CLINICAL CHARACTERISTICS AND ANTIBIOTIC RESISTANCE PATTERN OF PATHOGENS IN PEDIATRIC URINARY TRACT INFECTION

Yupaporn Amornchaicharoensuk

Faculty of Medicine, Navamindradhiraj University, Bangkok, Thailand

Abstract. Medical records of children less than 15-years of age admitted to hospital for urinary tract infection (UTI) from January 2010 to December 2014 were reviewed. Among 100 children (59% males and 41% females) with upper UTI, the most common pathogen (88%) was *Escherichia coli*, of which 69% were non-extended spectrum beta-lactamase (ESBL) and 19 % ESBL producers. Resistance to ampicillin and trimethoprim/sulfamethoxazole was 90% and 60%, respectively. All ESBL-producing *E. coli* were resistant to ampicillin and third generation cephalosporins (cefotaxime and ceftriaxone), while 87% and 1.5% of non ESBL-producing *E. coli* were resistant to ampicillin and the two third generation cephalosporins, respectively. These data highlight the high prevalence of ESBL-producing *E. coli* in pediatric UTI and the potential problem in treating such infections.

Keywords: *Escherichia coli*, extended spectrum beta lactamase-producing bacteria, urinary tract infection, children

INTRODUCTION

Pediatric urinary tract infection (UTI) is common and of importance in clinical practice (Jungthirapanich *et al*, 2001). Clinical manifestations are not specific, *viz* fever, vomiting, diarrhea, upper respiratory tract infection or seizure, and only a few children present with dysuria or hematuria (Jungthirapanich *et al*, 2001). If clinicians are not alerted to the possibility of UTI, a urine test will not be carried out, leading to a delay in proper treatment, which may cause subsequent renal scaring (Hellerstein, 2000). Pediatric urinary tract infection is comorbid with a variety of genitourinary tract anomalies, including vesicoureteral reflux (29%), neurogenic bladder (14%), posterior urethral valve (10%), and ureteropelvic junction obstruction (9%) (Tapaneeya-Olarn *et al*, 1989).

Moreover, empirical treatment of UTI is an issue of concern because of the tendency to produce antibiotic-resistance organisms. Calbo *et al* (2006) reported that the prevalence of extended-spectrum β-lactamase (ESBL) producing *Escherichia coli* from urine culture increases from 0.47% in 2000 to 1.7 % in 2003. The prevalence of ESBL producing *E. coli* from urine culture reported by Chen *et al* (2014) is 11%.

Thus, the objective of this study was to determine the clinical manifestations, duration and type of antibiotic prescription, prevalence of genitourinary tract anomalies, and prevalence of urinary organisms and antimicrobial resistance patterns of urinary organisms in pediatric UTI.

Correspondence: Yupaporn Amornchaicharoensuk, Department of Pediatrics, Faculty of Medicine, Navamindradhiraj University, Bangkok 10300, Thailand.
Tel: +66 (0) 2244 3156; Fax: +66 (0) 2668 7065
E-mail: yupapornlee@gmail.com

MATERIALS AND METHODS

Collection of samples

One hundred and seventeen children < 15 years of age, admitted to the Faculty of Medicine, Vajira Hospital, Bangkok, Thailand from January 2010 to December 2014 and diagnosed with UTI, were recruited retrospectively. Inclusion criteria were patients infected with a single species of pathogen with $>10^5$ colony forming unit (CFU)/ml) in voiding urine, or $>10^4$ CFU/ml in catheterized urine or $>10^3$ CFU/ml in suprapubic urine. Exclusion criteria were neurogenic bladder, catheter-related UTI or hospital acquired UTI. Data collected included age, gender, clinical manifestations, results of urinalysis, urinary organisms, duration and type of intravenous antibiotics prescribed, genitourinary tract anomalies, and antimicrobial resistance patterns of cultured urinary organisms.

The study was approved by Vajira Hospital Institutional Review Board (reference no. COA 23/2557). Written consent of legal guardian was obtained prior to patient's enrollment.

Clinical investigations

Voiding cystourethrogram (VCUG) was indicated if ultrasound (kidney urinary bladder) (KUB) revealed hydronephrosis, ureteric dilatation, renal hypoplasia, duplicated system and bladder abnormalities, or urine culture revealed bacteria other than *Escherichia coli*, or has septicemia, or has abnormal bladder emptying, or has vesicoureteral reflux (VUR), or is likely a non-complying patient (www.thaipediatrics.org/html/download/CPG-UTI-21102556.pdf). Technetium-99m-labeled dimercaptosuccinic acid (DMSA) scan was undertaken in a patient with VUR to explore for evidence of renal scarring as shown by decreasing uptake of labeled DMSA with cortical thinning.

Statistical analysis

Minimum sample size ($n = 96$) was calculated using the formula $n = Z\alpha^2\ PQ/d^2$, where Z = value for the selected alpha level at 95 % confidence interval (1.96), α = alpha level (0.05), P = prevalence of genitourinary tract anomalies in children (0.46) (Tapaneya-Olarn *et al*, 1989), Q = 1 - P, and d = maximum allowance error (0.1). Results were analyzed using SPSS version 22 statistical package (IMB, Armonk, NY). Data are presented as frequency and percentage for categorical data and compared between groups using chi-square test or Fisher's exact test. Continuous data are presented as mean ± SD and compared between groups by independent *t*-test or Mann-Whitney *U* test depending on distribution of data. A p-value < 0.05 is regarded as statistical significant.

RESULTS

A hundred cases out of 117 children diagnosed with UTI had positive urine bacterial culture, consisting of 59 % males and 41% females, with median age of 6.5 months [interquartile range (IQR) = 9.46]. Clinical manifestations included fever (94%), vomiting (13%), diarrhea (13%), convulsion (10%), dysuria (9%), hematuria (1%), phimosis (60%) and labial adhesion (7%). Methods of urine collection for culture were urinary catheterization (87%), mid-stream collection (6%), clean void collection (6%), and suprapubic aspiration (1%). Urinalysis revealed proteinuria (78%) (ranging from trace to 4+) and microscopic hematuria (94%). Hemoculture was positive in only 9% of the cases.

UTI was first diagnosed in 92% of patients and 8% had recurrent UTI. Intravenous antibiotics prescribed were cefotaxime (53% of cases), ceftriaxone (44%),

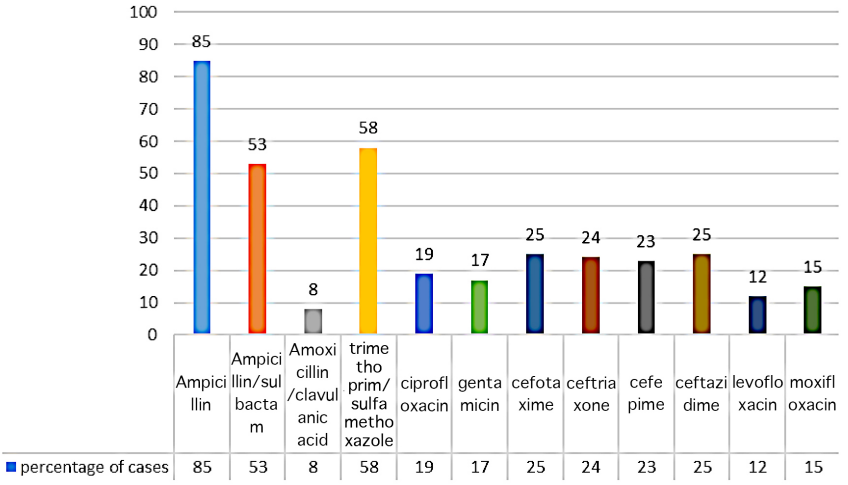

Fig 1–Antibiogram of urinary organisms isolated from 100 pediatric cases at Vajira Hospital, Bangkok.

meropenem (5%), amikacin (5%) and gentamicin (1%). Duration of intravenous antibiotics ranged from 2-17 days, the majority of cases being administered for 3 days. After fever (mean duration 30 ± 24 hours) had subsided antibiotics administration were switched to oral route according to antimicrobial sensitivity patterns. Oral cefixime was prescribed in 64% of cases, cefdinir in 8%, amoxicillin/clavulanic acid in 9%, ciprofloxacin in 2%, ofloxacin in 1% and ampicillin/sulbactam in 1%.

DMSA scans were conducted in 10 cases with VUR. Renal scar was detected in 30%. VUR was found in 7/54 (13%) cases with normal ultrasound KUB.

Prevalence of the most common urinary organism *E. coli* was 88% (non-ESBL producing = 69% and ESBL producing = 19 %), with prevalences of other urine organisms being *Klebsiella pneumoniae* 5%, *Streptococcus* spp 2%, *Enterobacter cloacae* 2%, *Pseudomonas aeruginosa* 1%, *Proteus mirabilis* 1%, and *Salmonella* gr E 1%. Resistance rate of all urinary pathogens to ampicillin was 85% and to trimethoprim/sulfamethoxazole 58% (Fig 1). Resistance of *E. coli* to ampicillin, trimethoprim/sulfamethoxazole and gentamicin was 90%, 60% and 1%, respectively. Non ESBL-producing *E. coli* had low antibiotic resistance rate to third generation cephalosporins and amoxicillin/clavulanic acid but high resistance to ampicillin (87%), ampicillin/sulbactam (58%) and trimethoprim/sulfamethoxazole (55%) (Table 1). All ESBL-producing *E. coli* were resistant to ampicillin, cefotaxime and ceftazidime.

There are no differences in the clinical characteristics of patients with non-ESBL- and ESBL producing *E. coli* urinary infection, except that the latter group had a longer duration of intravenous antibiotics treatment (Table 2). As expected, the proportion of patients with antimicrobial susceptible urinary *E. coli* responsive to treatment is statistically significantly higher than patients infected with resistant bacteria (Table 3).

Prevalence of hydronephrosis in patients with *E. coli* in urine is not statistically significant different from that of non-*E. coli*-infected group; however, prevalence of VUR in patients with urinary *E. coli* infection (14%) is statistically significantly lower than in non-*E. coli* infected group (Table 4). Prevalence of hydronephrosis and VUR is not statistical significant different between males and females (Table 5). The prevalence of hydronephrosis in cases of first diagnosis

Table 1
Antibiotics resistance patterns of urinary non-ESBL- and ESBL-producing *E. coli*.

Drugs	Non ESBL-producing *E. coli* (*N*= 69), *n* (%)	ESBL-producing *E. coli* (*N* = 19), *n* (%)	*p*-value
Ampicillin	60 (87)	19 (100)	0.097
Ampicillin/sulbactam	40 (58)	10 (53)	0.279
Amoxicillin/clavulanic acid	3 (4)	1 (5)	0.829
Trimethoprim/sulfamethoxazole	38 (55)	15 (79)	0.163
Ciprofloxacin	10 (14)	8 (42)	0.026
Gentamicin	4 (6)	9 (50)	0.000
Cefotaxime	1 (1)	19 (100)	0.000
Ceftriaxone	1 (1)	18 (95)	0.000
Ceftazidime	1 (1)	19 (100)	0.000
Cefepime	1 (1)	18 (95)	0.000

Table 2
Clinical characteristics of patients with non ESBL- and ESBL producing *E. coli* urinary infection.

	Non ESBL-producing *E. coli* (*N* = 69), *n* (%)	ESBL-producing *E. coli* (*N* = 19), *n* (%)	*p*-value
Age			
< 1 year	50 (72)	12 (63)	0.267
1-5 years	15 (22)	7 (37)	
> 5 years	4 (6)	0 (0)	
History of previous antibiotics treatment	8 (12)	5 (26)	0.109
Hemoculture positive	6 (9)	2 (10)	0.738
Urine nitrite positive	29 (42)	7 (37)	0.664
Serum creatinine (mg/dl)	0.4 ± 0.2[a]	0.5 ± 0.2	0.695
Genitourinary anomalies			
Hydronephrosis	16 (23)	7 (37)	0.452
VUR	7 (10)	3 (16)	0.173
Cyst	1 (1)	0 (0)	-
Renal scar	0 (0)	1 (5)	0.081
Recurrent UTI	3 (4)	3 (16)	0.171
Duration of intravenous antibiotics (day)	4.6 ± 2.4	6.3 ± 4.4	0.029
Duration of fever (hour)	29 ± 22	35 ± 34	0.315

[a]Mean ± SD.

of UTI is significantly lower than that in recurrent UTI, whereas prevalence of VUR in first diagnosed UTI patients is significantly lower than that in cases with recurrent UTI (Table 6).

Ultrasound KUB were performed in 82 % of cases, and genitourinary anomalies present in 28 (34%) patients. VCUG was performed in 53 cases and 15 (28%) presented VUR.

Table 3
Proportion of response to treatment in patients with antibiotic resistant and susceptible urinary pathogens.

	Response to treatment ($N = 90$)	Non response to treatment ($N = 10$)	p-value
Resistant pathogen, *n* (%)	20	7	0.005
Susceptible pathogen, *n* (%)	70	3	-

Table 4
Prevalence of genitourinary tract (GU) abnormality in patients with *E. coli* and non *E. coli* urinary infection.

GU abnormality	*E. coli* ($N = 88$)	Non *E. coli* ($N = 12$)	p-value
Hydronephrosis, *n* (%)	24 (27)	4 (33)	0.282
VUR, *n* (%)	12 (14)	5 (42)	0.013

Table 5
Prevalence of genitourinary tract (GU) abnormality in male and female patients.

GU abnormality	Male ($N = 59$)	Female ($N = 41$)	p-value
Hydronephrosis, *n* (%)	18 (30)	10 (24)	0.526
VUR, *n* (%)	9 (15)	6 (15)	0.405

Table 6
Prevalence of genitourinary tract (GU) abnormality in patients with first and recurrent urinary tract infection (UTI).

GU abnormality	First UTI ($N = 92$)	Recurrent UTI ($N = 8$)	p-value
Hydronephrosis, *n* (%)	25 (27)	3 (37)	0.000
VUR, *n* (%)	9 (10)	6 (75)	0.000

DISCUSSION

Before 2013, pediatric patients with first diagnosed febrile UTI had imaging study performed according to good clinical practice guideline (www.thai-pediatrics.org/cpg_file/UTI.doc), which recommended to conduct both ultrasound and VCUG if age < 5 years, but if > 5 years to carry out VCUG only when abnormal ultrasound is present. The new good clinical practice guidelines by Thai Pediatric Nephrology Association for management of UTI in febrile infants and children recommend that ultrasound KUB should be carried out after diagnosis of UTI

(www.thaipediatrics.org/html/download/CPG-UTI-21102556.pdf). Phimosis and labial adhesion was not counted as GU anomalies.

In this study, the most common clinical manifestation of pediatric upper UTI were fever (94%) and other nonspecific symptoms, such as vomiting, diarrhea and convulsion, were found in 10-13 % of the patients, similar to the study from Siriraj Hospital, Mahidol University, Bangkok (Sumboonnanonda *et al*, 1994).

E. coli was the most common microbial pathogen (88%) found in this study, comparable to that (74.7%) of Wu *et al* (2004). The median age of patients in the present study was 6.5 months lower than that of 4 years reported by Weisz *et al* (2010) (*E. coli* prevalence of 75.8%).

In our study, resistance of *E. coli* to ampicillin (90%) and trimethoprim/sulfamethoxazole (60%) was slightly higher (82% and 55%, respectively) than the study of Wu *et al* (2004). We found a prevalence of ESBL-producing *E. coli* of 19%, higher than that (11%) reported by Chen *et al* (2014), possibly suggesting an increasing trend. This is a worrying phenomenon as nearly 100% of such urinary pathogen were, in our survey, resistant, to third generation cephalosporin and trimethoprim/sulfamethoxazole. Therefore, empirical treatment using these common antibiotics should be avoided if there is no clinical improvement and urine culture reveals ESBL-producing *E. coli*. On the other hand, we found that 60% and 38% of non ESBL-producing *E. coli* were resistant to ampicillin and trimethoprim/sulfamethoxazole respectively, which was lower than that (80% and 53%, respectively) reported by Chen *et al* (2014). The duration of intravenous administration of antibiotics is statistically significant longer in patients infected with urinary ESBL- than non ESBL-producing *E. coli*. In addition, we found no significant difference in the percent of patients with a history of previous antibiotics treatment between ESBL- and non ESBL-producing *E. coli* infection group.

Only 82% of the cases underwent ultrasound KUB due to some patients being discharged before imaging procedure and others lost to follow-up studies. The prevalence of genitourinary tract anomalies was 34%, lower than that (46%) of a previous study (Tapaneeya-Olarn *et al*, 1989) but the prevalence of primary vesicoureteral reflux was similar (28% *vs* 29%). The present study was retrospective, enrolling patient during 2010-2014. During 2010-2013, VCUG was performed on first diagnosed UTI in patients < 5 years of age even though ultrasound was normal (www.thaipediatrics.org/cpg_file/UTI.doc). However, during 2013-2014 imaging study was performed, with subsequent VCUG if there were indications (www.thaipediatrics.org/html/download/CPG-UTI-21102556.pdf). In recurrent UTI, as prevalence of VUR was high (75%) VCUG was performed on all patients in this group. VCUG revealed VUR in 13% of patients who had normal ultrasound KUB. Therefore, patients with negative investigations for genitourinary tract anomalies should be closely followed for possible recurrent UTI.

DMSA scan was not performed routinely to confirm diagnosis of UTI because the results do not affect management and cost of DMSA scan is high. However, DMSA scan should be conducted in patients with VUR to detect renal scar after 6 months of acute infection. The presence (30%) of renal scars in patients with VUR was lower than that (38%) previously reported (Amornchaicharoensuk and Parklug, 2013).

In summary, results of the study show that (i) prevalence of hydronephrosis in patients with non *E. coli* infection is not significantly different from *E. coli*-infected group; (ii) prevalence of VUR in non *E. coli*-infected group is significantly higher than *E. coli*-infected group and, therefore, patients with urinary non-*E. coli* VCUG should be performed even though ultrasound is normal; (iii) there is no significant difference in the prevalence of hydronephrosis or VUR between male and female patients; (iv) there was a noticeable increase in the prevalence of multidrug resistance of urinary pathogens especially in ESBL-producing *E. coli*, but nearly a quarter of patients with antimicrobial resistance pathogens responded to the prescribed antibiotics without the need to change the prescribed drug regimens; (v) the most frequent antibiotic prescribed was third generation cephalosporin, both intravenous and oral form; (vi) as regards urinary ESBL-producing *E. coli,* the appropriate antibiotics were amikacin, ciprofloxacin or meropenem; and (vii) there was no risk factor for the occurrence of ESBL-producing *E. coli*, but, nonetheless, further studies should be conducted to determine risk factors associated with infection of urinary antimicrobial-resistant pathogens.

ACKNOWLEDGEMENTS

The author thank the Faculty of Medicine, Vajira Hospital, Bangkok for funding support, Ms Nitchaphak Phoemphoonthanyakit for statistical analysis and Assistant Professor Pongsak Noipayak for manuscript revision.

REFERENCES

Amornchaicharoensuk Y, Parklug P. Prevalence and risk factors of renal scar in pediatric patients with urinary tract infection and vesicoureteral reflux. *Vajira Med J* 2013; 57: 81-8.

Calbo E, Romani V, Xercavins M. Risk factors for community-onset urinary tract infections due to *Escherichia coli* harbouring extended-spectrum B lactamases. *J Antimicrob Chemother* 2006; 57: 780-3.

Chen PC, Chang LY, Lu CY, *et al*. Drug susceptibility and treatment response of common urinary tract infection pathogens in children. *J Microbiol Immunol Infect* 2014; 47: 478-83.

Hellerstein S. Long-term consequences of urinary tract infections. *Curr Opin Pediatr* 2000; 12: 125-8.

Jungthirapanich J, Tungsathapornpong A, Chaumrattanakul U, Chotipanich C. Urinary tract infection in Thai children. *J Infect Dis Antimicrob Agent* 2001; 18: 103-7.

Sumboonnanonda A, Laopornpichayanuwat, Vongjirad A, Suntornpoch V. Urinary tract infection in Thai children. *Siriraj Hosp Gaz* 1994; 46: 347-57.

Tapaneya-Olarn C, Tapaneya-Olarn W, Assadamongkol K. Genitourinary tract anomalies in Thai children with urinary tract infection. *J Med Assoc Thai* 1989; 72 (suppl 1): 47-51.

Weisz D, Seabrook JA, Lim RK. The presence of urinary nitrites is a significant predictor of pediatric urinary tract infection susceptibility to first- and third-generation cephalosporins. *J Emerg Med* 2010; 39: 6-12.

Wu CY, Chiu PC, Hsieh KS, Chiu CL, Shih CH, Chiou YH. Childhood urinary tract infection: a clinical analysis of 597 cases. *Acta Paediatr Taiwan* 2004; 45: 328-33.