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ORIGINAL ARTICLE

Drug susceptibility and treatment response of common urinary tract infection pathogens in children



Pei-Chun Chen^a, Luan-Yin Chang^{a,*}, Chun-Yi Lu^a,
Pei-Lan Shao^a, I-Jung Tsai^a, Yong-Kwei Tsau^a, Ping-Ing Lee^a,
Jong-Ming Chen^b, Po-Ren Hsueh^b, Li-Min Huang^a

^a Division of Pediatric Infectious Diseases, Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

^b Department of Laboratory Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

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Background/Purpose: To document the trends of sensitivity and to find whether it is necessary to change antibiotics in selected patients according to the sensitivity test results in our clinical practice.

Methods: We collected urine culture results from 0–18-year-old patients in the National Taiwan University Hospital from January 1, 2003 to October 31, 2012. Their medical chart was reviewed to identify true pathogens responsible for their urinary tract infection (UTI). We checked the percentage of susceptibility of these pathogens to ampicillin, amoxicillin–clavulanate (AMC), cefazolin, cefmetazole, ceftriaxone, gentamicin, and trimethoprim–sulfamethoxazole (TMP–SMX) according to the Clinical and Laboratory Standards Institute (CLSI) guideline. The extended-spectrum-beta-lactamases (ESBLs) rate was also checked. In addition, we reviewed the treatment response of different antibiotics. Defervescence within 48 hours after initial antibiotics use was considered responsive.

Results: A total of 7758 urine cultures positive for *Escherichia coli* infection were collected during the 10-year period. The *E. coli* cefazolin susceptibility rate was 62–73% during 2003–2010, but it dropped to 23% in 2011 and 28% in 2012 after the new CLSI guideline (M100-S21) was released. However, other antibiotics did not show a significant difference. In UTI caused by *E. coli*, on average, the sensitivity rates for various antibiotics were as follows:

* Corresponding author. Division of Pediatric Infectious Diseases, Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University, Number 8, Chung-Shan South Road, Taipei 100, Taiwan.

E-mail addresses: ly7077@tpts6.seed.net.tw, lychang@ntu.edu.tw (L.-Y. Chang).

cefmetazole, 90%; ceftriaxone, 85%; gentamicin, 77%; AMC, 61%; TMP–SMX, 47%; and ampicillin, 20%. The ESBL rate was also found to increase (2–11%; $p < 0.01$). The overall response rate of UTI caused by *E. coli* to first-line antibiotics such as first-generation cephalosporin and/or gentamicin was 78%.

Conclusion: The susceptibility of common urinary tract pathogens to cefazolin has decreased dramatically since 2010. This trend may be due to the change in the CLSI guideline. Although the susceptibility rate to first-line empirical antibiotics shows a decreasing trend, we found that the clinical response was acceptable for our first-line empirical antibiotics.

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Introduction

Urinary tract infection (UTI) is a common disease in children and usually causes hospitalization. We found that the common pathogens of UTI (*Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus* spp.) had increasing resistance to our empirical antibiotics.

In most hospitals, the drug susceptibility is usually tested according to the Clinical and Laboratory Standards Institute (CLSI) guideline. However, the cefazolin and ceftriaxone breakpoints have been revised in the CLSI guideline released in 2010 and 2011.^{1–3} In our microbiological laboratory setting, we used zone diameter as breakpoints to interpret drug sensitivity. Prior to 2010, the zone diameter cutoff point for cefazolin to test isolates of Enterobacteriaceae was ≥ 18 mm (sensitive), 15–17 mm (intermediate), and ≤ 14 mm (resistance); for ceftriaxone, it was ≥ 21 mm (sensitive), 14–20 mm (intermediate), and ≤ 13 mm (resistance).¹ However, in the new CLSI standard, the cutoff point for cefazolin is ≥ 23 mm (sensitive), 20–22 mm (intermediate), and ≤ 19 mm (resistance).² For ceftriaxone, it is ≥ 23 mm (sensitive), 20–22 mm (intermediate), and ≤ 19 mm (resistance). The minimum inhibitory concentration (MIC) or zone diameter breakpoints of other commonly used antibiotics such as ampicillin, amoxicillin–clavulanate (AMC), cefmetazole, gentamicin, and trimethoprim–sulfamethoxazole (TMP–SMX) were not changed in the new CLSI guideline.

In our clinical practice, it is crucial to choose a suitable antibiotic for the treatment of UTI. In the new CLSI guideline (M100-S21) era,² it seems that the common UTI pathogens have high resistance to the empirical antibiotics such as the first-generation cephalosporin. We wondered whether changing antibiotics according to the sensitivity test results is necessary in specific patients. The aim of this study was to investigate the trends of antibiotic sensitivity and evaluate the clinical response of different antibiotics in children with UTIs.

Methods

Patient collection

We collected the urine culture results from 0–18-year-old patients in the National Taiwan University Hospital from January 1, 2003 to October 31, 2012. Patient's medical

chart was reviewed to identify true UTI pathogens. True UTI pathogen was defined as a single pathogen with adequate colony formation unit (CFU) in one urine culture specimen according to the sampling methods (i.e., $>100,000$ CFU/mL in voiding urine; $>10,000$ CFU/mL in catheterized urine; and >1000 CFU/mL in suprapubic puncture).⁴

Drug susceptibility test

In vitro susceptibility was determined by the broth microdilution method and susceptibility profiles were determined based on the CLSI guideline.^{1–3} We used zone diameter as breakpoints to measure drug sensitivity. The MIC interpretive standard for cefazolin to test isolates of Enterobacteriaceae was ≤ 8 $\mu\text{g/mL}$ (sensitive), 16 $\mu\text{g/mL}$ (intermediate), and ≥ 32 016 $\mu\text{g/mL}$ (resistance) prior to 2010, and these were revised to ≤ 2 $\mu\text{g/mL}$ (sensitive), 4 $\mu\text{g/mL}$ (intermediate), and ≥ 8 $\mu\text{g/mL}$ (resistance) after 2010. For ceftriaxone, the MIC interpretive standard was ≤ 8 $\mu\text{g/mL}$ (sensitive), 16–32 $\mu\text{g/mL}$ (intermediate), and ≥ 64 $\mu\text{g/mL}$ (resistance) prior to 2010, and these were revised to ≤ 1 $\mu\text{g/mL}$ (sensitive), 2 $\mu\text{g/mL}$ (intermediate), and ≥ 4 $\mu\text{g/mL}$ (resistance) after 2010.^{1–3} The MIC or zone diameter breakpoints of other commonly used antibiotics such as ampicillin, AMC, cefmetazole, gentamicin, and TMP–SMX were not changed in the new CLSI guideline.

Extended-spectrum-beta-lactamases (ESBLs) testing is accomplished by a double-disk synergy test according to the CLSI guideline.^{1–3} A greater than 5-mm increase in a zone diameter for either antimicrobial agent tested in combination with clavulanic acid versus the zone diameter of the agent when tested alone is defined as ESBL-producing strains (i.e., a ceftazidime–clavulanic acid zone 5 mm bigger than a ceftazidime zone is called ESBL-producing strains). Carbapenemase-producing isolates are tested according to the disk diffusion method based on the CLSI guideline. Intermediate or resistant to one or more carbapenems is defined as carbapenem resistance (CR). We used ertapenem nonsusceptibility, which is the most sensitive indicator of carbapenemase production, as the standard of defining CR.

Clinical data collection

E. coli, *K. pneumoniae*, *Proteus* spp., and *Enterococcus* spp. are the most common pathogens responsible for causing UTI in children. Those people who had a positive

urine culture of *E. coli*, *K. pneumoniae*, *Proteus* spp., and *Enterococcus* spp. fit into the criteria of "true" UTI and were included in our database.⁴ We checked the percentage of susceptibility to ampicillin, AMC, ceftazolin, cefmetazole, ceftriaxone, gentamicin, and TMP–SMX. The ESBLs rate was also checked.

In addition, we reviewed the treatment response of different antibiotics. Patients with *E. coli* UTI in 2012 were included. We subdivided the patients into the following three groups based on susceptibility to ceftazolin: the ceftazolin-sensitive group, the ceftazolin-intermediate group, and the ceftazolin-resistant group. Defervescence within 48 hours after initial antibiotics use was considered responsive if patients had fever. For those without fever, we used symptoms relief drugs within 48 hours instead. Because there were other possible causes that could interfere with the treatment response results, those without pyuria (positive urine culture result only, though with adequate colony count) were excluded. The patients with other concomitant diagnosis that may cause fever, (such as pneumonia and acute gastroenterocolitis) were excluded as well. We also excluded patients lost to follow-up or those who had inadequate information to evaluate the clinical response.

Statistics

Chi-square test with Yates correction was used to check whether ESBL-producing *E. coli* increased significantly. Among the three groups of *E. coli* UTI in 2012, classified as the ceftazolin-sensitive, ceftazolin-intermediate, and ceftazolin-resistant groups, Chi-square test with Yates correction was used to compare the clinical characteristics and treatment response. A *p* value < 0.05 was considered statically significant.

Results

Drug susceptibility trends

A total of 7758 urine cultures positive for *E. coli* infection were collected during the 10-year period. The ceftazolin-sensitive rate was 72% in 2003 and 2004, 68% in 2005, 73% in 2006, 69% in 2007, 64% in 2008, 67% in 2009, 62% in 2010, which then dropped to 23% in 2011 and 28% in 2012. By contrast, the sensitivity of *E. coli* to other antibiotics did not have a significant change during the study period. In *E. coli* UTI, on average, cefmetazole had 87–93% sensitive rate (average 90%), whereas ceftriaxone had 85% (80–90%), gentamicin had 77% (73–80%), AMC had 61% (53–70%), TMP–SMX had 47% (43–50%), and ampicillin had 20% (16–23%). Fig. 1 shows the trends of susceptible rates of *E. coli* to different antibiotics from 2003 to 2012.

A total of 449 ESBL-producing and 10 CR *E. coli* were identified. Two had both ESBL and CR, with one in 2011 and the other in 2012. The number of ESBL *E. coli* UTI cases is increasing every year as shown in Fig. 2 (*p* < 0.01). It was 2% in 2003, 3% in 2004, 4% in 2005 and 2006, 3% in 2007, 6% in 2008, 5% in 2009, 7% in 2010, 9% in 2011, and 11% in 2012. No CR *E. coli* was identified prior to 2010. Overall, 10 CR *E. coli* were found, seven in 2011 and three in 2012.

The age distribution of *E. coli* UTI during 2003 and 2012 revealed that most patients were aged <1 year, which accounted for 40–49% of the children infected (mean: 44%). The mean percentage was 36% (range: 33–38%) in 1–4-year-old children, 13% (range: 10–16%) in 5–10-year-old children, and 9% in 11–17-year-old patients (range: 6–12%). This trend shows that the younger the patient, the more likely they have *E. coli* UTI.

In addition, 8680 urine culture data were collected for a 5-year period (2008–2012), which included 4347 (50%) *E. coli*, 2242 (26%) *Enterococcus* spp., 1008 (12%) *K. pneumoniae*, and 1083 (12%) *Proteus* spp. cases. *E. coli* continued to be the most common UTI pathogen in children. The drug susceptibility trends of *K. pneumoniae* and *Proteus* spp. had a decreased sensitivity rate to ceftazolin. The sensitivity rate of *K. pneumoniae* to ceftazolin was 72% in 2008, 67% in 2009, 66% in 2010, and this decreased to 40% and 44% in 2011 and 2012, respectively. For *Proteus* spp., the sensitivity rate to ceftazolin was 60% in 2008, 62% in 2009, 68% in 2010, 15% in 2011, and 10% in 2012. The trend was similar to *E. coli*, which showed significant drops in ceftazolin sensitivity rates after the CLSI guideline was revised. Fig. 3 shows the trends of susceptibility rates of *E. coli*, *K. pneumoniae*, and *Proteus* spp. to ceftazolin during the 5-year period.

Treatment response of *E. coli* UTI in 2012

The patients with *E. coli* UTI in 2012 were included. They were subdivided into three groups based on ceftazolin sensitivity (the ceftazolin-sensitive, ceftazolin-intermediate, and ceftazolin-resistant groups). After cases without pyuria were excluded, 32 patients were included in the ceftazolin-sensitive group, 46 patients in the ceftazolin-intermediate group, and 41 patients in the ceftazolin-resistant group. The clinical characteristics are summarized in Table 1. The percentage of inpatient, percentage of abnormal echo, or bacteremia did not show any significant difference among the three groups.

For those without fever, we used symptoms relief drugs instead. Common empirical antibiotics such as ceftazolin, ceftazolin plus gentamicin, ampicillin plus gentamicin, and oral cephalexin were included for treatment response evaluation. In the ceftazolin-sensitive group with *E. coli* UTI, 25 patients used common empirical antibiotics described previously, whereas 33 patients were included in the ceftazolin-intermediate group and 28 patients in the ceftazolin-resistant group.

Table 2 shows the treatment response of different antibiotics among the three groups. The overall treatment response rate to first-line empirical antibiotics was 78%. Most patients received ceftazolin plus gentamicin combination therapy as empirical antibiotics, and the overall response rate was 72%, with 73% response rate in the ceftazolin-sensitive group, 70% in the ceftazolin-intermediate group, and 75% in the ceftazolin-resistant group, respectively (*p* = 0.95). Other treatment methods (ampicillin plus gentamicin and oral cephalexin) also did not have a significantly different response among the three groups. Oral cephalexin had the overall response rate of 96% (25/24), with 100% (6/6) in the ceftazolin-intermediate group and 90% (9/10) in the ceftazolin-resistant group. Only

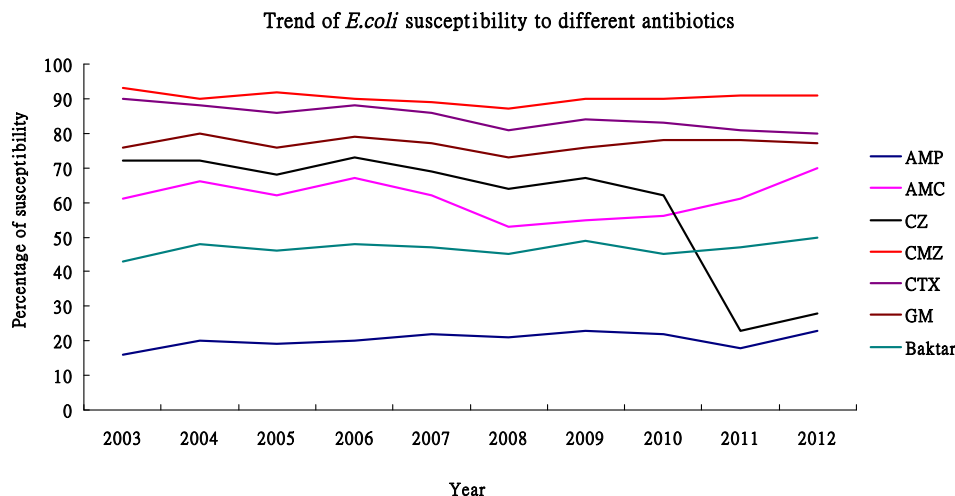


Figure 1. Drug susceptibility trend of *Escherichia coli* from 2003 to 2012. *E. coli* is most susceptible to CMZ, followed by CTX, GM, CZ, AMC, Baktar and AMP. The susceptibility rate of *E. coli* to cefazolin dropped dramatically from 2010 to 2011 (from 62% to 23%, respectively). AMC = ampicillin–clavulanate; AMP = ampicillin; Baktar = trimethoprim–sulfamethoxazole; CZ = cefazolin; CMZ = cefmetazole; CTX = ceftriaxone; GM = gentamicin.

two cases received cefazolin alone and the response could not be analyzed due to limited sampling size. The response rate to different antibiotics was not significantly different among the three groups ($p = 0.90$).

Discussion

UTI is an important cause of fever in children. It will be of great help to decide the treatment plan and improve clinical outcome of UTI if the common uropathogens and the antibiotic susceptibility are available. We found that cefazolin sensitivity of *E. coli* was 62–73% during 2003–2010, but dropped to 23% in 2011 and 28% in 2012 after the new CLSI guideline (M100-S21)² was used. The average sensitivity rate of *E. coli* UTI to various antibiotics is as follows: cefmetazole, 90%; ceftriaxone, 85%; gentamicin, 77%; AMC, 61%; TMP–SMX, 47%; and ampicillin, 20%. The rate of ESBL is increasing by years (2–11%).

Cefazolin is a first-generation parenteral cephalosporin, which is excreted through the kidneys. Although the

resistance rate is increasing, it continues to remain as an important drug of choice for the treatment of acute UTI.⁵ A retrospective study of 338 children supports that cefazolin or cephalexin is an appropriate treatment method for community-acquired, first episode of symptomatic UTI.⁶ The successful treatment by cefazolin in uncomplicated UTI cases is because of higher drug concentration in the urine than in the blood. Our study provides more direct evidence that there is no difference in the treatment response with regard to the status of cefazolin sensitivity. For example, oral cephalexin had an overall response rate of 96% (25/24), with 100% (6/6) in the cefazolin-intermediate group and 90% (9/10) in the cefazolin-resistant group. Therefore, the susceptibility test result according to the new CLSI guideline (M100-S21), although has stricter criteria, is not the only standard to decide the choice of antibiotic treatment in patients with UTI. The discrepancy between antibiotics susceptibility rate and clinical response of UTI in our study raises the question of whether different criteria are required in different sites of infections. For example, the MIC criteria of pneumococcal

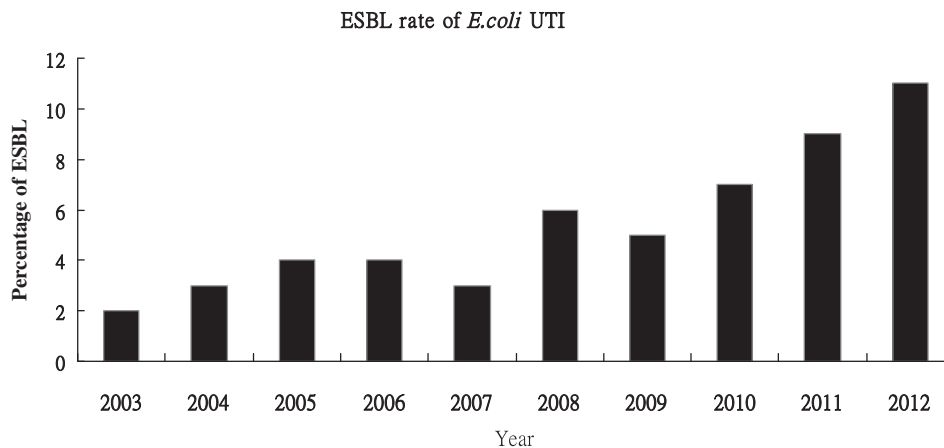


Figure 2. ESBL rate of *Escherichia coli* in children with UTI. The ESBL rate increased gradually from 2003 to 2012 ($p < 0.01$). ESBL = extended-spectrum beta-lactamase; UTI = urinary tract infection.

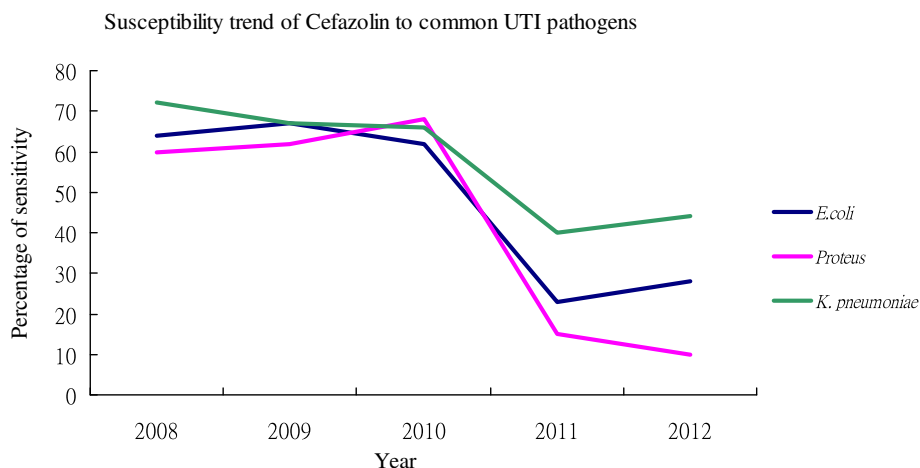


Figure 3. Drug-susceptibility trend of *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus* spp. to cefazolin from 2008 to 2012. Because of stricter criteria of the new CLSI guideline (M100-S20), all three common pathogens had similar trends of decreased susceptibility to cefazolin. CLSI = Clinical and Laboratory Standards Institute; UTI = urinary tract infection.

meningitis are different from pneumococcal bacteremia and pneumonia.^{1–3} Therefore, the MIC criteria for bacteremia and UTI may be different. Thus, we consider that the new CLSI guideline (M100-S21) may be the standard for bacteremia, but it may be too stern for UTI.

The impact of revised CLSI breakpoints on the susceptibility to third-generation cephalosporin among Enterobacteriaceae isolates in the Asia-Pacific region was investigated by the Study for Monitoring Antimicrobial Resistance Trends between 2002 and 2010.⁷ Enterobacteriaceae isolates in the study were obtained from intra-abdominal infections. Most Enterobacteriaceae, except *K. pneumoniae*, had decreased rates of susceptibility to ceftriaxone and ceftazidime during the study period.⁷ For *E. coli*, the total susceptibility rate to ceftriaxone was 70.2% according to the 2009 CLSI guideline and 50.5% according to the 2011 CLSI guideline.⁷ The trend of *E. coli* susceptibility rate is decreasing by years. If the CLSI 2009 criteria were used as the standard, the susceptibility rate to ceftriaxone was 86.1% in 2002 and 55.2% in 2010; if we use the CLSI 2010 criteria as the standard, the susceptibility rate to ceftriaxone was 82.7% in 2002 and 50.8% in 2010.⁷ The susceptibility is lower compared with our study (90% susceptibility rate of *E. coli* to ceftriaxone in 2003, and 83% susceptibility rate in 2010). Possible explanations are different focus of infection, and that strains from UTI

specimens may be less resistant compared with strains from intra-abdominal infection.

In another study, the epidemiology and antimicrobial susceptibility profiles of Gram-negative bacteria causing UTIs in the Asia-Pacific region during the period from 2009 to 2010 were evaluated.⁸ The susceptibility of *E. coli* to ceftazidime and cefotaxime was 68.7% and 54.6%, respectively, based on the CLSI 2012 guideline.⁹ In the CLSI 2011 criteria, the MIC range for cefazolin to Enterobacteriaceae was changed to a great extent, and it is hard to standardize 2009 and 2011 CLSI criteria because we do not have the original MIC data. However, the same trend of decreasing susceptibility rate is predictable.

One study in Greece compared the antibiotics susceptibility trend in community-acquired UTI between 2005 and 2010. Two periods (2005–2007 vs. 2008–2010) were compared and a significant increase in the resistance of *E. coli* isolates to beta-lactams, monobactams, aminoglycosides, quinolones, and co-trimoxazole was found.⁹

Another study evaluated the changing trend in antimicrobial resistance of pediatric uropathogens in Taiwan.¹⁰ A total of 368 isolates were obtained from urine samples between January 1991 and December 2005 in children < 18 years. The resistance rate of different antibiotics was compared in the early (1991–2000) and late (2001–2005) periods of the study. Ampicillin had a significant increasing resistance rate in the late period compared with the early period. However, resistance to co-trimoxazole, cephalothin, gentamicin, or nitrofurantoin was not different. In our study, 47% of *E. coli* was susceptible to TMP–SMX but only 20% to ampicillin, which may be not suitable for the treatment of UTI.

The rate of ESBL-producing *E. coli* is increasing by years. In our study, it was 2% in 2003, but increased to 11% in 2012. The rate of ESBL-producing Enterobacteriaceae comprised 28.2% of all isolates of Gram-negative bacteria causing UTI in the Asia-Pacific region.⁸ China is the area with highest ESBL *E. coli* prevalence rate (55.6%), whereas Taiwan had 11.5% in 2010.⁷ In North America, the rate of ESBL-producing *E. coli* in complicated UTI cases during 2009–2010 is 8.5%, and in Europe it was 17.6%.¹¹

Table 1 Comparison of *Escherichia coli* UTI clinical characteristics between the cefazolin-sensitive, cefazolin-intermediate, and cefazolin-resistant groups

Cefazolin susceptibility	Sensitive (N = 32)	Intermediate (N = 46)	Resistant (N = 41)	<i>p</i>
Inpatient	18 (56)	28 (61)	21 (51)	0.66
Abnormal echo	14 (44)	23 (50)	19 (46)	0.86
Bacteremia	2 (6)	4 (9)	3 (7)	0.92

Data are presented as *n* (%).

The three groups have similar clinical characteristics according to the percentage of inpatient, normal echo, or bacteremia.

UTI = urinary tract infection.

Table 2 Treatment response of different antibiotics among the cefazolin-sensitive, cefazolin-intermediate, and cefazolin-resistant groups of *Escherichia coli* UTI

Antibiotics/groups	Sensitive	Intermediate	Resistant	Total	<i>p</i>
Cefa	NA	1/1 (100)	1/1 (100)	2/2 (100)	NA
Cefa + GM	8/11 (73)	14/20 (70)	9/12 (75)	31/43 (72)	0.95
Amp + GM	3/5 (60)	5/6 (83)	2/5 (40)	10/16 (63)	0.32
Ulex	9/9 (100)	6/6 (100)	9/10 (90)	24/25 (96)	0.46
Total	20/25 (80)	26/33 (79)	21/28 (75)	67/86 (78)	0.90

Data are presented as *n* (%).

Amp = ampicillin; Cefa = cefazolin; GM = gentamicin; Ulex = cephalexin.

There are some limitations of this study. First, most urine samples were collected by urine bag technique or by voiding. The method to obtain the specimen is better through catheterization or suprapubic aspiration (SPA). SPA is the gold standard to diagnose UTI. However, SPA has lower success rates (60–66%), compared with catheterization (78–83%) in two randomized control trials.^{12,13} Urine culture from bag specimens is the easiest way to check for pathogens. The sensitivity is near 100%, but the specificity was shown to range between 14% and 84%.¹⁴ Second, we did not have the original MIC data and the standard of susceptibility is different prior to and after 2010. Third, we used cefazolin and gentamicin combination therapy most often as the first-line treatment, which makes treatment response evaluation difficult because gentamicin had 80% susceptibility rate in the treatment of UTI. The patient number included in the treatment response evaluation is few, and more cases are needed in future studies.

In conclusion, this is the first study to evaluate the susceptibility of *E. coli* to cefazolin after the CLSI 2010 criteria era to date. There is an increasing trend of ESBL-producing *E. coli*. In the past 2 years, the susceptibility of common urinary tract pathogens to cefazolin decreased dramatically, possibly due to the change in the CLSI guideline. However, the response rate of *E. coli* UTI to first-line empirical antibiotics remained well within ranges and showed no significant difference among the three groups based on cefazolin susceptibility (the cefazolin-sensitive, cefazolin-intermediate, or cefazolin-resistance groups). This result implicates that we may use cefazolin and gentamicin as the first-line treatment for children with UTI.

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

- Clinical and Laboratory Standards Institute (CLSI). *Performance standards for antimicrobial susceptibility testing; 19th informational supplement (CLSI document M100-S19)*. Wayne, PA: Clinical and Laboratory Standards Institute; 2009.
- Clinical and Laboratory Standards Institute (CLSI). *Performance standards for antimicrobial susceptibility testing; 21st informational supplement (CLSI document M100-S21)*. Wayne, PA: Clinical and Laboratory Standards Institute; 2011.
- Clinical and Laboratory Standards Institute (CLSI). *Performance standards for antimicrobial susceptibility testing; 20th informational supplement (CLSI document M100-S20)*. Wayne, PA: Clinical and Laboratory Standards Institute; 2010.
- Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics* 2011;128:595–610.
- Infectious Diseases Society of the Republic of China, Medical Foundation in Memory of Dr. Deh-Lin Cheng, Foundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and Education, Lee CY's Research Foundation for Pediatric Infectious Diseases and Vaccine. Guidelines for antimicrobial therapy of urinary tract infections in Taiwan. *J Microbiol Immunol Infect* 2000;33:271–2.
- Lu KC, Chen PY, Huang FL, Yu HW, Kao CH, Fu LS, et al. Is combination antimicrobial therapy required for urinary tract infection in children? *J Microbiol Immunol Infect* 2003;36:56–60.
- Huang CC, Chen YS, Toh HS, Lee YL, Liu YM, Ho CM, et al. Impact of revised CLSI breakpoints for susceptibility to third-generation cephalosporins and carbapenems among Enterobacteriaceae isolates in the Asia-Pacific region: results from the Study for Monitoring Antimicrobial Resistance Trends (SMART), 2002–2010. *Int J Antimicrob Agents* 2012;40S:54–10.
- Lu PL, Liu YC, Toh HS, Lee YL, Liu YM, Ho CM, et al. Epidemiology and antimicrobial susceptibility profiles of Gram-negative bacteria causing urinary tract infections in the Asia-Pacific region: 2009–2010 results from the Study for Monitoring Antimicrobial Resistance Trends (SMART). *Int J Antimicrob Agents* 2012;40S:537–43.
- Maraki S, Mantadakis E, Michailidis L, Samonis G. Changing antibiotic susceptibilities of community-acquired uropathogens in Greece, 2005–2010. *J Microbiol Immunol Infect* 2012;46:202–9.
- Tseng MH, Lo WT, Lin WJ, Teng CS, Chu ML, Wang CC. Changing trend in antimicrobial resistance of pediatric uropathogens in Taiwan. *Pediatr Int* 2008;50:797–800.
- Hoban DJ, Lascos C, Nicolle LE, Badal R, Bouchillon S, Hackel M, et al. Antimicrobial susceptibility of Enterobacteriaceae, including molecular characterization of extended-spectrum beta-lactamase-producing species, in urinary tract isolates from hospitalized patients in North America and Europe: results from the SMART study 2009–2010. *Diagn Microbiol Infect Dis* 2012;74:62–7.
- Kozer E, Rosenbloom E, Goldman D, Lavy G, Rosenfeld N, Goldman M. Pain in infants who are younger than 2 months during suprapubic aspiration and transurethral bladder catheterization: a randomized, controlled study. *Pediatrics* 2006;118:e51–6.
- El-Naggar W, Yiu A, Mohamed A, Shah V, Manley J, McNamara P, et al. Comparison of pain during two methods of urine collection in preterm infants. *Pediatrics* 2010;125:1224–9.
- Downs SM. Technical report: urinary tract infections in febrile infants and young children. The Urinary Tract Subcommittee of the American Academy of Pediatrics Committee on Quality Improvement. *Pediatrics* 1999;103:e54.