

RISK FACTORS AND CLINICAL OUTCOMES OF FEBRILE URINARY TRACT INFECTION FROM CEFTRIAXONE-RESISTANT ENTEROBACTERACEAE IN CHILDREN

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Abstract

Background: Febrile urinary tract infection (FUTI) is one of the most common bacterial infections in children. It is a major cause of hospitalization and long-term renal complications, with Enterobacteriaceae being the main pathogens. Third-generation cephalosporins, particularly ceftriaxone, are widely used as first-line empirical antibiotics because of their broad-spectrum activity. Previous studies have shown that the prevalence of ceftriaxone-resistant Enterobacteriaceae is increasing both domestically and internationally. However, these studies have reported inconsistent findings regarding differences in clinical manifestations and treatment outcomes between ceftriaxone-resistant and ceftriaxone-susceptible FUTI.

Methods: We conducted a retrospective cohort study of pediatric patients diagnosed with Enterobacteriaceae-associated FUTI at Naresuan University Hospital, a tertiary hospital in the lower northern part of Thailand, from November 1, 2018, to October 31, 2024. Patients were categorized into ceftriaxone-resistant and susceptible groups. We analyzed clinical data, laboratory findings, treatment outcomes, and post-infectious imaging.

Results: Of the 52 pediatric cases, *Escherichia coli* was the most common pathogen (86.5%), with 77.8% ceftriaxone sensitivity. Patients with previous antibiotic use within 3 months and a history of hospitalization tended to have ceftriaxone resistance, though the difference was not significant. Moreover, patients with ceftriaxone-resistant FUTI had longer hospital stays and longer durations of intravenous antibiotic therapy; however, these differences were not statistically significant. Patients with FUTI due to ceftriaxone-resistant Enterobacteriaceae were more likely to require a change in antibiotic therapy than those with FUTI due to ceftriaxone-susceptible Enterobacteriaceae.

Conclusion: There is no significant difference in risk factors and treatment outcomes between ceftriaxone-resistant and susceptible Enterobacteriaceae FUTI. This finding indicates that third-generation cephalosporins can be used as an appropriate empirical therapy for community-onset FUTI. However, patients with FUTI should be promptly switched to targeted antimicrobials based on sensitivity results if they deteriorate clinically.

Keywords: febrile urinary tract infection, ceftriaxone-resistant Enterobacteriaceae, antibiotic resistance, prevalence, risk factors, clinical outcomes

J Southeast Asian Med Res 2026; 10: e0297

<https://doi.org/10.55374/jseamed.v10.297>

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Received: 3 April 2026

Revised: 9 August 2026

Accepted: 17 August 2026

Introduction

Febrile urinary tract infections (FUTI) are among the most common bacterial infections in children, often leading to short-term life-threatening complications such as sepsis and long-term complications like chronic kidney disease. *Escherichia coli*, a Gram-negative enteric bacterium in the family Enterobacteriaceae, is the primary pathogen causing FUTI (80–90%).^(1, 2) Numerous studies have identified risk factors for FUTI; however, a growing concern in clinical practice is the increasing prevalence of FUTI caused by multidrug-resistant (MDR) organisms (86.1%), particularly those caused by extended-spectrum beta-lactamase (ESBL) -producing bacteria, with the overall prevalence of 33.75% and the prevalence in first and recurrent episodes of FUTI of 27.3% and 46.5%, respectively.⁽³⁻⁶⁾ These resistant pathogens pose a significant therapeutic challenge because they substantially reduce the effectiveness of third-generation cephalosporins, which remain the standard empirical therapy.⁽⁷⁾

Research across various countries indicates a marked increase in antibiotic-resistant FUTI cases.^(5, 7) There were several risk factors for MDR febrile FUTI, such as recurrent UTIs, antibiotic use in the last three months, and hospitalization in the last six months. Furthermore, patients infected with resistant bacteria often require prolonged intravenous antibiotic therapy and an extended hospital stay, resulting in considerably higher healthcare costs.⁽⁷⁻⁹⁾

Antibiotics of choice depend on several factors, including local bacterial sensitivity patterns, infection severity, urinary tract structural and functional abnormalities, recurrent UTI, continuous antibiotic prophylaxis, and antibiotic use in the past 30 days.^(10, 11) Despite the increasing prevalence of FUTI due to third-generation cephalosporin-resistant bacteria and empirical antibiotic discordance, most patients improved clinically, and therapy escalation was minimal.⁽¹²⁾ We conducted this study to enhance our understanding of the prevalence of FUTI

due to third-generation cephalosporin-resistant bacteria, as well as the clinical differences in initial presentations, future complications, and the antimicrobial agents administered and their effectiveness.

Methods

This retrospective cohort study was conducted at Naresuan University Hospital, a medical school and tertiary care center in the lower north of Thailand, from November 2018 to October 2024. Approval was granted by the Institutional Review Board of Naresuan University, Phitsanulok, Thailand, under project number P3-0103/2566. This study was a retrospective observational study; informed consent was not obtained.

Patient characteristics

Pediatric patients from 1 month to 15 years of age who were diagnosed with the first episode of community-acquired FUTI with a positive urine culture were enrolled in this study. We excluded several patients who had immunodeficiency status, cancers, congenital anomalies of the kidneys and urinary tract (CAKUT), or concurrent systemic infections during hospitalization.

Data collection

Both paper and electronic medical records of the participants were reviewed. demographic data including age and sex, clinical data such as underlying diseases, presence of phimosis in male or labial adhesion in female, presence of bacteremia, use of antibiotics within 3 months, history of continuous antibiotic prophylaxis for UTI, history of hospitalization within the past 30 days and history of recurrent UTI and laboratory data like urine analysis, urine culture results along with antibiotic susceptibility of pathogenic bacteria, hemoglobin concentration, white blood cell count, platelet count, inflammatory markers, renal function tests, and blood culture. We also reviewed imaging studies, including renal

bladder ultrasonography and voiding cystourethrogram (VCUG), for CAKUT, particularly vesicoureteral reflux (VUR). The severity of VUR was thereby graded I-V using the International Reflux Study Classification based upon the urinary tract's particular appearance on a contrast VCUG.⁽¹³⁾

The primary outcome was the clinical response to empirical antibiotic therapy comparing patients with FUTI due to ceftriaxone-resistant and ceftriaxone-susceptible Enterobacteriaceae. Representative variables of clinical response included duration of fever after antibiotic administration, escalation of therapy, duration of intravenous antibiotic therapy, length of hospital stay, and recurrent UTIs within 2 weeks after discharge. The secondary outcome was to identify risk factors for FUTI due to ceftriaxone-resistant Enterobacteriaceae.

Definitions

In this study, FUTI was diagnosed based on clinical manifestations and laboratory results including fever $\geq 38^{\circ}\text{C}$, presence of pyuria defined as white blood cell ≥ 5 cells per high-power field (HPF) from centrifuged urine or ≥ 10 cells/ μL in uncentrifuged urine, or positive leukocyte esterase test, or positive nitrite test; and positive urine culture defined as a single uropathogen $\geq 50,000$ colony-forming units (CFU)/mL in the absence of pyuria or $\geq 10,000$ CFU/mL in the presence of pyuria with sterile catheterization, or $\geq 100,000$ CFU/mL with midstream clean-catch. (14) In this study, community-onset infection was defined as an infection in patients who had not been hospitalized within 90 days before urine collection.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing for bacteria was performed at the clinical microbiology

laboratory unit using the disk diffusion method, following interpretation criteria outlined in the Clinical and Laboratory Standards Institute (CLSI) M100, 34th edition.⁽¹⁵⁾ Only multidrug-resistant organisms (MDR) and carbapenem-resistant Enterobacteriaceae (CRE) were reported as resistant pathogens. All isolates from the Enterobacteriaceae group underwent ceftriaxone susceptibility testing by disk diffusion, with interpretation based on the CLSI zone diameter criteria: ≥ 23 mm was interpreted as susceptible, 20–22 mm as intermediate, and ≤ 19 mm as resistant.

Statistical analysis

Categorical variables were presented as frequencies and percentages. Continuous variables with a normal distribution were reported as mean and standard deviation, while continuous variables with a non-normal distribution were described using the median and interquartile range. For analytic statistics, categorical variables were analyzed using Fisher's exact probability test. Continuous variables with a normal distribution were analyzed using the Independent Student's t-test, while those with a non-normal distribution were analyzed using the Mann-Whitney U test. Statistical significance was set at 0.05, with a 95% confidence interval.

Results

A total of 85 participants were identified as first-episode FUTI. Of these, 33 were excluded based on the following criteria: non-Enterobacteriaceae FUTI ($n = 18$), known CAKUT ($n = 12$), immunocompromised patients ($n = 6$), and patients with concurrent systemic infections ($n = 9$). We enrolled 52 participants (22 males and 30 females) (**Figure 1**). These participants were divided into 2 groups based on drug sensitivity: the ceftriaxone-susceptible group ($n = 42$) and the ceftriaxone-resistant group ($n = 10$).

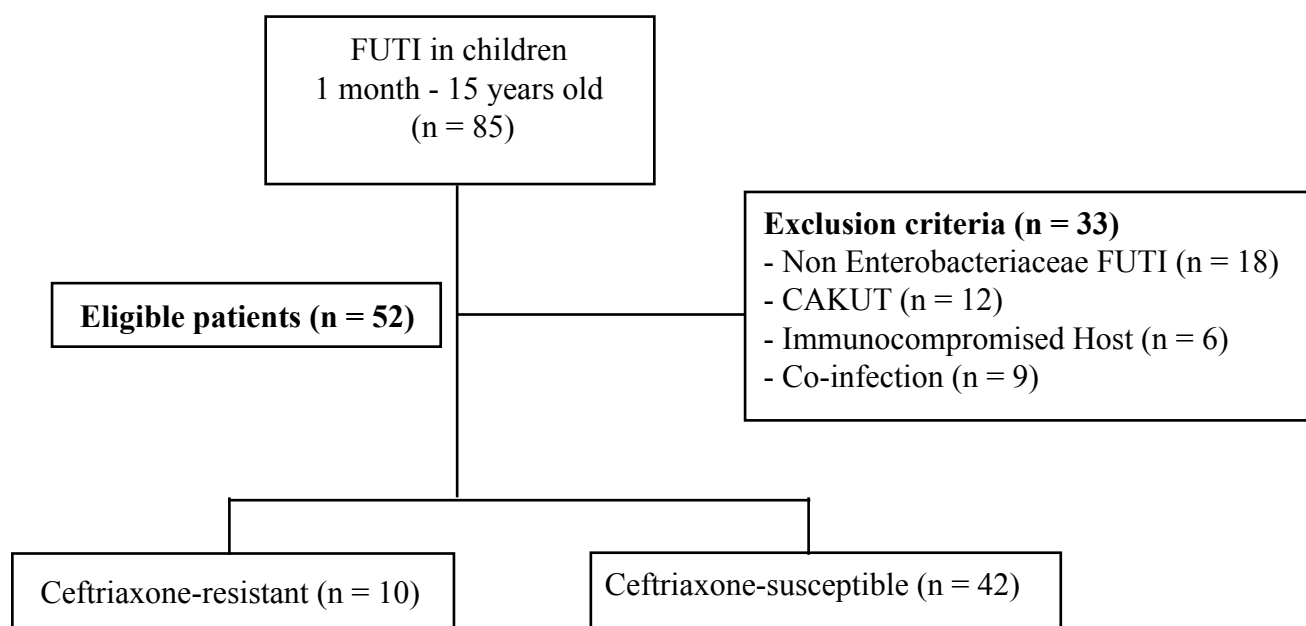


Figure 1. Patient enrollment flow diagram.

The median age (IQR) of the participants was 33.54 months (6-43 months), with a minimum age of 1 month and a maximum age of 13.9 years. Females and males were in equal proportions in the ceftriaxone-resistant and ceftriaxone-susceptible groups. **Table 1** demonstrates demographic data and clinical characteristics of FUTIs in the ceftriaxone-susceptible and ceftriaxone-resistant groups.

Laboratory findings

E. coli was the most common pathogen causing

FUTI, accounting for 86.5%. The prevalence of FUTIs due to ceftriaxone-resistant Enterobacteriaceae was 19.2%. The median (IQR) CRP level was 72.85 mg/dL (49.29, 140.7) in the ceftriaxone-susceptible group, significantly higher than the ceftriaxone-resistant group (12.51 mg/dL (0.84, 24.17)), $p = 0.035$. There were only 4 episodes of FUTIs among ceftriaxone-susceptible Enterobacteriaceae with bacteremia (7.69%). **Table 2** shows other laboratory results.

Table 1. Demographic data and clinical characteristics of children with FUTI

	Ceftriaxone-resistant Enterobacteriaceae FUTI		<i>p</i> -value
	Yes (n=10)	No (n=42)	
Age			
1 - 2 months, n (%)	0	2 (4.8)	1.000
> 2 months – 1 year, n (%)	4 (40)	20 (47.6)	0.736
> 1 – 5 years, n (%)	5 (50)	12 (28.6)	0.264
> 5 – 15 years, n (%)	1 (10)	8 (19)	0.670
Gender			
Male, n (%)	5 (50)	17 (40.5)	0.725
Female, n (%)	5 (50)	25 (59.5)	0.725

Table 1. Demographic data and clinical characteristics of children with FUTII (Cont.)

	Ceftriaxone-resistant Enterobacteriaceae FUTII		<i>p</i> -value
	Yes (n=10)	No (n=42)	
Highest body temperature (°C)	39.5 ± 1.05	39.36 ± 0.96	0.728
38 – < 39 °C, n (%)	2 (20)	13 (31)	0.704
≥ 39 °C, n (%)	5 (50)	20 (47.6)	1.000
Clinical manifestations			
Constipation, n (%)	1 (10)	9 (21.4)	0.664
Diarrhea, n (%)	3 (30)	11 (26.2)	1.000
Nausea and vomiting, n (%)	4 (40)	11 (26.2)	0.448
Non-renal comorbidities, n (%)	5 (50)	8 (19)	0.097
Phimosis, n (%)	2 (40)	10 (58.8)	1.000
Labial adhesion, n (%)	0	2 (8)	1.000
Previous antibiotic use within 3 months, n (%)	2 (20)	3 (7.1)	0.242
Previous hospitalization within 30 days, n (%)	1 (10)	2 (4.8)	0.481

Table 2. Laboratory investigations and imaging

	Ceftriaxone-resistant Enterobacteriaceae FUTII		<i>p</i> -value
	Yes (n=10)	No (n=42)	
Urine Analysis			
Nitrite, n (%)	4 (40)	12 (28.6)	0.475
Leukocyte, n (%)	10 (100)	42 (100)	N/A
Red blood cell, median (IQR)	10 (3, 10)	10 (3, 10)	0.991
White blood cell (cells/HPF), median (IQR)	75 (30, 300)	100 (30, 200)	0.897
< 100, n (%)	7 (70)	25 (59.5)	0.541
≥ 100, n (%)	3 (30)	17 (40.5)	0.541
Serum Analysis			
Hemoglobin (g/dL), mean ± SD	11.46 ± 1.46	11.41 ± 2.12	0.949
White blood cell (10 ³ /μL), median (IQR)	14.28 (12.32, 19.12)	16.11 (13.63, 19.33)	0.531
Absolute neutrophil count (10 ³ /μL), median (IQR)	10.51 (7.91, 12.07)	10.55 (7.06, 13.42)	0.871
Platelet count (10 ³ /μL), median (IQR)	305 (243, 449)	379 (264, 484)	0.457
C-reactive protein (mg/L), median (IQR)	12.51 (0.84, 24.17)	72.85 (49.29, 140.7)	0.035
Blood urea nitrogen (mg/dL), median (IQR)	7.35 (5.7, 11.1)	7.2 (4.5, 10.8)	0.612
Creatinine (mg/dL), median (IQR)	0.24 (0.21, 0.38)	0.29 (0.23, 0.44)	0.390
Positive hemoculture, n (%)	0	4 (9.5)	0.576
Imaging			
RBUS performed, n (%)	8 (80)	30 (71.4)	0.710
Abnormal RBUS, n (%)	1 (10)	5 (11.9)	1.000
VCUG, n (%)	0	3 (7.1)	1.000

Table 2. Laboratory investigations and imaging (Cont.)

	Ceftriaxone-resistant Enterobacteriaceae FUTI		<i>p</i> -value
	Yes (n=10)	No (n=42)	
No reflux	0	3 (7.1)	1.000
Low-grade reflux (grade 1-3)	0	2 (4.8)	1.000
High-grade reflux (grade 4-5)	0	1 (2.4)	1.000

Tc-99m DMSA, Tc-99m dimercaptosuccinic acid renal scan; HPF, high power field; RBUS, renal and bladder ultrasound; VCUG, voiding cystourethrography

Antibiotic administration and outcomes

Ceftriaxone was the most used antibiotic in FUTI (96.15%). The antibiotic-switching rate was 50% in the ceftriaxone-resistant group, significantly higher than in the ceftriaxone-susceptible group ($p=0.004$). Two common reasons for antibiotic switching were persistent fever after empirical antibiotic administration (71.4%) and sensitivity results (28.5%). **Table 3** shows antibiotic treatment and outcomes.

The antimicrobial susceptibility analysis of *E. coli* revealed variable resistance patterns across different antibiotic classes. Amikacin exhibited high efficacy, with a susceptibility rate of

97.8%. Carbapenems, including ertapenem, imipenem, and meropenem, as well as netilmicin, demonstrated complete activity (100% susceptibility). Ceftriaxone, a third-generation cephalosporin and the drug of choice for FUTI, showed moderate activity with a 77.8% susceptibility rate, while cefotaxime and ceftazidime showed susceptibility rates of 77.8% and 82.2%, respectively. Trimethoprim-sulfamethoxazole displayed limited effectiveness, with only 42.2% of isolates being susceptible. These highlight the high resistance to several first-line agents and emphasize the importance of local susceptibility patterns in guiding empirical antibiotic selection (**Figure 2**).

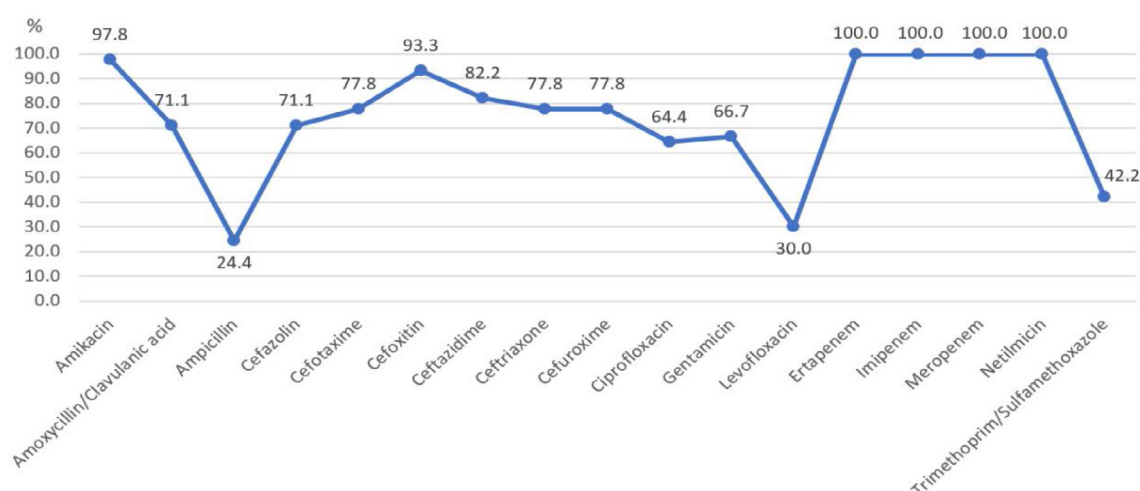
Table 3. Antibiotic treatment and clinical outcomes

	Ceftriaxone-resistant Enterobacteriaceae FUTI		<i>p</i> -value
	Yes (n=10)	No (n=42)	
IV antibiotic duration (days), median (IQR)	5.5 (3, 7)	3 (2, 5)	0.093
IV and PO antibiotic duration (days), median (IQR)	14 (7, 14)	11 (9, 14)	0.784
Duration of fever after initial antibiotic (hours), n (%)			
< 24 hours	2 (20)	15 (35.7)	0.467
24 - < 48 hours	2 (20)	3 (7.1)	0.242
48 - < 72 hours	3 (30)	4 (9.5)	0.120
≥ 72 hours	0	5 (11.9)	0.569
Empirical intravenous antibiotics, n (%)			
ceftriaxone	10 (100)	40 (95.2)	1.000
cefotaxime	0	2 (4.8)	1.000
Antibiotic switching, n (%)	5 (50)	3 (7.1)	0.004
Reasons for antibiotic switching			
persistent fever > 72 hours, n (%)	3 (30)	2 (4.8)	0.043
according to antibiotic sensitivity results, n (%)	2 (20)	0	0.034
Length of hospital stay (days), median (IQR)	7 (5, 8)	6 (4, 6)	0.161
Relapse in 2 weeks, n (%)	0	1 (2.4)	1.000

Table 3. Antibiotic treatment and clinical outcomes (Cont.)

	Ceftriaxone-resistant Enterobacteriaceae FUTI		<i>p</i> -value
	Yes (n=10)	No (n=42)	
Recurrence, n (%)	3 (30)	7 (16.7)	0.382
PICU admission, n (%)	1 (10)	0	0.192

IV, Intravenous; PO, per oral

Figure 2. Antimicrobial susceptibility of *Escherichia coli*

Discussion

This retrospective cohort study showed that *E. coli* was the predominant urinary pathogen in both resistant and susceptible strains, consistent with previous literature citing *E. coli* as the leading uropathogen in children.⁽¹⁶⁻¹⁷⁾ A systematic review and meta-analysis on the prevalence of urinary tract infection caused by ESBL-producing Enterobacteriaceae, which included 16 studies conducted between 1996 and 2014 from various countries worldwide, found a prevalence of 14% (95% CI 8, 21). The prevalence of FUTI from cephalosporin-resistant Enterobacteriaceae in this study was 19.2%, consistent with 2 studies from Bangkok, Thailand, during 2006–2019, which reported a prevalence of 19–20%, reflecting a stable trend.⁽¹⁶⁾ Most studies have found that the ESBL-producing Enterobacteriaceae commonly causing urinary tract infections are *E. coli* and *K. pneumoniae*. Some studies have reported that the ESBL-producing Enterobacteriaceae responsible for urinary tract infections consist only of *E. coli* or *K. pneumoniae*. In our study, the

cephalosporin-resistant Enterobacteriaceae identified were *E. coli* (100%).

Age, sex, symptoms such as diarrhea, nausea, and vomiting, and clinical signs including fever and phimosis could not predict cephalosporin-resistant Enterobacteriaceae FUTI. This finding is consistent with the study conducted in Thailand, which also reported that age and sex were not predictive factors for cephalosporin-resistant Enterobacteriaceae FUTI.⁽⁶⁾ Previous studies demonstrated that a history of UTI, previous antibiotic use within 30–90 days, and VUR predispose children to infection with ESBL-producing Enterobacteriaceae.^(16, 18) Although the difference did not reach statistical significance, a higher proportion of patients in the resistant group were aged 1–5 years (50%) and had prior antibiotic exposure within the preceding 3 months (20%). These findings, although limited by the small sample size, are consistent with previous evidence indicating that prior antibiotic use is a risk factor for antimicrobial resistance.

C-reactive protein (CRP), an acute-phase reactant produced by the liver during inflammation or infection, has high sensitivity for detecting gram-negative septicemia in neonates.⁽¹⁹⁾ CRP is also a predictor of significant gram-negative bacteriuria in young children, especially in those less than 2 years of age.⁽²⁰⁾ In this study, the sensitivity of CRP as a predictor of gram-negative FUTI was 62.5% using a cut-off value of 60 mg/dL. Unfortunately, the number of patients with cephalosporin-resistant Enterobacteriaceae FUTI was relatively small, with only 2 out of 10 patients having CRP measurements. Therefore, we could not determine whether CRP could serve as a reliable indicator of UTI from cephalosporin-resistant Enterobacteriaceae. Further research with a larger sample size is warranted to clarify whether CRP can serve as a predictive marker for UTI associated with cephalosporin-resistant Enterobacteriaceae.

Our study also showed no statistically significant differences in length of hospital stay, time to defervescence after initial antibiotic use, rates of recurrence and relapse, or PICU admission rates between patients with cephalosporin-resistant Enterobacteriaceae FUTI and those with cephalosporin-susceptible Enterobacteriaceae FUTI. Carbapenems, especially ertapenem, are a first-line therapy for ESBL-producing Enterobacteriaceae FUTI.⁽²¹⁾ The study from South Korea demonstrated no significant difference in outcomes such as time to defervescence and relapse rate in patients with FUTI due to ESBL-producing Enterobacteriaceae treated with carbapenem and non-carbapenem antibiotics. The proposed reason for the clinical response in patients treated with antimicrobials to which ESBL-producing Enterobacteriaceae are not susceptible is the high concentrations of these agents excreted in the urine.⁽²²⁾ After a single 1,000-mg intravenous injection, the urinary concentration of ceftriaxone was three times higher than the serum concentration. In addition, the urinary concentration exceeded the minimum inhibitory concentration of 4 µg/mL by tenfold.⁽¹⁷⁾ This highlights that third-generation cephalosporins, especially ceftriaxone, can be used as empirical

therapy for children with FUTI in our center. A systematic review and meta-analysis of the prevalence of ESBL-producing Enterobacteriaceae in pediatric urinary tract infections found that UTIs caused by ESBL-producing Enterobacteriaceae are associated with increased hospital length of stay.⁽¹⁶⁾ In this study, patients with FUTI due to ceftriaxone-resistant Enterobacteriaceae were more likely to require a change in antibiotic therapy than those with FUTI due to ceftriaxone-susceptible Enterobacteriaceae. Consequently, patients with FUTI should be closely monitored for clinical deterioration after administration of an empirical antimicrobial and promptly switched to targeted antimicrobials based on sensitivity results if deterioration occurs.

Nonetheless, this study is limited by its small sample size, particularly in the resistant group, which may limit the detection of significant differences across several variables. Additionally, the single-center design limits the generalizability of the findings.

Conclusion

Our study emphasized the clinical significance of ceftriaxone-resistant Enterobacteriaceae in pediatric FUTI, with *E. coli* as the predominant causative organism. 22.7% of *E. coli* strains were resistant to ceftriaxone, posing a challenge to empirical antibiotic selection.

Demographic, clinical characteristics, and outcomes did not differ significantly between patients with ceftriaxone-resistant and ceftriaxone-susceptible Enterobacteriaceae FUTI. Therefore, ceftriaxone can be used as an appropriate empirical therapy for children with FUTI. Clinical response should be closely monitored, and patients with ceftriaxone-resistant Enterobacteriaceae FUTI should promptly receive antimicrobial switching if clinical response is not achieved within 72 hours following the initial antimicrobial.

Declaration of conflict of interest

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Acknowledgement

This research received financial support from the Faculty of Medicine, Naresuan University Hospital, Phitsanulok, Thailand.

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