CLINICAL MANIFESTATIONS AND RISK FACTORS IN URINARY TRACT INFECTION CAUSED BY COMMUNITY-ACQUIRED EXTENDED-SPECTRUM BETA-LACTAMASE ENZYME PRODUCING BACTERIA IN CHILDREN

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Abstract. Urinary tract infection (UTI) among infants and children due to community-acquired extended-spectrum beta-lactamase (CA-ESBL) producing bacteria are becoming more common. We aimed to determine the clinical characteristics and risk factors for UTI due to CA-ESBL producing bacteria among children attending Thammasat University Hospital, Pathum Thani, Thailand. We conducted a prospective case-control study during June 2016-May 2017, among patients aged 1 month to 5 years diagnosed with a UTI caused by CA-ESBL producing bacteria (n=40) and CA-non-ESBL producing bacteria (n=40). On univariate analysis, significant potential factors were: underlying kidney, pulmonary or neuromuscular disease, previous hospitalization within 1-3 months and a history of antimicrobial therapy within the previous 3 months. On multivariate analysis, only underlying kidney disease [Odds ratio=5.62; 95% confidence interval (CI): 1.08-41.31; p=0.047) was significantly associated with a UTI due to CA-ESBL producing bacteria. Patients with a UTI due to CA-ESBL producing bacteria had a significantly: (i) longer length of stay in the hospital (9.7±5.0 *vs* 5.8±2.3 days, p<0.00), (ii) longer time to fever defervescence (3.8±2.4 *vs* 2.2±0.8 days, p<0.0004), (iii) longer time to pyuria resolution (4.9±1.89 *vs* 3.4±2.0 days, p<0.0004) and (iv) a delay in receiving appropriate antimicrobial therapy (3.5±1.3 days). Empiric antimicrobials covering CA-ESBL producing bacteria should be considered as first line treatment for infant and young children with pre-existing kidney disease with a UTI until urine culture results are back.

Keywords: urinary tract infection (UTI), community-acquired extended-spectrum beta-lactamase (CA-ESBL), Thailand

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INTRODUCTION

A urinary tract infection (UTI) is one of the most common pediatric infections with 8% of girls and 2% of boys having at least one episode by seven years of age (Williams *et al*, 2006). Common uropathogens include *Escherichia coli*, *Kleb-*

siella pneumoniae and *Proteus* spp (Edlin *et al*, 2013). During the past 3 decades, the prevalence of resistant bacteria has increased worldwide (Gould, 2008). Extended-spectrum beta-lactamase (ESBL) comprises of a group of enzymes that can hydrolyze penicillins, cephalosporins, and aztreonam (Brandford, 2001). ESBL-producing organisms have become widespread in hospitals (Philippon *et al*, 1994) and reports of community acquired (CA)-ESBL producing bacteria started to emerge in the mid-2000s (Rodriguez-Bano *et al*, 2004; Pitout *et al*, 2005; Apisarnthanarak *et al*, 2008, Ben-Ami *et al*, 2009). The majority of CA-ESBL-producing bacterial infections are UTIs caused by *E. coli* (Briongos-Figuero *et al*, 2012). Several studies have evaluated the factors associated with UTIs due to CA-ESBL producing bacteria among adults (Calbo *et al*, 2006; Yang *et al*, 2010; Kung *et al*, 2015) but few studies described these among Asian children (Fan *et al*, 2014; Kim *et al*, 2017) and those that have were retrospective chart reviews. Therefore, we determined UTI risk factors prospectively among Thai children attending a tertiary referral center.

MATERIALS AND METHODS

Study design and setting

We conducted this prospective case control study during June 2016-May 2017 at Thammasat University Hospital, Pathum Thani, Thailand, a tertiary-care hospital situated in the Bangkok conurbation. Inclusion criteria were patients aged 1 month to 5 years with an axillary body temperature >37.5°C, pyuria >5 white blood cell (WBC) per high power field, a positive urine culture from: (i) a suprapubic aspiration, (ii) a catheterized specimen with $>10^4$ colonies per milliliter of urine, or (iii) a clean-catch or midstream specimen with $>10^5$ colonies per milliliter of urine. Exclusion criteria were anyone of: (i) UTI diagnosed after >72 hours of hospitalization, (ii) hospital admission in the previous 30 days, (iii) immuno-compromised illness, and (iv) parent/guardian refusing to participate in the study. For each subject with a UTI due to CA-ESBL producing bacteria, a subject with a UTI due to CA-non-ESBL producing bacteria was included in the study. Cases and controls were matched by age and sex in a 1:1 ratio.

A study nurse interviewed the parent/guardian of each subject using a structured questionnaire containing information on age, sex, co-morbid conditions, previous UTI episodes and urine culture results, use of UTI prophylaxis, previous hospitalizations and antimicrobial therapy within previous 3 months. We supplemented these data from the medical records and interviews about accompanying symptoms, body temperature, history of phimosis/labial adhesions, laboratory tests, antibiogram of the uropathogen, antimicrobial therapy and its duration, radiologic imaging, time to fever defervescence time to clear of pyuria and hospital length of stay (LOS).

Every month for 6 months after discharge, the nurse called the parent/guardian of the subject to ask about UTI recurrence, adherence to antimicrobial therapy and/or prophylaxis.

The ethics review committee of the Faculty of Medicine, Thammasat University, approved this study protocol (Ref No. MTU-EC-PE-2-031/59; 2016 Mar 24).

Microbiological analysis

Uropathogens were identified using routine biochemical tests. Antimicrobial susceptibility was performed using the disk diffusion method following the

Clinical and Laboratory Standards Institute (CLSI) susceptibility criteria (CLSI, 2010). ESBL production was identified using phenotype tests for ceftazidime (30 μg), cefotaxime (30 μg), ceftazidime-clavulanate (30 μg-10 μg) and cefotaxime-clavulanate (30 μg-10 μg) disks. A ≥5 mm increase in the clearance diameter of the zone around a ceftazidime or cefotaxime disk combined with clavulanic acid was defined as ESBL enzyme production (CLSI, 2010).

Sample size calculation and statistical analysis

The calculation of sample size is based on the study of Topaloglu *et al* (2010) who demonstrated that hospitalization within the previous one to three months was an independent risk factor associated with a UTI due to CA-ESBL producing bacteria (47.7% *vs* 18.7%, p=0.001). Forty subjects with a UTI due to CA-non-ESBL producing bacteria and 40 subjects with a UTI due to CA-ESBL producing bacteria were included in the study.

Frequencies, percentages, ranges, means, and standard deviations were calculated where appropriate. The chi-square test and unpaired *t*-test were used to compare variables. Variables with a p-value <0.05 on univariate analysis were included in the multivariate model. Multivariate logistic regression analysis was conducted in a stepwise fashion, calculating odds ratios (OR) and their 95% confidence intervals (CIs). A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

A total 80 patients with community-acquired UTI (CA-UTI) were included in the study, 40 cases and 40 controls. The demographics and important clinical features of the study subjects are shown in Table 1. The median age at enrollment was 7.1 months of both groups. There were no significant differences between the two groups with respect to symptoms, signs, history of phimosis/labial adhesions, method of obtaining the urine specimen and laboratory tests performed (Table 2).

The most frequent causative microorganism identified among study subjects of both groups was *Escherichia coli*, found in 92.5% of those with a UTI due to ESBL producing bacteria and 87.5% of those with non-ESBL producing bacteria, followed by *K. pneumoniae* and *Proteus* spp, respectively.

The most common initial empiric antimicrobial treatment for the UTI in both groups was a third generation cephalosporin, either cefotaxime or ceftriaxone, given in 53% and 50% of those with a UTI due to CA-ESBL and CA-non-ESBL producing bacteria, respectively, followed by gentamicin (43% and 50%, respectively). The physicians changed treatment if symptoms, fever or pyuria did not improve after 2-3 days of empiric treatment. This occurred in 20 cases (50%) of the subjects with a UTI due to CA-ESBL producing bacteria compared to 1 subject (2.5%) with a UTI due to CA-non-ESBL producing bacteria (p< 0.000). The mean time of delay to receive appropriate antimicrobial therapy was 3.5±1.3 days (range 2-7 days). The choice of antimicrobial agent was based on the susceptibility pattern of the urine culture results. The most common antimicrobial chosen was amikacin (65%), followed by carbapenem (30%). The other 20 cases of a UTI due to CA-ESBL producing bacteria improved with initial empiric antimicrobial therapy of cefotaxime/ceftriaxone (n=12) and gentamicin (n=8).

The UTI due to CA-ESBL producing bacteria cases had a significantly longer

Table 1
Demographic and clinical features of children with a urinary tract infection (UTI) due to extended-spectrum beta-lactamase (ESBL) producing bacteria and non-ESBL producing bacteria.

Variable	Patients, *n* (%)		
	ESBL producing bacteria (*N*=40)	Non-ESBL producing bacteria (*N*=40)	*p*-value
Median age in months (range)	7.1 (1.2-60.0)	7.1 (1.2-49.2)	0.70
Male gender	24 (60)	18 (45)	0.26
Co-morbid conditions			0.00
None	18 (44)	36 (90)	
Kidney disease	8 (20)	1 (3)	
Chronic lung disease/asthma	7 (18)	1 (3)	
Neuromuscular disease	7 (18)	2 (4)	
Previous hospitalizations			0.00
None	21 (53)	37 (93)	
Within 1-3 months	16 (40)	2 (5)	
>3 months	3 (7)	1 (2)	
Antimicrobial therapy within previous 3 months			0.028
None	22 (55)	29 (73)	
Amoxicillin/clavulanate	7 (18)	8 (20)	
Cephalosporins	7 (18)	0 (0)	
Azithromycin	0 (0)	1 (2)	
Aminoglycosides	1 (2)	0 (0)	
Unknown	3 (7)	2 (5)	
Recurrent UTI	5 (13)	4 (10)	0.737
UTI prophylaxis	4 (10)	2 (5)	0.675
Renal abnormalities	5 (13)	2 (5)	0.432

N, total number; *n*, number.

mean LOS in the hospital than those with a UTI due to CA-non-ESBL producing bacteria (mean 9.7±5.0 *vs* 5.8±2.3 days; $p<0.00$). The mean time to fever defervescence was also significantly longer in cases with a UTI due to CA-ESBL producing bacteria than cases with a UTI due to CA-non-ESBL producing bacteria (mean 3.8±2.4 *vs* 2.2±0.8 days; $p<0.0004$) as was the mean time to pyuria resolution (mean 4.9±1.9 *vs* 3.4±1.0 days; $p<0.0004$). No patient developed a perinephric or renal abscess or urosepsis.

On radiologic imaging, renal and collecting system abnormalities were not significantly different between the two groups, found in 15% of those with a UTI due to CA-ESBL producing bacteria and 5% of those with CA-non-ESBL producing bacteria ($p=0.154$). During the monthly follow-up phone calls, 3 cases with a UTI due to CA-non-ESBL producing bacteria developed a recurrent UTI. None of the isolates on recurrent UTI were ESBL producing bacteria (2 cases due to *E. coli* and 1 case due to *K. pneumoniae*). No cases of

Table 2
Accompanying symptoms, physical examination and laboratory tests of children study subjects.

Variable	UTI due to CA-ESBL producing bacteria (*N*=40)	UTI due to CA-non-ESBL producing bacteria (*N*=40)	*p*-value
Accompanying symptoms			
Mean length of fever in days ± (SD)	2.83 ± 2.52	2.53 ± 1.36	0.96
Poor intake, *n* (%)	23 (58)	15 (38)	0.117
Nausea, *n* (%)	17 (43)	11 (28)	0.24
Strong-smelling urine, *n* (%)	11 (28)	7 (18)	0.422
Turbid urine, *n* (%)	8 (20)	7 (18)	1.00
Diarrhea, *n* (%)	7 (18)	12 (30)	0.293
Drowsiness, *n* (%)	7 (18)	6 (15)	1.00
Decreased urine output, *n* (%)	3 (8)	6 (15)	0.481
Seizure, *n* (%)	2 (5)	5 (13)	0.432
Constipation, *n* (%)	2 (5)	2 (5)	1.00
Abdominal pain, *n* (%)	2 (5)	1 (3)	1.00
Weight loss, *n* (%)	1 (3)	0 (0)	1.00
Physical examination			
Maximum temperature in °C, mean±SD	39.0 + 0.8	39.3 + 0.8	0.14
Phimosis/labial adhesions, *n* (%)	23 (58)	22 (55)	1.00
Abdominal tenderness, *n* (%)	2 (5)	1 (3)	1.00
Laboratory tests			
Complete blood count			
WBC (cells/mm^3), mean±SD	18,057.5 ± 1,132.0	20,222.5 ± 6,594.1	0.16
Neutrophil, mean±SD	56.2 ± 17.4	59.9 ± 14.7	0.31
Urine analysis			
WBC (cells/HPF), mean±SD	101.5 ± 83.7	110.25 ± 75.7	0.44
RBC (cells/HPF), mean±SD	17.0 ± 34.9	23.0 ± 45.5	0.69
BUN (mg/dl), mean±SD	9.8 ± 4.1	9.8 ± 3.6	0.97
Cr (mg/dl), mean±SD	0.6 ± 0.8	0.4 ± 0.1	0.68
Urine culture methods			0.675
Urethral catheterization	36 (90)	38 (95)	
Midstream collection	4 (10)	2 (5)	
Pathogen in urine culture			
ESBL producing *E. coli*, *n* (%)	37 (93)	0 (0)	
Non-ESBL producing *E. coli*, *n* (%)	0 (0)	35 (88)	
ESBL producing *K. pneumoniae*, *n* (%)	3 (7)	0 (0)	
Non-ESBL producing *K. pneumoniae*, *n* (%)	0 (0)	3 (7)	
Non-ESBL producing *Proteus* spp, *n* (%)	0 (0)	2 (5)	

SD, standard deviation; CA, community acquired; UTI, urinary tract infection; ESBL, extended-spectrum beta-lactamase; *n*, number; *N*, total number; C, centigrade; WBC, white blood cell count; RBC, red blood cell count; BUN, blood urea nitrogen; Cr, creatinine; HPF, high power field.

Table 3
Antimicrobial susceptibilities of bacteria isolated from study subjects.

Antimicrobial agents	Patients, *n* (%)		*p*-value
	UTI due to CA-ESBL producing bacteria (*N*=40)	UTI due to CA-non-ESBL producing bacteria (*N*=40)	
Ampicillin	0 (0)	4 (10)	0.116
Amoxicillin-clavulanate	20 (50)	32 (80)	0.009
Piperacillin-tazobactam	39 (98)	40 (100)	1.000
Cefazolin	0 (0)	33 (83)	0.000
Cefoxitin	39 (98)	40 (100)	1.000
Cefotaxime/ceftriaxone	0 (0)	39 (98)	0.000
Ceftazidime	0 (0)	40 (100)	0.000
Cefoperazone-sulbactam	34 (85)	40 (100)	0.026
Quinolones	17 (43)	35 (88)	0.000
Gentamicin	7 (18)	36 (90)	0.000
Amikacin	37 (93)	40 (100)	0.241
Carbapenems	40 (100)	40 (100)	1.000
Trimethoprim-sulfamethoxazole	9 (23)	17 (43)	0.094

N, total number; *n*, number; CA, community acquired; UTI, urinary tract infection; ESBL, extended-spectrum beta-lactamase.

recurrent UTI occurred in subjects with a UTI due to CA-ESBL producing bacteria. The antimicrobial susceptibilities of the isolates in both groups are shown in Table 3.

On univariate analysis, the factors significantly associated with a UTI due to CA-ESBL producing bacteria were the presence of co-morbid illness (any or individual kidney, pulmonary or neuromuscular disease), hospitalization within previous 1-3 months and history of antimicrobial therapy within previous 3 months. On multivariate analysis, the only independent factor was underlying kidney disease (Table 4).

DISCUSSION

The incidence of infections due to ESBL-producing Enterobacteriace in recent years has increased significantly and is now found in the community, especially in children (Topaloglu *et al*, 2010; Kizilca *et al*, 2012; Dayan *et al*, 2013; Dotis *et al*, 2013; Fan *et al*, 2014; Sakran *et al*, 2015; Kim *et al*, 2017). In our study of CA-UTI, *E. coli* was the most common causative microorganism similar to other studies (Topaloglu *et al*, 2010; Kizilca *et al*, 2012; Dotis *et al*, 2013). Studies have found urinary tract abnormalities, previous history of UTI, pre-existing neurological disease, antibiotic use in the previous 3 months, recent hospitalization, history of antimicrobial UTI prophylaxis, age<1 year were all associated with a UTI due to CA-ESBL producing bacteria (Kizilca *et al*, 2012; Dayan *et al*, 2013; Fan *et al*, 2014; Kim *et al*, 2017).

In our study, subjects with a UTI due to CA-ESBL- producing bacteria had

Table 4
Factors significantly associated with a community acquired urinary tract infection due to extended-spectrum beta-lactamase producing Enterobacteriaceae.

Factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Co-morbid conditions				
Any	11 (3.29-36.75)	0.000	6.36 (1.28-31.56)	0.024
Kidney	15.89 (3.08-47.15)	0.001	5.62 (1.08-41.31)	0.047
Chronic lung disease/asthma	13.22 (2.15-76.01)	0.020		
Neoromuscular disease	6.61 (1.24-35.19)	0.027		
Previous hospitalizations	11.16 (2.95-42.19)	0.000		
Hospitalization within previous 1-3 months	14.09 (2.95-67.38)	0.001		
Antimicrobial therapy within previous 3 months	1.45 (1.03-2.04)	0.035		

OR, odds ratio; CI, confidence interval.

a longer duration of fever similar to a previous study and a prolonged hospital stay, similar to times reported previously (Fan *et al*, 2014; Kim *et al*, 2017). Numerous studies have demonstrated that most ESBL-producing Enterobacteriaceae are resistant to multiple antibiotic classes (Brandford, 2001; Endimiani *et al*, 2004; Rodriguez-Bano *et al*, 2004; Calbo *et al*, 2006; Kim *et al*, 2017). Carbapenems are the current treatment of choice for treating patients infected with ESBL-producing strains (Pitout *et al*, 2008; Rodriguez-Bano *et al*, 2012). Higher morbidity and mortality rates have been reported when patients infected with ESBL-producing bacteria are treated with non-carbapenem treatment regimens (Endimiani *et al*, 2004; Paterson *et al*, 2004; Tamma *et al*, 2015).

Use of third generation cephalosporins or gentamicin to treat acute pyelonephritis due to ESBL-producing bacteria may result in renal damage due to delayed appropriate treatment. The susceptibility rates of ESBL-producing bacteria to third generation cephalosporins (0%) and gentamicin (18%) in our study were low, similar to other studies in which reported susceptibility rates were 0.7-1.9% for third generation cephalosporins and 19.1-24.3% for gentamicin (Kizilca *et al*, 2012; Doi *et al*, 2013). Although carbapenems are usually effective for ESBL-producing bacteria, cefoperazone-sulbactam, amikacin and piperacillin-tazobactam may be useful alternatives based on our study results.

The number of oral drugs available for treatment ESBL-producing bacteria in the outpatient setting is limited. The efficacy of amoxicillin-clavulanate potassium to treat a UTI due to CA-ESBL producing bacteria was only 56% (Rodrí-

guez-Baño *et al*, 2008). In our study, 50% of ESBL producing isolates were resistant to amoxicillin-clavulanate, making it an unacceptable choice.

Since 2010, the Clinical Laboratory Standards Institute (CLSI) has reduced the cut-off levels for most cephalosporins against Enterobacteriaceae and eliminated the specific testing for ESBL production. ESBL producing bacteria have variable susceptibility to third-generation cephalosporins (CLSI, 2010). In our study, 12 cases (30%) of a UTI due to CA-ESBL producing bacteria were successfully treated with third generation cephalosporins. Our findings are similar to previous studies (Peco-Antić *et al*, 2012; Lee *et al*, 2013). This suggests finding an ESBL producing phenotype *in vitro* may not be predictive of its susceptibility *in vivo*. The main limitation in our study is the small number of patients and this limited our statistical power to detect significant associations on multivariate analysis.

In conclusion, a UTI due to CA-ESBL-producing Enterobacteriaceae especially *E. coli*, was found in the study hospital and had low rates of susceptibility to antibiotics used commonly in the community. Patients with a CA-UTI due to ESBL-producing bacteria receive appropriate antibiotics alter, had longer hospital stays, and longer times to fever and pyuria clearance. The most important factor for ESBL related UTIs was underlying kidney disease. Clinicians should be aware of this problem. Consideration should be given to using more appropriate empiric antimicrobials in children with underlying kidney disease and CA-UTI at the study hospital. Further study is needed to determine appropriate empiric antimicrobial therapy in children with underlying kidney disease and a UTI at the study hospital.

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