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Use of cefuroxime for women with community-onset acute pyelonephritis caused by cefuroxime-susceptible or -resistant *Escherichia coli*

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Background/Aims: Efforts to decrease the use of extended-spectrum cephalosporins are required to prevent the selection and transmission of multi-drug resistant pathogens, such as extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae. The objectives of this study were to assess the clinical efficacy of intravenous cefuroxime as an empirical antibiotic for the treatment of hospitalized women with acute pyelonephritis (APN) caused by *Escherichia coli*.

Methods: We analyzed the clinical and microbiologic database of 328 hospitalized women with community-onset APN.

Results: Of 328 women with APN, 22 patients had cefuroxime-resistant *E. coli* APN, and 306 patients had cefuroxime-susceptible *E. coli* APN. The early clinical success rates were significantly higher (p = 0.001) in the cefuroxime-susceptible group (90.8%, 278/306) than in the cefuroxime-resistant group (68.2%, 15/22) at 72 hours. The clinical cure rates at 4 to 14 days after completing antimicrobial therapy were not significantly different in the cefuroxime-resistant or -susceptible groups, with 88.2% (15/17) and 97.8% (223/228; p = 0.078), respectively. The microbiological cure rates were not significantly different and were 90.9% (10/11) and 93.4% (128/137), respectively (p =0.550). The median duration of hospitalization in the cefuroxime-resistant and -susceptible groups was 10 days (interquartile range [IQR], 8 to 13) and 10 days (IQR, 8 to 14), respectively (p=0.319).

Conclusions: Cefuroxime, a second-generation cephalosporin, can be used for the initial empirical therapy of community-onset APN if tailored according to uropathogen identification and susceptibility results, especially in areas where the prevalence rate of ESBL-producing uropathogens is low.

Keywords: Cefuroxime; Acute pyelonephritis; Escherichia coli

INTRODUCTION

Acute pyelonephritis (APN) is one of the most common community-onset infections, and *Escherichia coli* is the most common etiologic organism in community-onset urinary tract infections (UTIs). Cefuroxime is an effective, second-generation cephalosporin antibiotic against Enterobacteriaceae species [1-3].

Since the introduction of third-generation cephalosporins such as cefotaxime and ceftriaxone, extended-spectrum β-lactam antibiotics have been recommended for treating community-onset APN in women, located in areas where the prevalence of fluoroquinolone resistance is relatively high [4,5]. However, efforts

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to decrease the use of third-generation cephalosporins are also required to prevent the selection and transmission of multidrug resistant pathogens, such as extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae.

Hospitalized women with APN may require the administration of intravenous antimicrobial agents. In this study, we administered the second-generation cephalosporin cefuroxime as the initial antibiotic regimen in hospitalized APN patients from January 2001 to December 2010. This treatment was consistent with the Catholic University St. Vincent's Hospital's antibiotic policy. This antibiotic policy was instituted to avoid the use of costly antibiotics with a broad spectrum of antibacterial activity, such as extended-spectrum cephalosporins, in managing hospitalized women with APN.

Cefuroxime has been used for the treatment of APN since the late 1970s. However, there have only been a limited number of clinical studies specifically investigating the administration of cefuroxime as an initial empirical antimicrobial agent to treat APN patients since the introduction of third-generation cephalosporin in the mid-1980s. Therefore, we conducted this study to assess and analyze the therapeutic efficacy of cefuroxime in treating APN. In this study, we analyzed the clinical and microbiologic data of 328 women with community-onset APN who were admitted to a single university hospital in Korea. We evaluated the therapeutic efficacy of cefuroxime as an initial empirical antimicrobial agent.

METHODS

Study design and patient population

This study was conducted retrospectively using medical records in a university-affiliated hospital. We gathered the data of all APN patients admitted to St. Vincent's Hospital from January 2001 to December 2010 and analyzed the clinical characteristics of APN patients treated with intravenous cefuroxime. The Institutional Review Board (IRB) of St. Vincent's Hospital, Suwon, South Korea examined and approved the clinical research protocol of this retrospective study (approval number VC13RISI0210). The IRB granted a waiver of informed consent in this retrospective chart review study.

We defined "APN" as the presence of fever (≥ 38.0°C), pyuria, and bacteriuria. Pyuria was defined as more than 5 to 10 leukocytes per high-power field upon microscopic examination of urine. Bacteriuria was defined as the presence of 10^5 or more of pathogenic bacteria per mL for clean voided urine or 10^4 or more pathogenic bacteria per mL for catheterized urine [6-10]. We also analyzed the presence of comorbid conditions (cerebrovascular disorder, chronic liver disease, chronic lung disease, chronic kidney disease, heart failure, autoimmune disorder, diabetes mellitus, malignancy, and menopause) and/or urinary tract abnormalities (renal calculi, vesicoureteral reflux, neurogenic bladder). We excluded the patients who had catheter-associated UTIs or who had an obstructive nephropathy demanding percutaneous nephrostomy, catheterization or surgery. We also excluded patients diagnosed with APN more than 48 hours after being admitted to the hospital.

Data collection

We gathered and analyzed the following information for all eligible patients by chart review: age, past medical records, comorbidities, UTI symptoms, physical signs of UTIs, clinical laboratory tests, duration of antimicrobial treatment, time to defervescence, length of hospitalization, and mortality.

Clinical outcome measures

We evaluated and determined the effectiveness of cefuroxime with respect to the following conditions: early clinical success, overall clinical outcome (clinical cure or failure), length of hospitalization, and time taken for defervescence of fever after starting antimicrobial therapy. Early clinical success was defined as the defervescence of fever with the improvement of UTI symptoms or signs within 72 hours after the initiation of intravenous cefuroxime therapy. The cases that did not fulfill the aforementioned criteria of early clinical success were considered to be early clinical failures. A clinical cure was defined by the absence of clinical signs or symptoms suggesting UTI during a 4 to 14 days follow-up period after antimicrobial treatment [11]. A clinical failure was defined as the reappearance of UTI symptoms and/or signs within the 4 to 14 days follow-up period after completion of antimicrobial treatment or death. Defervescence of fever was defined

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as the afebrile state in which the body temperature remained at 37.0°C or below for more than 24 hours [7]. The time to defervescence was defined as the time from the beginning of intravenous cefuroxime therapy to an afebrile state. The patient's body temperatures were measured every 6 hours during the hospital admission using a tympanic thermometer.

Microbiologic data

Quantitative urine cultures were performed to identify the causative agents of UTI. Blood cultures were performed prior to the start of antimicrobial therapy. The etiological pathogens were confirmed by the presence of ≥ 10^4 colony forming unit/mL organisms isolated in urine cultures or by the identification of uropathogens from blood cultures [12,13]. The species identification and antibacterial susceptibility of the uropathogens were confirmed by either a semiautomated system (Microscan, DADE Behring, West Sacramento, CA, USA) or disk diffusion susceptibility tests. This approach is consistent with the criteria provided by the Clinical and Laboratory Standard Institute [14]. The minimum inhibitory concentration cutoff value for cefuroxime resistance was ≥ 16 mg/L.

Statistical methods

The categorical variables are expressed as numbers (percentage), and were compared using Fisher exact test or the Pearson chi-square test. The results of continuous variables are presented as the median (interquartile range [IQR]) and were analyzed by the Mann-Whitney test. A logistic regression analysis was conducted to estimate the effects of independent variables on clinical outcomes. A multivariate analysis was performed using logistic regression to determine the influences of independent variables on early clinical failure in the APN patients who were initially treated with intravenous cefuroxime. All *p* values were two-tailed and tests with a probability of less than 0.05 were considered as representing statistical significance. The data were analyzed using the SPSS version 21.0 (IBM Co., Armonk, NY, USA).

RESULTS

Demographic and clinical characteristics

We screened a total of 1,014 hospitalized women diagnosed with community-onset APN. There were 413 cases treated with cefuroxime as the initial antimicrobial agent. The remaining 601 cases received other antibiotics. Of the 413 patients treated with cefuroxime, 85 were excluded because they had a non-*E. coli* uropathogen, renal abscess, or other obstructive lesions requiring urological intervention. Thus, the study assessed a total of 328 cefuroxime-administered patients with community-onset APN due to *E. coli*.

Of the 328 patients, 22 had cefuroxime-resistant *E. coli* APN, and 306 had cefuroxime-susceptible *E. coli* APN. Table 1 shows a comparative demographic and clinical data of the cefuroxime-resistant and cefuroxime-susceptible groups. The median ages of the cefuroxime-resistant and cefuroxime-susceptible groups were 66 years (IQR, 61 to 71) and 64 years (IQR, 50 to 73), respectively (p = 0.534). The two groups showed no statistically significant differences in the following characteristics: initial body temperature, costovertebral angle tenderness, lower UTI symptoms, white blood cell counts, C-reactive protein (CRP) level, azotemia, hematuria, bacteremia, or age. The frequencies of comorbid conditions were not significantly different between the cefuroxime-resistant and -susceptible groups (Table 1).

Microbiological data

In this study, the cefuroxime susceptibility rate for the 328 *E. coli* isolates was 93.3%. This rate was not significantly different from 561 *E. coli* samples isolated from women who received other antibiotics (93.3% vs. 95.9%, p = 0.087). The antimicrobial resistance profiles of the 22 cefuroxime-resistant and 306 cefuroxime-susceptible *E. coli* isolates are displayed in Table 2. Cefuroxime-resistant *E. coli* were susceptible to less than 80.0% of various antibiotics with the exceptions of amikacin (95.5%), piperacillin/tazobactam (95.5%), and imipenem (100%). In the cefuroxime-resistant group, the *E. coli* susceptibilities to cefotaxime, ceftriaxone, ceftazidime, and cefepime were 27.3%, 29.4%, 63.6%, and 29.4%, respectively. Conversely, the susceptibilities of *E. coli* to cefotaxime, ceftriaxone, ceftazidime, and cefepime in the cefuroxime-susceptible group were 99.7%, 100%,

Table 1. Comparative demographic and clinical data of hospitalized patients with community-onset acute pyelonephritis according to the susceptibility to cefuroxime of the *Escherichia coli* strain

Characteristic	APN due to cefuroxime resistant *E. coli* (n = 22)	APN due to cefuroxime susceptible *E. coli* (n = 306)	*p* value
Demographic data			
Age, yr, median (IQR)	66 (61–71)	64 (50–73)	0.534[a]
Elderly ≥ 65 yr	14 (63.6)	149 (48.7)	0.176[b]
Comorbid condition			
Cerebrovascular disorders	3 (13.6)	26 (8.5)	0.428[b]
Chronic liver disease	0	18 (5.9)	0.621[b]
Chronic lung disease	1 (4.5)	13 (4.2)	> 0.999[b]
Chronic renal disease	2 (9.1)	21 (6.9)	0.660[b]
Congestive heart failure	1 (4.5)	23 (7.5)	> 0.999[b]
Connective tissue disorders	0	12 (3.9)	> 0.999[b]
Diabetes mellitus	9 (40.9)	111 (36.3)	0.663[b]
Malignancy	0	13 (4.2)	> 0.999[b]
Menopause	19 (86.4)	233 (76.1)	0.432[b]
Urinary tract condition			
Neurogenic bladder	3 (13.6)	15 (4.9)	0.111[b]
Urolithiasis	0	8 (2.6)	> 0.999[b]
Vesicoureteral reflux	0	4 (1.3)	> 0.999[b]
Clinical feature			
Body temperature, °C, median (range)	38.9 (38.0–40.3)	38.6 (38.0–40.7)	0.150[a]
Costovertebral angle tenderness	17 (77.3)	250 (81.7)	0.606[b]
Lower urinary tract infection symptoms	14 (63.6)	196 (64.1)	0.969[b]
Laboratory finding			
Bacteremia	8 (36.4)	84 (27.5)	0.369[b]
C-reactive protein, mg/dL, median (IQR)	12.3 (7.1–16.8)	12.0 (7.7–18.9)	0.938[a]
C-reactive protein ≥ 20 mg/dL	4 (18.2)	63 (20.6)	> 0.999[b]
Hematuria	11 (50.0)	181 (59.2)	0.400[b]
White blood cell counts, /mm^3, median (IQR)	11,815 (9,558–14,758)	11,755 (9,035–14,783)	0.803[a]
White blood cells ≥ 20,000/mm^3 of blood	1 (4.5)	22 (7.2)	> 0.999[b]
Past history			
Antibiotic use within 1 year	4/20[c] (20.0)	47/286[c] (16.4)	0.755[b]
Previous urinary tract infection history	4/20[c] (20.0)	54/287[c] (18.8)	> 0.999[b]
Prior history of hospitalization within 1 year	5/20[c] (25.0)	58/287[c] (20.2)	0.608[b]

Values are presented as number (%).
APN, acute pyelonephritis; IQR, interquartile range.
[a]Mann-Whitney *U* test.
[b]Pearson chi-square test or Fisher exact test.
[c]Denominators were the number of patients whose data were available in each group.

99.7%, and 100%, respectively. These values were all significantly higher than in the cefuroxime-resistant group.

There was no significant changes in the susceptibility rates of *E. coli* to cefuroxime observed between the 2001 to 2005 and 2006 to 2010 periods (92.9% in 2001 to 2005 vs. 93.5% in 2006 to 2010, $p = 0.820$). Additionally, there was also no significant change in the cefurox-

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Table 2. Other antimicrobial susceptibility of cefuroxime-resistant or -susceptible *Escherichia coli* from acute pyelonephritis patients

Antibiotic	Cefuroxime resistant *E. coli*				Cefuroxime susceptible *E. coli*			
	Resistant	Susceptible	Total	Susceptibility, %	Resistant	Susceptible	Total	Susceptibility, %
Amikacin	1	21	22	95.5	3	303	306	99.0
Ampicillin	18	1	19	5.3	139	97	236	41.1
Cephalothin	7	1	8	12.5	68	90	158	57.0
Cefotaxime	16	6	22	27.3	1	305	306	99.7
Ceftriaxone	12	5	17	29.4	0	220	220	100
Ceftazidime	8	14	22	63.6	1	305	306	99.7
Cefepime	12	5	17	29.4	0	219	219	100
Ciprofloxacin	10	12	22	54.5	42	264	306	86.3
Gentamicin	10	12	22	54.5	69	237	306	77.5
Imipenem	0	22	22	100	0	306	306	100
Levofloxacin	8	9	17	52.9	33	185	218	84.9
Piperacillin	12	1	13	7.7	110	85	195	43.6
SXT	16	6	22	27.3	105	201	306	65.7
Tobramycin	9	8	17	47.1	49	169	218	77.5
TZP	1	21	22	95.5	8	297	305	97.4

SXT, trimethoprim/sulfamethoxazole; TZP, piperacillin/tazobactam.

ime susceptibility rates of *E. coli* when the initial 2-year period was compared to the last 2-year period of this study (93.0% in 2001 to 2002 vs. 93.3% in 2009 to 2010, $p = 0.946$).

Clinical outcomes

The clinical outcomes were analyzed and compared between the cefuroxime-resistant and -susceptible groups (Table 3). The median duration of cefuroxime therapy was 7 days (IQR, 5 to 7) in the cefuroxime-resistant group and 7 days (IQR, 6 to 7) in the cefuroxime-susceptible group ($p = 0.461$). The total antimicrobial therapy was 14 days (IQR, 14 to 15) in the cefuroxime-resistant group and 14 days (IQR, 14 to 14) in the cefuroxime-susceptible group ($p = 0.125$). Finally, 245 of the 328 patients (74.7%) had follow-up at 4 to 14 days and 143 patients (43.6%) had follow-up at 28 to 42 days after the end of antibiotic treatment.

There were 8 of 22 patients (36.4%) in the cefuroxime-resistant group that changed to alternative intravenous therapy. There were three patients (13.6%), two (9.1%), two (9.1%), and one (4.5%) who switched to piperacillin/tazobactam, imipenem, gentamicin, and amikacin after 3 to 7 days of cefuroxime monotherapy. Among the eight patients, four had defervescence before transitioning into the alternative antibiotics, and four had defervescence after receiving alternative intravenous antibiotics. Fourteen of 22 patients (63.6%) in the cefuroxime-resistant group received continuing cefuroxime therapy. There were 12 patients (54.5%) and two (9.1%) with defervescence within 72 and 96 hours of cefuroxime therapy, respectively. Seven patients (2.3%) in the cefuroxime-susceptible group were switched to alternative intravenous therapy. There were four, two, and one cases in the cefuroxime-susceptible group switched to gentamicin, amikacin, and ceftriaxone after 3 to 6 days of cefuroxime therapy. After the intravenous antimicrobial therapy there were 18 patients (81.8%) in the cefuroxime-resistant group and 304 patients (99.3%) in the cefuroxime-susceptible group who changed to oral therapy. The early clinical response rates were 68.2% (15/22) and 90.8% (278/306) at 72 hours in the cefuroxime-resistant and -susceptible groups, respectively. These results indicate the clinical response rate was significantly higher in the cefuroxime-susceptible group ($p = 0.001$) (Table 3). The rates of defervescence were sig-

Table 3. Clinical outcomes of patients with acute pyelonephritis treated with intravenous cefuroxime as an initial empirical antibiotic

Variable	APN due to cefuroxime resistant *E. coli* (n = 22)	APN due to cefuroxime susceptible *E. coli* (n = 306)	*p* value
Dose of cefuroxime, mg/day	2,250	2,250	
Dosing type of cefuroxime	750 mg at 8 hr interval	750 mg at 8 hr interval	
Duration of cefuroxime, day, median (range)	7 (3–9)	7 (3–14)	0.461[a]
No. of cases with alternative intravenous antibiotics	8 (36.4)	7 (2.3)	< 0.001[b]
Alternative intravenous antibiotics			
Piperacillin/tazobactam	3	-	
Imipenem	2	-	
Gentamicin	2	4	
Amikacin	1	2	
Ceftriaxone	-	1	
Switch to oral antibiotics			
Amoxicillin	-	60	
Ciprofloxacin	8	24	
First cephalosporin	-	93	
Second cephalosporin	6	102	
Third cephalosporin	2	6	
Trimethoprim-sulfamethoxazole	2	17	
Amoxicillin/clavulanate	-	2	
Duration of oral antimicrobial Tx[c], day, median (range)	7 (0–9)	7 (0–10)	0.147[a]
The rate of defervescence, hr			
Within 24	0	18 (5.9)	0.621[b]
Within 48	7 (31.8)	154 (50.3)	0.093[b]
Within 72	15 (68.2)	278 (90.8)	0.001[b]
Within 96	18 (81.8)	295 (96.4)	0.013[b]
Within 120	18 (81.8)	300 (98.0)	0.002[b]
Over 120 hours or antibiotics change	4 (18.2)	6 (2.0)	0.002[b]
Time to defervescence, hr, median (range)	51.5 (39–70)	46 (38–68)	
Duration of hospital stay, day, median (range)	10 (8–13)	10 (8–14)	0.319[a]
Clinical cure at 4–14 days after the end of Tx[c]	15/17[d] (88.2)	223/228[d] (97.8)	0.078[b]
Microbiological cure at 4–14 days after Tx[c]	10/11[d] (90.9)	128/137[d] (93.4)	0.550[b]
Overall mortality	0	0	

Values are presented as number (%).
APN, acute pyelonephritis; *E. coli*, *Escherichia coli*; IQR, interquartile range.
[a]Mann-Whitney *U* test.
[b]Pearson chi-square test or Fisher exact test.
[c]Tx, overall therapy including alternative intravenous and oral antibiotics (tailored according to uropathogen identification and susceptibility results) as well as initial intravenous cefuroxime.
[d]Denominators were the number of patients whose data were available in each group.

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nificantly higher in the cefuroxime-susceptible group than in the cefuroxime-resistant group at both 96 hours and 120 hours (96.4% vs. 81.8% at 96 hours, and 98.0% vs. 81.8% at 120 hours; $p = 0.013$ and $p = 0.002$, respectively). However, the rates of defervescence at 24 and 48 hours were not significantly different between the cefuroxime-resistant and -susceptible groups, though higher rates of defervescence were noted in the latter (Table 3). The median time to defervescence was 51.5 hours (IQR, 39 to 70) and 46 (IQR, 38 to 68) in the cefuroxime-resistant and cefuroxime-susceptible groups, respectively. In the cefuroxime-susceptible group, the median time to defervescence in bacteremic and non-bacteremic APN patients was 55 hours (IQR, 43 to 70) and 45 (IQR, 36 to 65), respectively. The median length of hospital stay in the cefuroxime-resistant and cefuroxime-susceptible groups was 10 days (IQR, 8 to 13) and 10 (IQR, 8 to 14), respectively. The median hospital stay was not significantly different between the groups. There were no deaths or other complications in either the cefuroxime-resistant or -susceptible groups (Table 3). The clinical cure rates at the follow-up visit during the 4 to 14 days period following the end of antimicrobial therapy were not significantly different in the cefuroxime-resistant or -susceptible groups, 88.2% versus 97.8% (15/17 vs. 223/228, $p = 0.078$), and microbiological cure rates were also not significantly different in the two groups, 90.9% versus 93.4% (10/11 vs. 128/137, $p = 0.550$) (Table 3).

The clinical outcomes were also compared between the early clinical success and the early clinical failure groups (Table 4) after the completion of antimicrobial therapy, which included initial cefuroxime treatment, alternative intravenous and oral antibiotics that were tailored according to the susceptibility results of *E. coli* isolated from each patient. Among 328 women with APN, 293 cases were assigned to the early clinical success group and only 35 to the early clinical failure group. The clinical cure rates were 97.2% (208/214) and 96.8% (30/31) at the follow-up visit 4 to 14 days following the end of therapy in the respective groups ($p > 0.999$), and microbiological cure rates were 93.7% (119/127) and 90.5% (19/21) in the two groups, respectively ($p = 0.635$). Furthermore, the clinical cure rates were 89.3% (108/121) and 95.5% (21/22) at the follow-up visit 28 to 42 days after completion of antibacterial therapy in the early clinical success and early clinical failure groups, respectively ($p = 0.696$) (Table 4).

Risk factor analysis for early clinical failure

There were no significant differences in median age, proportion of elderly women, frequency of a prior history of hospitalization, previous history of UTI, or antibiotic usage before the hospital visit between the early clinical success and early clinical failure groups. The proportions of patients with a CRP level above 20 mg/dL in the blood and patients with bacteremia were significantly higher in the early clinical failure group ($p < 0.001$ and $p < 0.001$). Moreover, *in vitro* resistance of *E. coli* to cefuroxime was significantly higher in the early clinical failure group (20.0% vs. 5.1%, respectively; $p = 0.001$) (Table 4).

A multivariate analysis was conducted to determine the influences of independent variables on early clinical failure in APN patients initially treated with intravenous cefuroxime (Table 5).

The variables analyzed included bacteremia, CRP level, chronic liver disease, and uropathogen resistant to cefuroxime. Bacteremia, CRP level ≥ 20 mg/dL, presence of chronic liver disease, and uropathogen resistant to cefuroxime differed significantly between groups with $p < 0.001$, $p < 0.001$, $p < 0.006$, and $p < 0.001$, respectively (Table 5).

DISCUSSION

Cefuroxime has been used to treat UTIs due to Enterobacteriaceae since its introduction in the late 1970s [1-3]. Extended-spectrum β-lactam antibiotics have also been prescribed as empirical antibiotics for the treatment of patients with community-acquired APN. Several clinical studies showed that cefuroxime was inferior to extended-spectrum cephalosporins in treating pneumococcal bacteremia [15]. However, the use of extended-spectrum cephalosporins might cause the selection and transmission of multidrug resistant pathogens, such as ESBL-producing Enterobacteriaceae [16-19]. In this study, we investigated cases where cefuroxime was used as the initial empirical antimicrobial agent in hospitalized women with APN. We also assessed the efficacy of cefuroxime and the influence of cefuroxime resistance of uropathogens on clinical out-

Table 4. Comparison of the clinical characteristics of early clinical success and failure groups in the acute pyelonephritis patients treated with empirical cefuroxime

Characteristic	Early clinical failure group at 72 hours (n = 35)	Early clinical success group at 72 hours (n = 293)	*p* value
Demographic data			
Age, yr, median (IQR)	64 (49–71)	65 (51–73)	0.521[a]
Elderly ≥ 65 yr	15 (42.9)	148 (50.5)	0.392[b]
Comorbid condition			
Cerebrovascular disorders	2 (5.7)	27 (9.2)	0.753[b]
Chronic liver disease	5 (14.3)	13 (4.4)	0.016[b]
Chronic lung disease	1 (2.9)	13 (4.4)	> 0.999[b]
Chronic renal disease	1 (2.9)	22 (7.5)	0.489[b]
Congestive heart failure	2 (5.7)	22 (7.5)	> 0.999[b]
Connective tissue disorders	1 (2.9)	11 (3.8)	> 0.999[b]
Diabetes mellitus	15 (42.9)	105 (35.8)	0.415[b]
Malignancy	2 (5.7)	11 (3.8)	0.637[b]
Menopause	26 (74.3)	227 (77.5)	0.671[b]
Urinary tract condition			
Neurogenic bladder	3 (8.6)	15 (5.1)	0.423[b]
Urolithiasis	1 (2.9)	7 (2.4)	0.599[b]
Vesicoureteral reflux	0	4 (1.4)	> 0.999[b]
Clinical feature			
Body temperature, °C, median (range)	38.9 (38.0–40.3)	38.5 (38.0–40.7)	0.021[a]
Costovertebral angle tenderness	29 (82.9)	238 (81.2)	0.815[b]
Lower urinary tract infection symptoms	22 (62.9)	188 (64.2)	0.879[b]
Laboratory finding			
Bacteremia	21 (60.0)	71 (24.2)	< 0.001[b]
C-reactive protein ≥ 20 mg/dL on admission	16 (45.7)	51 (17.4)	< 0.001[b]
E. coli with extended spectrum β-lactamase	6 (17.1)	10 (3.4)	< 0.001[b]
Hematuria	24 (68.6)	168 (57.3)	0.202[b]
In vitro resistance to cefuroxime	7 (20.0)	15 (5.1)	0.001[b]
White blood cells ≥ 20,000/mm^3 of blood	4 (11.4)	19 (6.5)	0.288[b]
Past history			
Antibiotic use within 1 year	4/34[c] (11.8)	47/272[c] (17.3)	0.625[b]
Previous urinary tract infection	3/34[c] (8.8)	55/273[c] (20.1)	0.161[b]
Prior hospitalization within 1 year	4/34[c] (11.8)	59/273[c] (21.6)	0.259[b]
Clinical outcome			
Duration of hospital stay, day, median (range)	11 (10–13)	10 (8–13)	0.011[a]
Clinical cure at 4–14 days after Tx[d]	30/31[c] (96.8)	208/214[c] (97.2)	> 0.999[b]
Microbiological cure at 4–14 days after Tx[d]	19/21[c] (90.5)	119/127[c] (93.7)	0.635[b]

Values are presented as number (%).
E. coli, *Escherichia coli*; IQR, interquartile range.
[a]Mann-Whitney *U* test.
[b]Pearson chi-square test or Fisher exact test.
[c]Denominators were the number of patients whose data were available in each group.
[d]Tx, overall therapy including alternative intravenous and oral antibiotics (tailored according to uropathogen identification and susceptibility results) as well as initial intravenous cefuroxime.

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Table 5. Related factors for the early clinical failure of acute pyelonephritis treated with empirical cefuroxime in the final model of multiple logistic regression

Factor	Odds ratio (95% CI)	*p* value
Bacteremia	4.245 (1.959–9.196)	< 0.001
C-reactive protein ≥ 20 mg/dL	4.236 (1.892–9.483)	< 0.001
Chronic liver disease	5.556 (1.637–18.856)	0.006
Uropathogen resistant to cefuroxime	6.440 (2.129–19.476)	0.001

Final model: bacteremia, C-reactive protein ≥ 20 mg/dL, chronic liver disease, uropathogen resistant to cefuroxime.
CI, confidence interval.

comes by reviewing medical records.

The clinical cure rate, microbiological cure rate, mortality rate, length of hospital stay, and duration of total antibiotic treatment were not significantly different between the cefuroxime-resistant (discordant therapy) and cefuroxime-susceptible (concordant therapy) groups. However, the resistant group demonstrated a lower initial clinical success rate than the susceptible group. The presence of resistant uropathogens was correlated with treatment failure in APN. Several studies have shown that the discordant use of initial empirical antibiotics was not a factor correlated with clinical failure in patients with APN because the therapy was followed by the administration of other antibiotics after confirming the antimicrobial susceptibility of uropathogens.

Although 22 of 328 *E. coli* isolates (6.7%) were resistant to cefuroxime in our study, 15 cases (68.2%) in the cefuroxime-resistant group showed a resolution of fever within 72 hours after the start of intravenous cefuroxime. Therefore, these cases were included in the early clinical success group. This finding indicates that the *in vivo* effects of cefuroxime are greater than its *in vitro* effect. In addition, 18 cases (81.8%) among the 22 women with cefuroxime-resistant uropathogens also showed resolution of fever within 96 hours after the start of intravenous cefuroxime. There were only 4 of 22 women (18.2%) in the cefuroxime-resistant group that showed persistent fever 120 hours after the start of intravenous cefuroxime or required a change to a different intravenous antimicrobial therapy. These results suggest that intravenous cefuroxime can be used as the initial empirical antimicrobial agent in hospitalized APN patients. The treatments can then change to other antimicrobial regimens that were confirmed effective by the microbiological susceptibility testing.

It was reported that discordant antimicrobial therapy based on cefuroxime was a risk factor for mortality in the treatment of pneumococcal bacteremia [15]. However, APN in women is not a severe disease entity compared to pneumococcal bacteremia. The empirical use of intravenous cefuroxime in hospitalized female patients with community-onset APN was effective. The patients in the cefuroxime-resistant group showed a slightly higher early clinical failure rate than those in the cefuroxime-susceptible group. Cefuroxime may be more effective *in vivo* than *in vitro* because cefuroxime is excreted in the urinary tract, where concentration of cefuroxime is high.

While the empirical use of intravenous cefuroxime is an independent risk factor for mortality in patients with bacteremia due to cefuroxime-resistant *Streptococcus pneumoniae*, we did not find that use of intravenous cefuroxime was related to the final clinical failure in treating APN. In our study, bacteremia, chronic liver disease, CRP ≥ 20 mg/dL, and uropathogen resistance to cefuroxime were shown to be independent factors of early clinical failure in women with APN.

In our study, *E. coli* isolates showed lower resistance rates to cefuroxime than to ciprofloxacin or gentamicin. The early clinical success rates were 89.3% and 95.4% at 72 and 96 hours, respectively. Additionally, the overall clinical cure rate at 4 to 14 days after the end of antimicrobial therapy was 97.1%, while the total resistance rate of *E. coli* to cefuroxime was 6.7%.

This study has a few limitations. First, the study, as a retrospective study, was not a randomized, controlled trial. We analyzed the medical records within a group of female APN patients who initially received only intravenous cefuroxime. Second, the microbiological cure rates might not have been accurately determined because the

microbiological data were available in only 148 of the 328 enrolled patients.

In conclusion, the intravenous use of a second-generation cephalosporin, such as a cefuroxime, can be an antibiotic option for initial empirical therapy of community-onset APN. The therapy must be tailored according to uropathogen identification and susceptibility results. Cefuroxime may be used for initial empirical therapy in areas where the prevalence rate of ESBL-producing uropathogen is low. The use of cefuroxime might contribute to fluoroquinolone-sparing or broad-spectrum cephalosporin-sparing in the treatment of APN. Additional large and adequately powered prospective trials are needed to investigate the use of cefuroxime as an initial therapy to treat APN.

KEY MESSAGE

1. Intravenous cefuroxime can be an antibiotic option for initially treating community-onset acute pyelonephritis in areas where the rate of resistance to second-generation cephalosporins in *Escherichia coli* is low.
2. The susceptibility test of *E. coli* to cefuroxime should be included in routine microbiological analysis to aid in choosing an adequate antimicrobial agent for treating acute pyelonephritis.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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