrobial susceptibility testing, the duration of fever during treatment, and medical history were recorded for patients with ESBL-producing E. coli infection.

All statistical analyses were performed using the SPSS statistical software package (version 24, SPSS Inc., Chicago, IL, USA and IBM, Armonk, NY, USA). Fisher’s exact test and the Mann-Whitney test were used to compare patient characteristics and to determine P values. P-values <0.05 were considered to be statistically significant. The study was approved by the Institutional Medical Ethics Committee of the National Hospital Organization Saitama Hospital. The approval number is R2018-31.

**Results**

During the observation period, 206 patients were diagnosed with fUTI; fUTI was caused by E. coli in 171 patients and caused by ESBL-producing E. coli in 17 (10%) patients. The median ages of the populations with fUTI caused by ESBL-producing E. coli and by non-ESBL-producing E. coli were significantly different, at 2 months and 5 months, respectively. Other characteristics, including male gender, a medical history of fUTI, the presence of bacteremia, abnormal ultrasound and VCUG findings, and recent antimicrobial use, were not significantly different between the groups (Table 1).

The percentage of ESBL-producing pathogens among total E. coli in the periods between May and April 2010–2011, 2011–2012, 2012–2013, 2013–2014, 2014–2015, 2015–2016, 2016–2017, and 2017–2018 were 0%, 15%, 6%, 0%, 4%, 11%, 16%, and 18%, respectively (Fig. 1). The proportion of infections caused by ESBL-producing E. coli decreased from 2011 to 2013. However, this proportion increased between 2013 and 2018.

A total of 16 of 17 patients with ESBL-producing E. coli were initially treated with cephalosporin antimicrobials, which are ineffective against ESBL-producing E. coli (Table 2). Treatment was switched to antimicrobials effective against ESBL in 14 of 16 patients after antimicrobial susceptibility was identified. The other patients continued receiving the same antimicrobials as before. All patients, including one with bacteremia, were afebrile within 48 h, which was before switching antimicrobials.
Discussion

Knowledge of the risk factors for ESBL-producing organism-related infections in children could help to identify high-risk patients and enable initiation of the appropriate empirical therapy. This is the first report discussing the risk of pediatric fUTI caused by ESBL-producing E. coli during treatment in the Japanese municipal hospital. Younger age was the only risk factor identified in this study. Previous studies from other countries have reported that the occurrence of previous UTI, current exposure to antimicrobials, and underlying diseases such as renal abnormalities and bacteremia are risk factors for ESBL-producing organism-related infections. However, in our study, gender, a medical history of fUTI, rates of bacteremia, and abnormal ultrasound and VCUG findings did not significantly differ between patients with ESBL and non-ESBL fUTI. A total of 16 of 17 patients did not have a history of previous episodes of fUTI and antibiotic use.

A majority of UTIs are ascending infections caused by bacteria from the fecal flora. Although stool cultures were not performed in the present study, we speculate that ESBL-producing E. coli were present in the fecal flora of patients. The infective strains colonizing infants usually originate from the mother’s vaginal and perineal microbiota, the skin flora of parents and siblings, breast milk, or other foods. It is probable that ESBL-producing E. coli are transmitted soon after birth. In the present study, the pathogens were possibly transmitted from family members, particularly the mother.

The incidence of fUTI caused by ESBL-producing Enterobacteriaceae has increased worldwide. Based on the findings of previous reports and the known strong association between ESBL-producing E. coli infections and antibiotic use, certain conditions need to be fulfilled for clinicians to suspect an infection to be related to ESBL-producing E. coli. First, the patient must have acquired the ESBL-producing E. coli through contact with a colonized health care worker or a contaminated fomite. Second, the isolate must emerge as a result of the selective effect of antibiotic use. In Japan, the Shimane Prefectural Central Hospital reported in 2018 a dramatic increase in the incidence of upper UTI caused by ESBL-producing E. coli in children. This was reflected in the findings of our study; the incidence of ESBL-producing E. coli significantly increased between 2013 and 2018.

Third-generation cephalosporins are the most commonly used antimicrobials for treating fUTI, but susceptibility tests show that ESBL-producing E. coli strains are resistant to drugs in this class. Despite carbapenems being the standard treatment for infections with ESBL-producing pathogens, third-generation cephalosporins, because of their high urinary concentrations, have been
Table 2. fUTI patients with ESBL-producing *E. coli*

| No. | Age in months | Sex | Initial antimicrobials | Time to afebrile (h) | Definitive therapy | Blood culture | Ultrasound | Voiding cystourethrogram | Recent antimicrobials use | Medical history |
|-----|---------------|-----|-----------------------|----------------------|-------------------|----------------|------------|--------------------------|--------------------------|-----------------|
| 1   | 9             | F   | Cefotaxime            | <12                  | Trimethoprim-sulfamethoxazole | neg           | normal     | normal                   | none                     | n.p.            |
| 2*  | 1             | M   | Ampicillin+ Cefotaxime| <12                  | Cefmetazole        | neg           | normal     | VUR grade 2               | none                     | n.p.            |
| 3*  | 2             | M   | Piperacillin/ Tazobactam| <12                 | Piperacillin/ Tazobactam | neg           | normal     | VUR grade 2               | Ampicillin+ Cefotaxime | fUTI            |
| 4   | 2             | M   | Ceftriaxone           | <24                  | Cefmetazole        | neg           | normal     | SFU grade 1               | none                     | n.p.            |
| 5   | 7             | F   | Cefotaxime            | <48                  | Cefazolin          | neg           | normal     | normal                   | none                     | n.p.            |
| 6   | 4             | M   | Cefotaxime            | <48                  | Meropenem          | neg           | normal     | normal                   | none                     | n.p.            |
| 7   | 3             | M   | Ceftriaxone           | <12                  | Trimethoprim-sulfamethoxazole | neg           | normal     | SFU grade 1               | none                     | n.p.            |
| 8   | 1             | M   | Cefotaxime            | <24                  | Cefmetazole        | neg           | normal     | SFU grade 1               | none                     | n.p.            |
| 9   | 3             | M   | Cefazolin             | <12                  | Cefazolin          | neg           | normal     | normal                   | none                     | n.p.            |
| 10  | 2             | M   | Cefotaxime            | <12                  | Cefmetazole        | neg           | normal     | SFU grade 1               | not performed            | none            |
| 11  | 2             | M   | Cefotaxime            | <12                  | Cefmetazole        | neg           | normal     | SFU grade 1               | none                     | n.p.            |
| 12  | 1             | M   | Cefotaxime            | <12                  | Cefmetazole        | neg           | normal     | SFU grade 1               | none                     | n.p.            |
| 13  | 2             | F   | Cefotaxime            | <48                  | Meropenem          | neg           | normal     | VUR grade 4               | none                     | n.p.            |
| 14  | 3             | M   | Cefotaxime            | <12                  | Cefotaxime         | neg           | normal     | not performed             | none                     | n.p.            |
| 15  | 4             | M   | Cefotaxime            | <12                  | Trimethoprim-sulfamethoxazole | neg           | normal     | not performed             | none                     | n.p.            |
| 16  | 1             | M   | Cefotaxime            | <24                  | Cefmetazole        | pos           | normal     | normal                   | none                     | n.p.            |
| 17  | 18            | F   | Cefotaxime            | <48                  | Cefmetazole        | neg           | normal     | VUR grade 2               | none                     | n.p.            |

*Cases 2 and 3 involve the same patient.
SFU: Society for Fetal Urology, VUR: vesicoureteral reflux, n.p: nothing particular.
successfully used to treat fUTI caused by these organisms.14 In the current study, most children with fUTI but without bacteremia received third-generation cephalosporins as empirical therapy and did well during the treatment period.15 In our study, 16 of 17 patients treated with first- or third-generation cephalosporins became afibrile within 48 h, even though one child had bacteremia. However, treatment based on an ineffective antimicrobial might have deleterious effects on patients with serious complications, such as bacteremia.13 The use of third-generation cephalosporins may be continued as empirical therapy for fUTI; however, antimicrobials should be selected carefully in seriously ill patients with suspected bacteremia. Furthermore, renal outcomes, including scarring, are still unclear in patients who are empirically treated with third-generation cephalosporins for ESBL-producing pathogens.

The current study has some limitations. First, according to the study design, the study population was drawn entirely from a single community hospital in Japan, and the sample size was small. Second, ultrasound and VCUG were not performed in all patients with fUTI.

In conclusion, to our knowledge, this is the first study discussing the risk of pediatric fUTI caused by ESBL-producing E. coli discovered during treatment in the Japanese municipal hospital. Younger patient age was the only risk factor for developing ESBL-producing E. coli infections identified in this study. In contrast to previous reports, other characteristics were not significantly different between the ESBL and non-ESBL groups. Further multicentric prospective studies are essential to elucidate the clinical characteristics of ESBL-producing E. coli infections and their most appropriate treatment.

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Conflict of interest

The authors declare that no conflict of interest exists.

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