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ORIGINAL ARTICLE

# Rise of community-onset urinary tract infection caused by extended-spectrum β-lactamase-producing *Escherichia coli* in children

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*Background:* Urinary tract infection (UTI) caused by resistant bacteria is becoming more prevalent. Few studies are available regarding community-onset UTIs caused by extended-spectrum β-lactamase (ESBL)-producing bacteria in children.
*Materials and methods:* During a 5-year period, hospitalized children with community-onset UTI caused by ESBL-producing *Escherichia coli* (case) and those with non-ESBL-producing *E. coli* (control) were identified. Patients with long-term care facility stay within the preceding month and those with urine cultures obtained >72 hours after admission were excluded. Clinical features and risk factors associated with the occurrence of ESBL-producing *E. coli* UTI were reviewed.
*Results:* The prevalence of UTI due to ESBL-producing *E. coli* increased slightly from 0.59% in 2002 to 0.96% in 2006. A total of 104 cases and 208 controls were included for comparison. The ciprofloxacin resistance of the ESBL-producing *E. coli* increased significantly in this period ($p = 0.006$). Pre-existing neurological diseases ($p < 0.001$), use of antibiotics in the past

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3 months ($p < 0.001$), and recent hospitalization within 1 month ($p < 0.001$) were found to be potential risk factors. Moreover, previous exposure to third-generation cephalosporins ($p < 0.001$) and aminoglycosides ($p < 0.001$) was associated with the selection of ESBL-producing *E. coli*. Children with ESBL-producing *E. coli* UTIs had a longer hospital stay ($p = 0.031$) than those without.

*Conclusions:* ESBL-producing *E. coli* gradually became coresistant to other broad-spectrum antibiotics, notably ciprofloxacin. UTIs caused by such resistant organisms led to a longer hospital stay and more antibiotic use. Reinforcement of infection control measures, especially hand washing in childcare settings and antibiotic stewardship, is critical to reduce the spread of ESBL-producing *E. coli*.



## Introduction

Extended-spectrum β-lactamases (ESBLs) are enzymes that mediate resistance to the newer β-lactam antibiotics, including extended-spectrum cephalosporins and monobactams.[1–3] ESBL-producing organisms were first reported in the early 1980s, shortly after the introduction of the oxyimino β-lactam agents, and have now become widespread all over the world.[4] These enzymes are produced by the members of the Enterobacteriaceae family, mainly *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*, which are the primary infectious agents that cause urinary tract infection (UTI) in children.[5]

Isolation of ESBL-producing organisms typically occurred in hospital settings and other healthcare facilities; however, such organisms have begun to disseminate in the community, and the incidence of community-onset UTIs due to ESBL-producing strains has increased worldwide.[6–10] Furthermore, the ESBL-producing strains are becoming increasingly resistant to other non-β-lactam antimicrobials, which poses significant therapeutic challenges.[7]

In order to understand the changing epidemiology and solve the therapeutic difficulties, several studies have been conducted to analyze the risk factors of infections associated with ESBL-producing strains in adults.[11,12] However, limited data are available regarding community-onset infections caused by ESBL-producing strains in children. The aim of this study was to determine the risk factors of community-onset UTIs caused by ESBL-producing *E. coli* in children.

## Materials and methods

### Study design and participants

A 5-year, retrospective, case–control study was designed to characterize the clinical manifestations, laboratory findings, antimicrobial susceptibilities, and risk factors of UTI due to ESBL-producing *E. coli* in children. The case group consisted of patients with culture-confirmed UTI due to ESBL-producing *E. coli* and the controls were those with UTI due to non-ESBL-producing *E. coli*. Cases and controls were matched by age and sex in a 1:2 ratio.

Hospitalized patients aged <15 years with any urine culture positive for *E. coli* were identified from the records of the Clinical Microbiology Laboratory of Chang Gung Children's Hospital during a 5-year period. Patients with UTI due to *E. coli* were selected for this study. Long-term care facility stay within the preceding month and isolates recovered more than 72 hours after hospitalization were the criteria of exclusion. The definitions of UTI were dependent on different urine collection methods.[13] If midstream urine or a urine bag was used for collection of midstream urine, UTI was defined by a positive urine culture ($\geq 10^5$ cfu/mL) or a positive urine culture ($10^4$–$10^5$ cfu/mL) with pyuria (≥10 leukocytes per high-power field). If catheterization was used for urine collection, UTI was defined by a positive urine culture ($\geq 10^3$ cfu/mL).

All decisions regarding the antibiotic therapy were made by the attending physicians who took care of the patients. The initial antibiotic regimen was administered after blood and urine samples had been taken for culture. The definitive antimicrobial therapy was given after the culture results were obtained. The antibiotic regimen was considered appropriate if it contained at least one drug that was active *in vitro* against the subsequent *E. coli* isolate. An inappropriate initial antimicrobial therapy comprised the use of a regimen without any appropriate drug to which the causative organism was sensitive. Early treatment failure or worsening clinical conditions meant that fever persisted for more than 3 days despite treating with antibiotics, and antibiotics would be changed within 3–5 days to improve the above clinical conditions.

ESBL determination was performed phenotypically with ceftazidime/ceftazidime clavulanate and cefotaxime/cefotaxime clavulanate disks, as recommended by the Clinical and Laboratory Standards Institute (CLSI).[14] Antimicrobial susceptibility testing was performed using the disk diffusion method, according to the CLSI standards.[14]

### Statistical analysis

Data were analyzed using SPSS, version 12.0 (SPSS Inc., Chicago, IL, USA). Student *t* test was used to analyze numerical data. If the data were not normally distributed, the Mann–Whitney *U* test was used to compare nonparametric data. A chi-square test or Fisher's exact test was used to analyze categorical data. A *p* value of <0.05 was considered statistically significant.

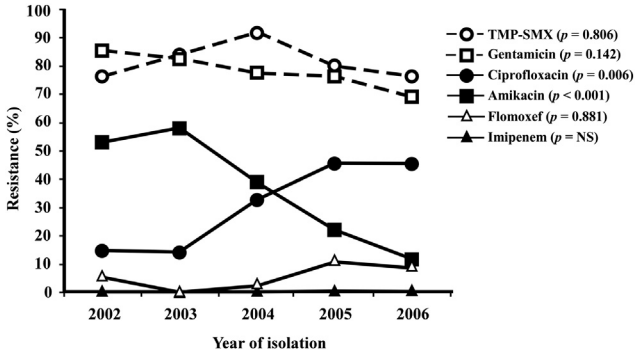


**Figure 1.** Longitudinal trends of antimicrobial resistance among ESBL-producing *Escherichia coli* isolates collected from urine cultures, 2002—2006. ESBL = extended-spectrum β-lactamase; NS = not significant; TMP-SMX = trimethoprim—sulfamethoxazole.

## Results

### Antimicrobial susceptibility of ESBL-producing *E. coli* causing UTI

During the study period, a total of 6467 culture samples were positive for *E. coli*, according to the records of the Clinical Microbiology Laboratory of Chang Gung Children's Hospital. In all, 312 patients with UTI due to *E. coli* were included in this study.

ESBL production was detected in 104 of the 312 (33.3%) *E. coli* isolates obtained from urine cultures. Each of the 312 *E. coli* strains was isolated from an individual patient. The proportions of ESBL-producing *E. coli* causing UTI were 0.59% in 2002, 0.81% in 2003, 0.85% in 2004, 0.90% in 2005, and 0.96% in 2006. Fig. 1 shows the longitudinal trends of resistance to different kinds of antimicrobial agents among the ESBL-producing *E. coli* obtained from urine cultures. Of these isolates, the antimicrobial resistance rate to aminoglycosides such as gentamicin or amikacin ($p < 0.001$) showed a decrease during the study period; however, rates of resistance to ciprofloxacin ($p = 0.006$) and flomoxef have been increasing over the years.

### Risk factors for the occurrence of ESBL-producing *E. coli* causing UTI

One hundred and four children with UTI due to ESBL-producing *E. coli* and 208 matched controls with UTI due to non-ESBL-producing *E. coli* were included in the study. Three main risk factors evaluated included underlying diseases, pre-existing medical conditions, and the use of antibiotics in the past 3 months. The underlying diseases were similar between the case patients and the controls, except that there were more cases with neurological diseases (21.2% vs. 5.3%, $p < 0.001$), failure to thrive (11.5% vs. 4.8%, $p = 0.032$), developmental delay (13.5% vs. 3.8%, $p = 0.032$), and implanted device (18.3% vs. 14.9%, $p < 0.001$) than the controls (Table 1). Furthermore,

**Table 1** Characteristics of UTI caused by ESBL-producing *Escherichia coli*

| Variables | ESBL-positive *E. coli* ($n = 104$) | ESBL-negative *E. coli* ($n = 208$) | *p* |
|---|---|---|---|
| *Underlying diseases* | | | |
| Percentage of underlying disease | 1.87 | 0.75 | <0.001 |
| Neurological disease | 22 (21.2) | 11 (5.3) | <0.001 |
| Epilepsy | 12 (11.5) | 4 (1.9) | 0.005 |
| Cerebral palsy | 22 (21.2) | 2 (1.0) | 0.012 |
| Failure to thrive | 12 (11.5) | 10 (4.8) | 0.032 |
| Developmental delay | 14 (13.5) | 8 (3.8) | 0.032 |
| Hemato-oncologic disease | 7 (6.7) | 2 (1.0) | 0.797 |
| Nephrologic disease | 20 (19.2) | 31 (14.9) | 0.228 |
| Vesicoureteral reflux | 6 (5.8) | 12 (5.8) | 0.548 |
| Neurogenic bladder | 12 (11.5) | 6 (2.9) | 0.058 |
| Endocrine and genetic disease | 7 (6.7) | 31 (14.9) | 0.193 |
| Implanted device | 19 (18.3) | 31 (14.9) | <0.001 |
| Foley | 7 (6.7) | 5 (2.4) | 0.118 |
| Nasogastric tube | 12 (11.5) | 4 (1.9) | <0.001 |
| *Previous medical conditions* | | | |
| Recurrent urinary tract infection | 29 (27.9) | 42 (20.2) | 0.018 |
| Frequent urinary tract infection (>3 times/y) | 14 (13.5) | 15 (7.2) | 0.113 |
| Use of antibiotics within previous 3 mo | 49 (47.1) | 37 (17.8) | <0.001 |
| Use of immunosuppressive agents within 1 mo | 2 (1.9) | 1 (0.5) | 0.538 |
| Recent operation within 1 mo | 6 (5.8) | 6 (2.9) | 0.349 |
| Recent hospitalization within 1 mo | 52 (50.0) | 39 (18.8) | <0.001 |
| Length of stay (d) | 18.2 | 5.9 | 0.003 |
| ICU care within previous 1 mo | 14 (13.5) | 4 (1.9) | <0.001 |

Data are presented as *n* (%) unless otherwise indicated. ESBL = extended-spectrum β-lactamase; ICU = intensive care unit; UTI = urinary tract infection.

**Table 2** Comparison of antimicrobial agents used in the past 3 months between children with UTIs due to ESBL-producing and non-ESBL-producing *Escherichia coli*

| Antibiotics class | ESBL-positive *E. coli* ($n = 104$) | ESBL-negative *E. coli* ($n = 208$) | $p$ |
|---|---|---|---|
| Any antibiotics | 49 (47.1) | 37 (17.8) | <0.001 |
| First-generation cephalosporins | 17 (16.3) | 16 (7.7) | 0.032 |
| Second-generation cephalosporins | 7 (6.7) | 10 (4.8) | 0.659 |
| Third-generation cephalosporins | 10 (9.6) | 2 (1.0) | <0.001 |
| Ceftazidime | 6 (5.8) | 0 (0.0) | 0.002 |
| Cefotaxime | 5 (4.8) | 0 (0.0) | 0.007 |
| Ceftriaxone | 3 (2.9) | 2 (1.0) | 0.425 |
| Fourth-generation cephalosporins | 1 (1.0) | 2 (1.0) | 0.538 |
| Penicillin-based antibiotics | 30 (28.8) | 23 (11.1) | <0.001 |
| Ampicillin | 24 (23.1) | 13 (6.3) | <0.001 |
| Amoxicillin | 6 (5.8) | 10 (4.8) | 0.928 |
| Quinolones | 1 (1.0) | 2 (1.0) | 0.538 |
| Trimethoprim—sulfamethoxazole | 3 (2.9) | 6 (2.9) | 0.720 |
| Aminoglycoside | 30 (28.8) | 14 (6.7) | <0.001 |
| Vancomycin | 9 (8.7) | 2 (1.0) | 0.002 |
| Macrolide | 3 (2.9) | 4 (1.9) | 0.252 |
| Carbapenem | 2 (1.9) | 0 (0.0) | 0.201 |

Data are presented as *n* (%) unless otherwise indicated. ESBL = extended-spectrum β-lactamase; UTI = urinary tract infection.

recurrent UTI (27.9% vs. 20.2%, $p = 0.018$), use of antibiotics in the past 3 months (47.1% vs. 17.8%, $p < 0.001$), recent hospitalization within 1 month (50% vs. 18.8%, $p < 0.001$), and care in intensive care units in the past 1 month (13.5% vs. 1.9%, $p < 0.001$) were more frequently found in the case patients than in the controls (Table 1). Table 2 shows a comparison of the antimicrobial agents used in the past 3 months. The use of first-generation (16.3% vs. 7.7%, $p = 0.032$) or third-generation (9.6% vs. 1.0%, $p < 0.001$) cephalosporins, aminoglycosides (28.8% vs. 6.7%, $p < 0.001$), and vancomycin (8.7% vs. 1.0%, $p < 0.002$) was found significantly more frequently in patients with UTI due to ESBL-producing *E. coli*.

## Clinical manifestations and outcomes

An analysis of the clinical features of UTI due to ESBL-producing *E. coli* is shown in Table 3. Longer febrile duration prior to admission (5.16 vs. 2.76 days, $p < 0.001$) and abdominal pain (6.7% vs. 4.3%, $p = 0.032$) were more frequently found in the case group. There was no significant

**Table 3** Analysis of clinical features of UTI due to ESBL-producing *Escherichia coli*

| Variables | ESBL-positive *E. coli* ($n = 104$) | ESBL-negative *E. coli* ($n = 208$) | $p$ |
|---|---|---|---|
| *Symptoms and signs* | | | |
| Fever (>38.3°C) | 72 (69.2) | 161 (77.4) | 0.154 |
| Febrile duration prior to admission (d) | 5.16 | 2.76 | <0.001 |
| Dysuria | 12 (11.5) | 28 (13.5) | 0.528 |
| Frequency/urgency | 5 (4.8) | 10 (4.8) | 0.779 |
| Abdominal pain | 7 (6.7) | 9 (4.3) | 0.032 |
| Flank pain | 0 (0.0) | 9 (4.3) | 0.073 |
| *Laboratory findings* | | | |
| WBC count (/μL) | 12,517.1 | 13,304.4 | 0.716 |
| Hemoglobin (g/dL) | 10.9 | 11.3 | 0.316 |
| Platelet (/μL) | 348,381.7 | 342,271.4 | 0.446 |
| Segment (%) | 48.9 | 52.7 | 0.283 |
| Band (%) | 2.3 | 3.0 | 0.121 |
| CRP (mg/L) | 53.9 | 66.5 | 0.351 |
| BUN (mg/dL) | 15.4 | 14.4 | 0.853 |
| Creatinine (mg/dL) | 0.4 | 0.6 | 0.188 |

Data are presented as *n* (%) unless otherwise indicated. BUN = blood urea nitrogen; CRP = C-reactive protein; ESBL = extended-spectrum β-lactamase; UTI = urinary tract infection; WBC = white blood cell.

**Table 4** Univariate logistic regression analyses of the hospitalization history associated with the occurrence of UTI due to ESBL-producing *Escherichia coli*

| Variables | ESBL-positive *E. coli* ($n = 104$) | ESBL-negative *E. coli* ($n = 208$) | $p$ |
|---|---|---|---|
| *Clinical characteristics* | | | |
| Total duration of fever (d) | 3.9 | 3.6 | 0.679 |
| Total duration of local urologic symptoms[a] (d) | 1.97 | 2.37 | 0.606 |
| Total duration of admission (d) | 12.08 | 6.88 | 0.031 |
| ICU hospitalization | 26 (25.0) | 38 (18.2) | 0.215 |
| Duration of ICU hospitalization | 27.4 | 15.1 | 0.129 |
| Positive findings in renal ultrasound[b] | 52 (75.4) | 122 (81.3) | 0.403 |
| *Antibiotic exposure* | | | |
| Total duration of antibiotics therapy (d) | 9.7 | 8.9 | 0.388 |
| Duration of fever after antibiotic treatment (d) | 1.9 | 1.7 | 0.624 |
| Duration of initial antibiotics usage (d) | 4.6 | 4.8 | 0.712 |
| Inappropriate initial antibiotics[c] | 64 (61.5) | 9 (4.3) | <0.001 |
| Early treatment failure[d] | 19 (18.3) | 14 (6.7) | 0.003 |
| *Clinical outcomes* | | | |
| Improvement without antibiotics | 11 (10.6) | 14 (6.7) | 0.338 |
| Improvement without modification of initial antibiotics | 31 (29.8) | 73 (35.1) | 0.420 |
| Improvement with modification of initial antibiotics | 59 (56.7) | 119 (54.8) | 0.840 |
| Initial antibiotic regimen inactive *in vitro* against the isolate from the initial urine culture | 31 (52.5) | 30 (26.3) | 0.001 |
| Due to worsening clinical conditions[d] | 24 (40.7) | 22 (10.6) | 0.004 |
| Due to improvement of initial clinical conditions[e] | 16 (27.1) | 80 (38.5) | <0.001 |
| Recurrent UTI | 35 (33.6) | 49 (23.6) | 0.078 |

[a] Local urological symptoms include dysuria, urinary frequency/urgency, and flank pain.
[b] Positive findings of renal ultrasound include renal pelviectasis, hydronephrosis, and bladder mucosa thickening.
[c] Inappropriate initial antibiotics mean that all antibiotics were inactive *in vitro* against isolates from the initial urine cultures.
[d] Early treatment failure or worsening clinical conditions mean that fever persisted for more than 3 days after antimicrobial therapy despite continuation of antibiotic treatment. Antibiotic regimen was usually modified in 3—5 days due to the worsening clinical conditions.
[e] The use of antibiotics was de-escalated because of the improvement of initial clinical conditions.
Data are presented as *n* (%) unless otherwise indicated. ESBL = extended-spectrum β-lactamase; ICU = intensive care unit; UTI = urinary tract infection.

difference in the laboratory findings between the case patients and the controls.

Table 4 reveals the univariate logistic regression analyses of the hospitalization history associated with UTI due to ESBL-producing *E. coli*. We found that children in the case group had longer durations of hospitalization (12.08 vs. 6.88 days, $p = 0.031$). Furthermore, early treatment failure, defined as fever persisting for more than 3 days despite antibiotic therapy, was more common in the case patients than in the controls (18.3% vs. 6.7%, $p = 0.003$). For their worsening clinical conditions, the case patients required antibiotic adjustment more frequently than the controls, according to the obtained urine culture results (40.7% vs. 10.6%, $p = 0.004$); however, the controls usually were overtreated with antibiotics initially and needed a de-escalation after the culture results were available (27.1% vs. 38.5%, $p < 0.001$).

## Discussion

The purpose of this study is to highlight the emergence of community-acquired ESBL-producing *E. coli* in children, and this emergence limits therapeutic choices and increases morbidity of pediatric UTI. More importantly, we report the clinical risk factors and characteristics of pediatric patients who acquired ESBL-producing *E. coli* from UTI.

A major concern regarding ESBL-producing *E. coli* is its high rate of coresistance to non-β-lactam antibiotics, particularly quinolones, trimethoprim—sulfamethoxazole, and aminoglycosides.[15] In this study, antimicrobial resistance to aminoglycosides was found to decrease; however, rates of resistance to ciprofloxacin and flomoxef have been increasing. These findings suggest that a change might have occurred in the clonal composition or the plasmid structure of the strains during the study period. High ciprofloxacin resistance among ESBL-producing *E. coli* was also found in other countries. Studies from Israel in 2004 and Spain in 2006 reported that ciprofloxacin resistance was 39% and 31.5% in ESBL-producing *E. coli* isolates, respectively.[6,8] In Turkey, an extremely high rate of ciprofloxacin resistance (84%) among ESBL-producing *E. coli* was reported.[15] Flomoxef, a cephamycin that is unique in its structure by containing a difluoromethylthioacetamido group at position 7, has better *in vitro* activity against ESBL-producing Enterobacteriaceae.[16] Consistent with the increasing

resistance of ESBL-producing Enterobacteriaceae to flomoxef observed in our study, an increase in bloodstream infections caused by flomoxef-resistant ESBL-producing *K. pneumoniae* was also reported from Taiwan in 2004.[16] Subsequent studies found that the *in vivo* acquisition of the plasmid-mediated AmpC β-lactamase gene ($bla_{DHA-1}$) leading to flomoxef nonsusceptibility has occurred in ESBL-producing Enterobacteriaceae following a prolonged exposure to flomoxef.[17] This multidrug resistance nature of ESBL-producing bacteria would cause problems in the treatment of infections caused by such organisms.

Regarding risk factors associated with the occurrence of UTI due to ESBL-producing *E. coli*, underlying diseases such as neurological diseases, failure to thrive, and developmental delay were found to be associated with such infection in children. The result was different from previous studies in that urinary abnormalities or previous urological operations, which were less frequently found in our series, were found to be potential risk factors associated with UTIs caused by ESBL-producing *E. coli*.[18,19] This discrepancy may be because these studies involved different patient populations (adults) and, in general, urological operations are less common in children than in adults. Nevertheless, recurrent UTI and recent hospitalization, two risk factors identified in our study, were also found to be associated with ESBL-producing *E. coli* infection in other reports.[9,15] These results suggest that children may acquire ESBL-producing *E. coli* during healthcare processes and become a reservoir for ESBL producers, which may subsequently result in the occurrence of UTI when they return to the community.

In terms of antibiotic use, our study showed that the previous use of aminoglycosides, first- and third-generation cephalosporins, and vancomycin was associated with UTIs caused by ESBL-producing *E. coli*. Similar findings have been reported by Topaloglu et al,[1] who found that exposure to second- and third-generation cephalosporins and other antibiotics (aminoglycosides, quinolones, and carbapenems) was a potential risk factor for the occurrence of ESBL-producing *E. coli* UTIs in children. By contrast, the results of other studies in adults with ESBL-producing bacteria were diverse. Previous use of cefuroxime, second- and third-generation cephalosporins, or quinolones was found to be associated with ESBL-producing bacteria.[6,8,18] These results suggest that third-generation cephalosporins or quinolones may select for ESBL-producing *E. coli* from the existing gastrointestinal flora when a patient is exposed to this agent. One study from Spain indicated that the prevalence of fecal ESBL-producing *E. coli* has increased in the past decade, and in fact, up to 5.5% of fecal *E. coli* present in feces of healthy volunteers was found to produce ESBLs.[20]

Comparing the clinical manifestations, longer febrile duration prior to admission, prolonged hospital stay, and early treatment failure were frequently found in ESBL-producing *E. coli* UTIs in children. The result implies that an unfavorable outcome may occur if ESBL-producing *E. coli* is present; however, in our series, there was no attributable mortality.

Our data showed an increasing trend in the occurrence of community-onset UTI caused by ESBL-producing *E. coli*. Although these infections are currently not very common in children, it is possible that clinicians will more frequently be confronted with such infections occurring in the community in the near future, a scenario similar to that of community-associated methicillin-resistant *Staphylococcus aureus* in pediatric patients.[3] Thus, to minimize the spread of ESBL-producing *E. coli*, aggressive infection control measures should be emphasized in both hospital and community settings. Most patients with ESBL-producing *E. coli* infections have previously been colonized by such organisms in the gastrointestinal tract.[20] Hand washing therefore is critical to prevent the spread of bacteria and occurrence of infection. Besides, judicious use of antibiotics is important. Kim et al[21] reported that restriction on the use of third-generation cephalosporins through a computer-assisted system can control the spread of ESBL-producing bacteria in hospital settings.

In conclusion, the incidence of community-onset UTIs caused by ESBL-producing *E. coli* in children seems to be increasing, and this emerging issue complicates the use of antibiotics in the management of UTI in children. Adequate infection control, rapid detection of the resistant bacteria, and antibiotic stewardship are important in terms of halting the spread of ESBL-producing bacteria. Further clinical investigations are needed to guide clinicians in the treatment of community-onset UTIs caused by ESBL producers in children.

## Conflicts of interest

All contributing authors declare no conflicts of interest.

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