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ORIGINAL ARTICLE

# Low relapse rate of urinary tract infections from extended-spectrum beta-lactamase-producing bacteria in young children

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## Abstract

**Background** Extended-spectrum-beta-lactamase (ESBL)-producing bacteria are an increasingly important cause of urinary tract infections (UTIs) worldwide. We evaluated clinical characteristics and associated risk factors of UTIs in young children according to ESBL-producing status and relapse rates.

**Methods** All urinary culture results in patients younger than 2 years old were assessed, and only children with febrile UTIs from gram-negative bacterial infections were reviewed.

**Results** Of 845 episodes evaluated, 146 (17.3%) were caused by ESBL-positive bacteria. Significant differences were observed in previous UTIs, use of antibiotics or history of hospitalization within previous 3 months, and underlying urinary abnormalities between the ESBL UTI and non-ESBL UTI groups. After 2 weeks of treatment completion, UTI relapse occurred in 2.7% of children in the ESBL group and 1.1% of children in the non-ESBL group ($P = 0.13$). In the ESBL UTI group, relapse rate was not significantly different between patients treated with susceptible antibiotics and those treated with non-susceptible but clinically effective antibiotics.

**Conclusions** Previous history of UTI, antibiotic treatment, or hospitalization within previous 3 months and underlying disease are risk factors for ESBL UTI in children under 24 months of age. However, relapse rate was < 3% regardless of in vitro susceptibility of the treating antibiotics, as long as the antibiotics were clinically effective. We cautiously propose that we may continue the use of initial empirical antibiotics when a definite clinical response is observed, although further study is necessary to confirm the findings of this study.

**Keywords** Urinary tract infections · Extended-spectrum beta-lactamase-producing bacteria · Child

## Introduction

Urinary tract infection (UTI) is the second most common type of bacterial infection in children, following otitis media [1]; it is often associated with urinary tract abnormalities. In particular, pyelonephritis that occurs in children younger than 2 years old (the period of kidney growth) requires prompt and effective treatment to prevent renal damage [2]. When UTIs are suspected in infants and young children, empirical antibiotic therapy is initiated without waiting for urine culture results. Therefore, physicians must select the appropriate antibiotics considering the antibiotic susceptibility of pathogens common in their area. The most common urinary tract pathogens are *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*). A third-generation cephalosporin is often selected for initial treatment [2, 3] and is administered either orally or parenterally according to the patient's condition. Other antibiotics including aminoglycosides, broad-spectrum

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penicillins such as piperacillin-tazobactam or amoxacillin-clavulanate, carbapenem, and trimethoprim/sulfamethoxazole may also be considered [4, 5].

Extended-spectrum beta-lactamase (ESBL), an enzyme that neutralizes beta-lactam antibiotics, was first isolated from *K. pneumoniae* in 1983 [6], and infections caused by pathogens producing ESBL have increased worldwide [7], including in the pediatric population with UTIs [3, 6–8]. Risk factors for UTIs caused by ESBL-producing pathogens (ESBL (+) UTI) include underlying urinary anomalies such as hydronephrosis, ureteropelvic junction obstruction, ureterovesical junction obstruction, vesicoureteral reflux, neurogenic bladder, and multiple congenital abnormalities, history of hospitalization, past infections, and previous use of antibiotics [8]. ESBL-producing pathogens tend to show resistance to beta-lactam antibiotics, and the initial empirical use of beta-lactam antibiotics is regarded as unlikely to resolve ESBL (+) UTI.

However, laboratory antibiotic susceptibility might differ from clinical responses to antibiotic treatment, and the emergence of antibiotic resistance from the frequent use of broad-spectrum antibiotics is a continuing concern. Several questions thus arise for treating an ESBL-producing pathogen in a UTI case in which the patient has become afebrile and pyuria has disappeared with the initial empirical antibiotic treatment. Should the antibiotic be changed to one reported as sensitive? Alternatively, should the initial empirical antibiotic be continued since a definite clinical response is observed? To answer these questions, the relapse rate in UTIs must be determined following clinically successful treatments of ESBL (+) UTI with initial empirical antibiotics.

Although several reports on the use of antibiotics for ESBL (+) UTI are available [9–12], studies using strict criteria for diagnosing pediatric UTI are scarce, particularly for follow-up for ESBL (+) UTI relapse. Therefore, a retrospective review of our clinical experience was conducted. This study's aim was to identify the characteristics and risk factors of ESBL (+) UTIs and to evaluate their relapse rates.

## Methods

This retrospective study included all patients aged 0 to 24 months who were diagnosed with febrile UTIs caused by gram-negative bacteria in the Seoul National University Children's Hospital from January 2010 to December 2016. This study was approved by the hospital's institutional review boards (IRB C-1703-067-839). Febrile UTI was defined as a triad of symptoms and signs including fever, pyuria, and a single pathogen titer of more than 50,000 colony-forming units per milliliter of urine obtained via urinary catheterization. Patients were excluded if (a) the patient's data about antibiotic use and urine culture were insufficient; (b) the patient's fever was caused by another condition, such as pneumonia, sepsis, or neutropenic fever; or (c) if the patient received intensive care unit treatment, because care for this group of patients was beyond the scope of this study. Relapsing episodes of UTIs were also excluded because the choices of empirical antibiotics were influenced by the outcomes of previous episode(s) of UTIs.

Medical records were reviewed to obtain information on gender, age at onset, time to defervescence, underlying disease, causative pathogen, antibiotic susceptibility of the pathogen, antibiotic used, results of urologic images including kidney ultrasonography, 99m-Tc dimercaptosuccinic acid (DMSA) renal scan, and voiding cystourethrography (VCUG), and relapse of UTIs after completion of treatment. Time to defervescence was defined as the duration from the time of the first antibiotic administration to the time of the beginning of fever resolution. Fever resolution was considered the maintenance of axillary body temperature below 38 °C for 24 h. Underlying diseases were classified into four groups: no underlying disease; urinary tract abnormalities including hydronephrosis vesicoureteral reflux (VUR) and urogenital anomalies; systemic diseases including heart diseases, malignancy, and metabolic diseases; and miscellaneous diseases such as prematurity, epilepsy, and non-urogenital congenital anomalies. Antibiotic susceptibility and ESBL production were determined using the disc diffusion test as recommended in the Clinical and Laboratory Standards Institute guidelines [13–16]. The following antimicrobial agents were tested: ampicillin, amoxicillin/clavulanic acid, piperacillin/tazobactam, cefazolin, cefotaxime, ceftazidime, cefepime, ertapenem, imipenem, meropenem, amikacin, gentamicin, ciprofloxacin, trimethoprim/sulfamethoxazole, nitrofurantoin, fosfomycin, colistin, and tetracycline. UTI relapse was defined as UTI caused by the same pathogen (same name and antibiotic sensitivity) as a previous infection within 2 weeks after the completion of treatment [17].

Enrolled cases were classified into ESBL and non-ESBL groups according to ESBL production by the causative pathogen of the UTI; the cases were also classified into relapse and non-relapse groups. Risk factors for infection by ESBL-producing bacteria and relapse were analyzed via statistical comparisons between the groups. A chi-square test or Fischer's exact test was used for the categorical variables, and a *t* test or Mann-Whitney test was used for the continuous variables. Multivariate analyses were performed using a logistic regression. A $P$ value of less than 0.05 was considered statistically significant. The statistical analyses were performed using IBM SPSS Statistics version 22.0 (IBM cooperation, Armonk, NY).

## Results

After applying the exclusion criteria, 845 consecutive episodes of febrile UTI diagnosed during the study period

were enrolled. Approximately two thirds of the episodes ($n = 583$, 69.0%) occurred in males. Age at UTI diagnosis was less than 12 months in 91.1% ($n = 670$) of cases and less than 6 months in 64.7% ($n = 547$) of cases. *E. coli* was cultured in 753 episodes (89.1%), and *K. pneumoniae* (9.2%) and others (*Pseudomonas aeruginosa* and *Klebsiella oxytoca,* 1.6%) were cultured in the remainder of subjects (Table 1). Follow-up culture was performed to confirm the disappearance of the bacteria in each case.

## ESBL group and non-ESBL group

Of the 845 cases of UTI, 146 (17.3%) episodes were caused by ESBL-producing bacteria. Gender and age did not differ significantly between children in the ESBL and non-ESBL groups. Children with ESBL (+) UTIs were more likely to have a previous history of UTI (22.6% vs. 13.6%, $P < 0.01$). A history of hospitalization (48.6% vs. 18.8%, $P < 0.01$) and the use of antibiotics (39.0% vs. 18.6%, $P < 0.01$) within 3 months were also more common in the ESBL group. The

**Table 1** Characteristics of Patients with UTI

| Factor | Total | ESBL group | | Non-ESBL group | | *P* value |
|---|---|---|---|---|---|---|
| | *N* (%) | *N* | % | *N* | % | |
| Number | 845 | 146 | 17.3 | 699 | 82.7 | |
| Gender (male) | 583 (69.2) | 92 | 63 | 491 | 70 | 0.09 |
| Age | | | | | | |
| Median (month) | | 7.2 (0–24) | | 6.2 (0–24) | | 0.05 |
| Group | | | | | | 0.14 |
| ≤ 3 mo | 320 (37.9) | 51 | 34.9 | 269 | 38.5 | |
| 4–12 mo | 450 (53.2) | 76 | 52.1 | 374 | 53.5 | |
| 13–24 mo | 75 (8.9) | 19 | 13 | 56 | 8 | |
| Pathogen | | | | | | < 0.01 |
| *E. coli* | 753 (79.1) | 117 | 80.1 | 636 | 91 | |
| *K. pneumoniae* | 78 (9.2) | 27 | 18.5 | 51 | 7.3 | |
| Others | 14 (1.7) | 2 | 1.41 | 12 | 1.7 | |
| Pyuria (/HPF) | | | | | | 0.13 |
| > 100 | 403 (47.7) | 63 | 43.2 | 340 | 48.6 | |
| 50–99 | 114 (13.5) | 19 | 13 | 95 | 13.6 | |
| 20–49 | 150 (17.8) | 27 | 18.5 | 123 | 17.6 | |
| < 20 | 178 (21) | 37 | 25.3 | 141 | 20.2 | |
| Previous history | | | | | | |
| UTI | 128 (15.1) | 33 | 22.6 | 95 | 13.6 | < 0.01 |
| Hospitalization | 202 (23.9) | 71 | 48.6 | 131 | 18.8 | < 0.01 |
| Antibiotics treatment | 187 (22.1) | 57 | 39 | 130 | 18.6 | < 0.01 |
| Underlying diseases | | | | | | |
| None | 556 (65.8) | 65 | 44.5 | 491 | 70.2 | < 0.01 |
| Urinary tract abnormalities[a] | 163 (19.3) | 43 | 29.5 | 120 | 17.2 | < 0.01 |
| Systemic diseases[b] | 58 (6.9) | 15 | 10.3 | 43 | 6.2 | < 0.01 |
| Miscellaneous | 68 (8) | 23 | 15.8 | 45 | 6.4 | < 0.01 |
| Imaging studies | | | | | | |
| Cortical defect on DMSA (acute phase)[c] | 231/496 (46.6) | 39/83 | 47 | 192/413 | 46.5 | 0.98 |
| Abnormal findings on kidney USG[d] | 179/822 (21.8) | 33/140 | 23.6 | 146/682 | 21.4 | 0.57 |
| VUR on VCUG[e] | 131/328 (39.9) | 26/52 | 50 | 105/276 | 38 | 0.12 |
| Time to defervescence | 2.48 | 2.39 (1–8) days | | 2.52 (1–20) days | | 0.34 |
| Initial empirical antibiotics | | | | | | 0.07 |
| Cephalosporin | 761 (90) | 106 | 72.6 | 655 | 93.7 | |
| Broad-spectrum penicillins | 55 (6.5) | 20 | 13.7 | 35 | 5 | |
| Carbapenem | 22 (2.6) | 17 | 11.6 | 5 | 0.7 | |
| Aminoglycosides | 6 (0.7) | 2 | 1.4 | 4 | 0.6 | |
| Sulfamethoxazole-trimethoprim | 1 (0.1) | 1 | 0.7 | 0 | 0 | |
| Intravenous antibiotics | 732 (86.6) | 127 | 87.6 | 605 | 86.4 | 0.79 |
| Empirical antibiotics | 146 (17.2) | 109 | 74.7 | 37 | 5.3 | < 0.01 |
| Non-susceptibility switching to susceptible antibiotics | 60 (41) | 49 | 33.6 | 11 | 1.6 | < 0.01 |
| Relapse | 12 (1.4) | 4 | 2.7 | 8 | 1.1 | 0.13 |
| Cortical defect on DMSA, follow-up | 17/21 (81) | 9/10 | 90 | 8/11 | 72.7 | 0.59 |

*DMSA* dimercaptosuccinic acid renal scan, *USG* ultrasonography, *VUR* vesicourinary reflux, *VCUG* voiding cystourethrogram

[a] Urinary tract abnormalities included hydronephrosis, vesicourethral reflux, and other urinary tract abnormalities

[b] Systemic diseases included heart disease, malignancy, and metabolic disease

[c] DMSA scans were performed in 496 cases (83 in the ESBL group and 413 in the non-ESBL group)

[d] Kidney sonography was performed in 822 cases (140 in the ESBL group and 682 in the non-ESBL group). Abnormalities on USG included hydronephrosis and anatomical anomalies

[e] VCUG was performed in 328 cases (52 in the ESBL group and 276 in the non-ESBL group)

proportion of subjects with "no underlying disease" was significantly higher in the non-ESBL group (70.2% vs. 44.5%, $P < 0.01$), whereas other underlying diseases were more common in the ESBL group (Table 1). None of the included patients had undergone organ transplantation, urinary catheterization, or had kidney stones. Although *E. coli* was the most common pathogen followed by *K. pneumonia* in both groups, *K. pneumoniae* was more common in the ESBL group ($P < 0.01$). The degree of pyuria, abnormal findings on imaging (ultrasonography, DMSA, and VCUG), and time to defervescence were similar in both groups (Table 1). A multivariate analysis was used to identify risk factors for UTI from ESBL (+) pathogens with factors including the history of UTI, the history of antibiotic treatment or hospitalization in the previous 3 months, and underlying disease. A history of antibiotic treatment in the previous 3 months (HR 2.9; 95% CI 1.9–4.5, $P < 0.01$) and urinary tract abnormalities (HR 1.6; 95% CI 1.0–2.7, $P = 0.04$) were independent risk factors for developing an ESBL (+) UTI.

Relapse occurred in four cases in the ESBL group (2.7%) and in eight cases (1.1%) in the non-ESBL group. This difference was not statistically significant.

### Antibiotic therapy

As shown in Table 1, third-generation cephalosporins were most commonly administered as the initial empirical antibiotic in both groups (90%), followed by piperacillin-tazobactam, a broad-spectrum penicillin (6.5%). The susceptibility rates were 25.3% in the ESBL group and 94.7% in the non-ESBL group; in other words, 109 ESBL (+) UTI cases and 37 non-ESBL UTI cases received non-susceptible initial therapy. The antibiotics were changed to a presumably more effective agent in 33.6% ($n = 49$) of the ESBL group and 1.6% ($n = 11$) of ESBL group cases ($P < 0.01$). Among the patients with ESBL (+) UTI who received non-susceptible therapy, approximately 11% ($n = 12$) were switched to a different antibiotic due to persistent fever (fever > 48 h after starting initial antibiotics) before the susceptibility results were reported. Patients with persistent fever did not differ from the rest of the patients in their clinical characteristics (including the proportion of ESBL (+) UTI) except that a cortical defect on the acute-phase DMSA was found more commonly (56.4% ($n = 146$) vs 35.9% ($n = 85$), $P < 0.01$).

In the ESBL (+) UTI group, the relapse rate did not differ statistically between the patients who were treated with susceptible antibiotics (2.3%) and those who were treated with non-susceptible but clinically effective antibiotics (3.3%). Scar formation rates on the follow-up DMSA were also not statistically different ($P = 0.74$) between patients who were treated with susceptible antibiotics (14 of 17 tested, 82.4%) and those who were treated with non-susceptible antibiotics (3/4 tested, 75%).

### UTI relapse

A relapse of UTI by the same pathogen within 2 weeks after treatment occurred in a total of 12 patients (Table 2). When compared to patients without relapse, a history of UTI, hospitalization, and the previous use of antibiotics were more common in the relapse group, as was VUR, urinary abnormalities, and cortical defect on the acute-phase DMSA. Conversely, there were no statistically significant differences in time to defervescence, ESBL positivity, or antibiotic non-susceptibility between the relapse and non-relapse groups (Table 3). Notably, antibiotic non-susceptibility was more common in the relapse group. In the multivariate analysis, a history of hospitalization (HR 4.0; 95% CI 1.2–12.9, $P = 0.02$) and cortical defect on acute-phase DMSA (HR 8.6; 95% CI 1.1–70.3, $P = 0.04$) were independent risk factors for UTI relapse.

## Discussion

With the increase of ESBL-producing microorganisms, ESBL (+) UTI has become increasingly common worldwide [4–8, 16]. In this study, approximately 17% of UTIs in children under 24 months old were caused by an ESBL (+) pathogen, a finding consistent with reports of ESBL (+) UTI accounting for 10–40% of all UTIs in children [18, 19]. Although many studies have examined ESBL (+) UTIs in pediatric populations [5, 8, 11], studies that focus on the relationship between antibiotic treatment and relapse in young children (age < 2) are difficult to find.

In this retrospective study, independent risk factors for young children for developing ESBL (+) UTI include the use of antibiotics in the previous 3 months and urinary tract abnormalities. This finding is consistent with previous studies [8, 11, 12]. Although younger age had been reported as a risk factor for ESBL (+) UTI previously [19], age did not differ between the ESBL and non-ESBL groups in this study, in which approximately 80% of UTI patients were less than 1 year old. Interestingly, VUR was not more common among subjects in the ESBL group, although urinary abnormalities were a risk factor for ESBL (+) UTI infection. Since only some patients were examined with the VCUG study results ($n = 328$, 38.7%), the presence of VUR might have been missed in some fraction of patients. Still, the rates of abnormal findings in imaging studies using ultrasonography and DMSA also did not differ between the groups, indicating that ESBL (+) UTI was not more damaging than non-ESBL UTI. Similarly, relapse after ESBL (+) UTI occurred in less than 3% of cases, which was not statistically different from relapse after non-ESBL UTI (1.1%). However, the number of relapse cases caused by the same pathogen within 2 weeks of treatment completion was too small to draw any definitive

**Table 2** Description of the first episodes of UTI in patients who experienced relapse

| Case | | Age/gender | Underlying disease | Previous history of UTI | History of hospitalization | History of ABx | USG | DMSA | VCUG | Pyuria | Fever duration (day) | Empirical antibiotics (susceptible or not susceptible) | Switching of ABx | LOS (day) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ESBL (+)** | 1 | M/5 months | Tetralogy of Fallot | N | Y | N | Normal | No cortical defect. | Not done | ≥ 100 | 2 | Cefotaxime (R) | Nr | 13 |
| | 2 | F/7 months | UPJ obstruction | Y | Y | Y | UPJ obstruction, Lt. | Cortical defect Lt. | No VUR | ≥ 100 | 2 | Piperacillin-tazobactam (S) | Yr | 5 |
| | 3 | M/12 months | HN with UPJ obstruction | Y | Y | Y | UPJ obstruction, Lt. | No cortical defect | No VUR | ≥ 100 | 4 | Cefotaxime (R) | Ys | 11 |
| | 4 | F/12 months | None | N | N | N | Normal | No cortical defect | No VUR | ≥ 100 | 3 | Cefotaxime (R) | Ys | 8 |
| **ESBL (−)** | 1 | F/12 months | VUR with ureteral duplication | Y | Y | Y | UPJ obstruction, Lt. | Not done | VUR II/I-V | 30–49 | 1 | Cefotaxime (S) | N | 4 |
| | 2 | F/4 months | Atrial tachycardia | N | N | N | Normal | Not done | No VUR | 50–99 | 2 | Piperacillin-tazobactam (R) | N | 17[a] |
| | 3 | M/12 months | Infantile fibrosarcoma, Rt. kidney | Y | Y | Y | Solid and cystic mass with dense calcifications, Rt. | Cortical defect Rt. | Not done | 50–99 | 1 | Cefotaxime (S) | N | 3 |
| | 4 | M/8 months | None | N | N | N | Normal | Cortical defect | No VUR | > 100 | 3 | Cefotaxime (S) | N | 8 |
| | 5 | F/2 months | Hydroureteronephrosis HIE, prematurity | N | Y | Y | Double ureter, HN Lt. | Multiple cortical defect Lt. | Not done | > 100 | 2 | Cefotaxime (S) | N | 10 |
| | 6 | M/13 months | Hydroureteronephrosis | N | N | Y | HN, Rt. | Not done | No VUR | > 100 | 5 | Cefotaxime (S) | N | 6 |
| | 7 | F/10 months | Vesicoureteral reflux | N | N | Y | Normal | Cortical defect, Rt. | VUR Rt. III | 20–29 | 2 | Cefotaxime (S) | N | 4 |
| | 8 | M/2 months | Vesicoureteral reflux prematurity | N | Y | N | HN | Not done | VUR both | 10–19 | 4 | Cefotaxime (S) | N | 12 |

*UTI* urinary tract infection, *ABx* antibiotic, *USG* ultrasonography, *DMSA* dimercaptosuccinic acid renal scan, *VCUG* voiding cystourethrogram, *UPJ* ureteropelvic junction, *HN* hydronephrosis, *VUR* vesicoureteral reflux ureteral duplication, *UPJ* ureteropelvic junction obstruction, *HIE* hypoxic ischemic encephalopathy, *LOS* length of stay in hospitalization, *Y* yes, *N* no

[a] This patient had a long hospital stay because of arrhythmia

**Table 3** Comparison of patients with relapse and those without documented relapse

| Factor | Total | Relapse group | | Non-relapse group | | *P* value |
|---|---|---|---|---|---|---|
| | *N* (%) | *N* | % | *N* | % | |
| Number | 845 | 12 | 1.4 | 833 | 98.6 | |
| ESBL (+) UTI | 146 (17.2) | 4 | 33.3 | 142 | 17 | 0.14 |
| Gender (male) | 583 (69.2) | 7 | | 576 | | 0.53 |
| Age | | | | | | |
| Median (months) | | 6.0 (2–13) | | 6.4 (0–24) | | 0.81 |
| Pathogen | | | | | | 0.25 |
| *E. coli* | 753 (79.1) | 9 | 75 | 744 | 89.3 | |
| *K. pneumoniae* | 78 (9.2) | 3 | 3.8 | 75 | 9 | |
| Others | 14 (1.7) | 0 | 0 | 14 | 1.7 | |
| Pyuria, > 100/HPF | 403 (47.7) | 7 | 58.3 | 396 | 47.5 | 0.29 |
| Previous history | | | | | | |
| UTI | 128 (15.1) | 5 | 41.7 | 123 | 14.8 | 0.02 |
| Hospitalization | 202 (23.9) | 7 | 58.3 | 195 | 23.4 | 0.03 |
| Antibiotics treatment | 187 (22.1) | 8 | 66.7 | 179 | 21.5 | < 0.01 |
| Underlying diseases | | | | | | |
| Urinary tract abnormalities | 163 (19.3) | 6 | 50 | 157 | 18.8 | 0.01 |
| Imaging studies | | | | | | |
| Cortical defect on DMSA (acute phase)[a] | 231/496 (46.6) | 8/9 | 88.9 | 223/487 | 45.8 | 0.01 |
| Abnormal findings on kidney USG[b] | 179/822 (21.8) | 3/12 | 25 | 176/810 | 21.7 | 0.62 |
| VUR on VCUG[c] | 131/328 (39.9) | 4/9 | 44.4 | 127/319 | 39.8 | 0.01 |
| Time to defervescence | 2.48 | 2.83 (1~8) days | | 2.49 (1~20) days | | 0.40 |
| Parenteral empirical ABx | 732 (86.6) | 12 | 100 | 720 | 86.4 | 0.39 |
| Initial empirical antibiotics | | | | | | 0.16 |
| Cephalosporin | 761 (90) | 10 | 96.4 | 751 | 98.7 | |
| Broad-spectrum penicillins | 55 (6.5) | 2 | 3.6 | 53 | 1.3 | |
| Carbapenem | 22 (2.6) | 0 | 0 | 22 | 2.6 | |
| Aminoglycosides | 6 (0.7) | 0 | 0 | 6 | 5.9 | |
| Sulfamethoxazole-trimethoprim | 1 (0.1) | 0 | 0 | 1 | 0.1 | |
| Final empirical antibiotics | | | | | | 0.3 |
| Cephalosporin | 717 (84.9) | 9 | 66.7 | 708 | 85 | |
| Broad-spectrum penicillins | 51 (6.0) | 2 | 16.7 | 49 | 5.9 | |
| Carbapenem | 21 (2.5) | 1 | 8.3 | 20 | 2.4 | |
| Aminoglycosides | 53 (6.3) | 0 | 0 | 53 | 6.4 | |
| Sulfamethoxazole-trimethoprim | 3 (0.4) | 0 | 0 | 3 | 1.4 | |
| Empirical antibiotics | 146 (17.2) | 4 | 2.7 | 142 | 97.3 | 0.14 |
| Non-susceptibility switching to susceptible antibiotics | 60 (41) | 2 | 16.7 | 58 | 7 | 0.2 |
| Cortical defect on DMSA, follow-up | 21 | 2/2 | 100 | 15/19 | 78.9 | 1.0 |

*DMSA* dimercaptosuccinic acid renal scan, *ABx* antibiotics, *UTI* urinary tract infection

[a] DMSA scans were performed in 496 cases (9 in the relapse group and 487 in the non-relapse group)

[b] Kidney sonography was performed in 822 cases (12 in the relapse group and 810 in the non-relapse group)

[c] VCUG was performed in 328 cases (9 in the relapse group and 276 in the non-relapse group)

conclusions. A larger, prospective study would be required to verify this finding.

In our community, third-generation cephalosporins (cefotaxime), amoxicillin-clavulanate, or ampicillin-sulbactam is commonly used as empirical antibiotics for UTIs [20]. We found that the ESBL-producing pathogens in this study were all resistant to cefotaxime and 40% were resistant to amoxicillin/clavulanic acid (data not shown). Other studies have reported resistance rates of up to 57% for amoxicillin and 100% for cefotaxime [21–23]. Considering antibiotic susceptibility reports, the initial empirical antibiotics were not appropriate in approximately 17% of total UTI episodes, corresponding to 74.7% ($n = 109$) and 5.3% ($n = 37$) of cases in the ESBL and non-ESBL groups, respectively. Although 11% ($n = 12$) of ESBL (+) UTI cases that were treated with non-susceptible antibiotics did not show clinical improvement with initial treatment and their antibiotics were changed before obtaining an antibiotics susceptibility test, 41% ($n = 60$) of ESBL (+) UTIs under non-susceptible antibiotics continued to be treated with the initial empirical antibiotics, which induced clinically responsive results, regardless of the laboratory susceptibility results. Furthermore, the relapse rate of ESBL (+) UTI did not differ between patients who were treated with susceptible antibiotics and patients who were treated with non-susceptible but clinically effective antibiotics (Fig. 1).

The discrepancy between the antibiotic susceptibility test results and clinical responses in UTI treatment might be due to the high concentration of antibiotics in the renal tubules and to the clearance of pathogens from the urinary tract by urinary flow [24, 25]. Previous studies have also shown that ESBL-producing organisms can be successfully treated with cephalosporins, regardless of in vitro susceptibility testing results [26–28]. The present study population was mainly treated with third-generation cephalosporins or piperacillin-

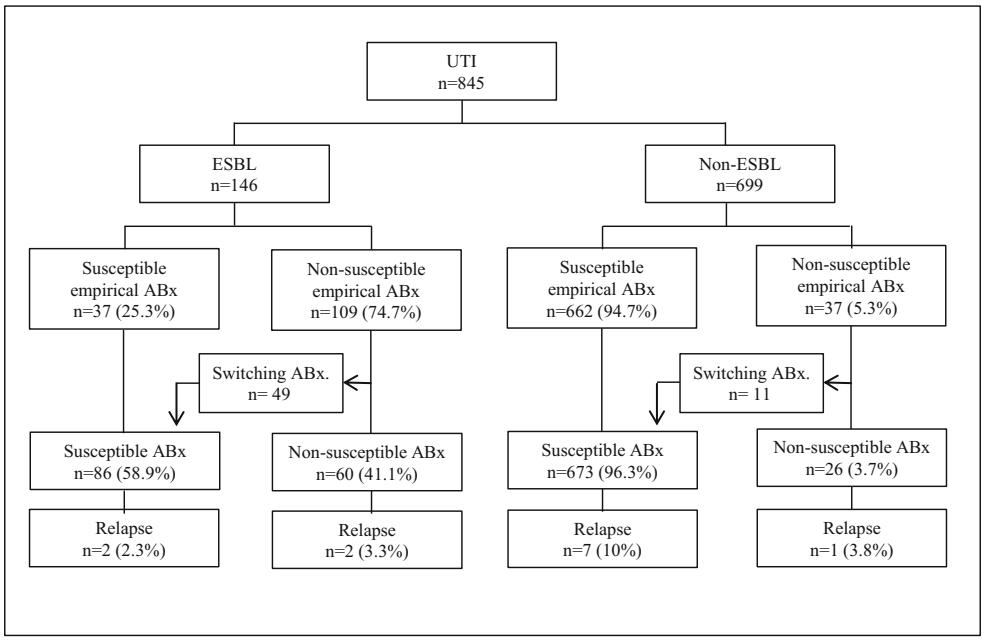


**Fig. 1** Relapse UTI according to susceptibility of antibiotics. UTI urinary tract infection, Abx antibiotics

UTI: Urinary tract infection, Abx: Antibiotics

tazobactam and, regardless of the in vitro susceptibility test results, the relapse rate was less than 3%. These results again suggest that the continuation of initial empirical antibiotics is appropriate as long as a definite clinical response is obtained.

Nonetheless, choosing an initial empirical antibiotic requires careful consideration of risk factors for ESBL (+) UTI since a significant portion of ESBL (+) UTI cases did not show a clinical response to empirical antibiotics. Moreover, suppressing the emergence of additional ESBL-producing pathogens is critical; Lee et al. suggests that using piperacillin-tazobactam instead of extended-spectrum cephalosporins would reduce the prevalence of ESBL-producing strains of *K. pneumoniae* and *E. coli* [29]. Several studies have suggested that piperacillin-tazobactam therapy was not inferior to carbapenems in patients with ESBL (+) UTIs [30, 31]. Therefore, we suggest using piperacillin-tazobactam or other antibiotics targeting ESBL-producing organisms as the initial empirical antibiotics for young children with UTI if the patients have risk factors of ESBL (+) UTI, such as a history of UTI, use of antibiotics, previous hospitalization, and underlying urinary abnormalities. Furthermore, patients with persistent fever (> 48 h) had a higher rate of cortical defects on acute-phase DMSA than the other patients; therefore, if patients do not show clinical improvement within 48 h, a change in their empirical antibiotics should be considered. Further, prospective studies are necessary regarding appropriate empirical antibiotics for UTIs in young children.

Although the relapse rate was low in this study, cortical defects on DMSA were more common in relapsing patients and were found to be an independent risk factor for UTI relapse according to the multivariate analysis, along with a previous history of hospitalization. Conversely, VUR lost its significance as a risk factor of UTI relapse in the multivariate analysis. Several studies have reported that VUR was associated with recurrent UTI [32, 33]; however, these studies did not specifically analyze relapse cases by the same pathogens. Therefore, it does not seem appropriate to compare these previous studies to our study assessing UTI relapse. Not all patients in our study underwent DMSA or VCUG assessment, and there were not enough relapse cases to perform a robust statistical analysis; therefore, it is beyond the scope our study to discuss whether the findings of imaging studies were significant risk factors of UTI relapse. Nonetheless, ESBL positivity itself was not a risk factor of relapse, nor was non-susceptibility of the initial empirical antibiotics, even in the univariate analysis. Therefore, we may conclude that our data does not support the notion that we must change antibiotics for ESBL (+) UTI according to the in vitro susceptibility of antibiotics as long as a definite clinical response is observed with the initial empirical antibiotics.

There are several limitations of this study. First, this is a retrospective observational study of a single center. Therefore, it is possible that the patients who relapsed may have been treated at other hospitals, although all the patients were instructed to return to our center if they experienced a UTI relapse. In addition, there were too few relapse cases to robustly analyze the risk factors. Moreover, the choice of initial empirical antibiotics was not uniform, which might have influenced the clinical outcomes. In addition, DMSA or VCUG results were not available for all patients, which might have affected the findings. Too few patients received follow-up DMSA evaluations to draw any meaningful conclusion.

Finally, in recent years, AmpC β-lactamase-producing bacteria has emerged worldwide to cause resistance to penicillins and most cephalosporins, and ESBL and AmpC β-lactamase co-producing bacteria are increasing [34, 35]. Therefore, Amp C resistance might have influenced this study, but we do not have information on AmpC β-lactamase in this study. Nonetheless, a large sample size of young children and a strict definition of UTI using urine collection by catheterization are strengths of the study.

## Conclusions

In this study, 17% of UTIs in children younger than 24 months were caused by ESBL-producing pathogens. Previous history of UTI, the use of antibiotics, history of hospitalization, and urinary tract abnormalities were independent risk factors for the development of ESBL (+) UTIs. A total of 8% of ESBL (+) UTI cases did not respond to initial empirical antibiotics, necessitating the change of antibiotics. However, the relapse rate was less than 3% regardless of the in vitro susceptibility of the treating antibiotics, as long as they were clinically effective. We cautiously propose that we may continue use of the initial empirical antibiotics when a definite clinical response is observed, although further study is necessary to confirm the findings of this study.

**Compliance with ethical standards** This study was approved by the hospital's institutional review boards (IRB C-1703-067-839).

**Conflict of interest** The authors declare that they have no conflict of interest.

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