A Prospective Study of Ceftriaxone Treatment in Acute Pyelonephritis Caused by Extended-Spectrum Beta-Lactamase-Producing Bacteria

Chusana Suankratay MD, PhD*,
Kamonwan Jutivorakool MD**, Supunnee Jirajariyavej MD***

** Division of Infectious Diseases, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok*
*** Department of Medicine, Chonburi Hospital, Chonburi*
**** Department of Medicine, Taksin Hospital, Bangkok*

Background: *Much controversy exists as to whether cephalosporin treatment is appropriate for infections caused by ESBL-producing organisms because no randomized controlled studies have been performed.*
Objective: *Evaluate the therapeutic outcomes of ceftriaxone treatment in acute pyelonephritis caused by ESBL-producing Escherichia coli, Klebsiella pneumoniae, or Proteus mirabilis.*
Material and Method: *The authors performed a prospective study in female patients hospitalized with acute pyelonephritis caused by ESBL-producing or ESBL-nonproducing E. coli, K. pneumoniae, or P. mirabilis in four hospitals in Thailand from 2004 to 2006. The clinical and microbiological outcomes were evaluated at 72 hours after empirical ceftriaxone treatment.*
Results: *One hundred eleven patients with the mean age of 65.29 years participated in this study. There were no differences in demographic and clinical characteristics and laboratory data between the ESBL-producing and ESBL-nonproducing groups except the higher rates of previous antibiotic use and urinary tract infection; and the lower frequency of costovertebral angle tenderness in the ESBL-producing group. Both clinical (65% and 93%) and microbiological (67.5% and 100%) responses at 72 hours after ceftriaxone treatment were poorer in the ESBL-producing group than in the ESBL-nonproducing group ($p < 0.0002$).*
Conclusion: *To the authors' knowledge, this is the first prospective study to evaluate the outcomes of ceftriaxone treatment in acute pyelonephritis caused by ESBL-producing Enterobacteriaceae. The present study confirms that acute pyelonephritis in the female patients caused by ESBL-producing strains could not be treated with ceftriaxone.*

Keywords: *Ceftriaxone, Acute pyelonephritis, Extended-spectrum-beta-lactamases, Escherichia coli, Klebsiella pneumoniae*

J Med Assoc Thai 2008; 91 (8): 1172-81
Full text. e-Journal: *http://www.medassocthai.org/journal*

Since the first clinical isolation in 1983, extended-spectrum beta-lactamase (ESBL)-producing organisms have become recognized as a worldwide problem[1-3]. Even though this type of beta-lactamase enzymes could be detected in a wide variety of gram-negative bacteria, *Escherichia coli* and *Klebsiella pneumoniae* have been found to be the most common species to produce ESBLs[4-6]. In the United States from 1998 to 2002, 6.1% of *K. pneumoniae* isolates in the intensive care units participating in the National Nosocomial Infections Surveillance (NNIS) system were not susceptible to third-generation cephalosporins[7]. The occurrence of ESBL-producing Enterobacteriaceae varies among different parts of the world. They may be more common

Correspondence to: Suankratay C, Division of Infectious Diseases, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand. Phone: 0-2256-4578, Fax: 0-2256-4578. E-mail: chusana.s@chula.ac.th

in some countries in Europe, Asia, and South America than in the United States[8-10].

Much controversy exists as to whether cephalosporin therapy is appropriate for infections caused by the ESBL-producing organisms. Most reports described the treatment failure with cephalosporins, despite an apparent *in vitro* susceptibility to some of these agents[8,11]. However, some authors regard this opinion as controversial[12,13]. To the best of the authors' knowledge, no randomized controlled trials have ever been performed to evaluate the outcome of treatment of infections caused by the ESBL-producing organisms. Currently, the carbapenems are regarded as the drug of choice against severe infections caused by these organisms since they are uniformly active *in vitro* and *in vivo* against these isolates[8,11,14-16]. A widespread use of carbapenems may be associated with further selection of pathogens with acquired *(K. pneumoniae, Pseudomonas aeruginosa, and Acinetobacter baumannii)* and inherited (*Stenotrophomonas maltophilia*) antibiotic resistance[17-19]. In addition, there are several reports of a successful treatment of urinary tract infection due to the ESBL-producing organisms by cephalosporins, regardless of the results from *in vitro* susceptibility test[4,12,13]. The objective of the present prospective study was to determine the outcome of empirical ceftriaxone treatment in acute pyelonephritis caused by ESBL-producing *E. coli*, *K. pneumoniae*, or *P. mirabilis*, compared with the ESBL-nonproducing isolates.

Material and Method

Study design

A prospective study of acute pyelonephritis caused by *E. coli*, *K. pneumoniae*, or *P. mirabilis* was performed in four hospitals in Thailand including King Chulalongkorn Memorial Hospital, Taksin Hospital, and Charoenkrung-Pracharuk Hospital in Bangkok, as well as Chonburi Hospital in Chonburi. The study period was between January 1, 2004 and December 31, 2006. Written informed consent was obtained from all patients, and the institutional review board at each participating site approved the protocol.

Patients

The inclusion criteria included the female patients older than 15 years old with a documented episode of either community-acquired or nosocomial acute pyelonephritis caused by *E. coli*, *K. pneumoniae*, or *P. mirabilis*. The exclusion criteria included 1) previous urinary tract infection (UTI) within four weeks, 2) previous use of cephalosporin within 72 hours, 3) immunocompromised host, 4) known functional or mec0hanical abnormality of the urinary tract, 5) creatinine clearance of < 30 mL/min, 6) absolute neutrophil count of $\leq$ 1,000 cells/mm^3, 7) alanine or aspartate aminotransferase levels of > 3 times the upper limit of normal, 8) any rapidly progressive disease, 9) heart failure, 10) retained Foley's catheter, 11) pregnancy or lactation, and 12) contraindication for cephalosporins. Regarding the designation as the case or control patients, the case and control patients were those who had ESBL-producing and ESBL-nonproducing *E. coli*, *K. pneumoniae*, or *P. mirabilis* infections, respectively.

Microbiological methods

All isolates were identified at the site laboratory, and the pathogens were tested for *in vitro* susceptibility by the disk diffusion method. All isolates were tested for the ESBL-production by the combined-disk method, according to the National Committee for Clinical Laboratory Standards (NCCLS) or the Clinical and Laboratory Standards Institute (CLSI) recommendation[20].

Clinical analysis

The data collected from both case and control patients included the demographic, clinical, and laboratory data. The preexisting conditions considered as possible risk factors included diabetes mellitus (DM), renal failure (RF), cerebrovascular disease (CVD), previous hospitalization, previous antibiotic use, and previous UTI. All patients were received intravenous ceftriaxone 2 g once daily. After 72 hours of empirical treatment, the antibiotic was switched to oral ciprofloxacin (500 mg twice daily) if the patient was afebrile and clinically improved, and the pathogen was susceptible to ciprofloxacin. Other oral or intravenous agents were permitted if the patient could not tolerate ciprofloxacin or if the causal pathogen was resistant. The total duration of intravenous plus oral antibiotic treatment was 10 to 14 days.

The primary end point of the study was the clinical outcome at 72 hours of empirical ceftriaxone treatment. The secondary end point included the microbiological outcome at 72 hours of ceftriaxone treatment.

Definitions

Definitions were defined a priori**.** Fever was defined as an oral temperature of $\geq$ 37.8°C. Acute pyelonephritis was defined as one of all of the following

presentations within 48 hours including fever, chills, urinary urgency, urinary frequency, flank pain, or costovertebral angle (CVA) tenderness, in association with pyuria of $\geq$ 10 white blood cells per high-power field (HPF) and positive urine culture of $\geq 10^5$ colony-forming units (CFU)/mL.

The clinical severity was classified into marked, moderate, and mild severities. Marked severity was defined as unstable vital signs or sepsis. Moderate severity was defined as fever > 39°C, severe flank pain, nausea, vomiting, or blood leukocytosis > 15,000 cells/mm^3. Mild severity was defined as absence of definition for severe and moderate severities.

The clinical outcome was assessed at 72 hours of treatment. A good outcome was defined as resolution of the signs and symptoms of UTI, and a poor outcome was defined as persistence of fever, flank pain, or other signs and symptoms of UTI as well as death.

The microbiological outcomes assessed at 72 hours of treatment were defined as no persistence (the urine culture grew < 10^4 CFU/mL), persistence (the urine culture grew $\geq 10^4$ CFU/mL), or superinfection (the urine culture grew $\geq 10^5$ CFU/mL of a pathogen other than the baseline pathogen during treatment). The microbiological outcome was classified into a good or poor outcome. A good outcome was defined as no persistence of infection, and a poor outcome was defined as persistence of infection or superinfection.

Statistical analysis

The present study was designed to test for the inferiority in the clinical efficacy of the ceftriaxone treatment in acute pyelonephritis caused by ESBL-producing *E. coli*, *K. pneumoniae*, or *P. mirabilis*, compared to that caused by ESBL-nonproducing isolates. Assuming that 30 percent of acute pyelonephritis would be caused by ESBL-producing isolates and the yield of positive urine or blood cultures of 60 percent in our institutes (unpublished data), a sample size of 28 patients per treatment arm was calculated. This calculation was based on the assumption of a 90- and 50-percent clinical response in the case and control patients, respectively, and alpha and beta errors were 0.05 and 0.20, respectively. The values were presented as the mean $\pm$ SD for the continuous variables or as the percentage of the group from which they were derived for the categorical variables. The continuous variables were compared using the Student's t-test. The Chi-square test or Fisher's exact test was used to compare the categorical variables. The variables, which were significantly different between the two groups in the univariate analysis, were further tested by the logistic regression model for the multivariate analysis. All p-values were two-tailed with those less than 0.05 were considered statistically significant. The SPSS software version 12 was used for these analyses.

Results

During the present study period, a total of 140 female patients with acute pyelonephritis were enrolled (Fig. 1). Five patients were excluded due to two neurogenic bladders, two hydronephrosis, and one renal stone, and ten patients were withdrawn from the study due to incomplete entry data. Of the remaining

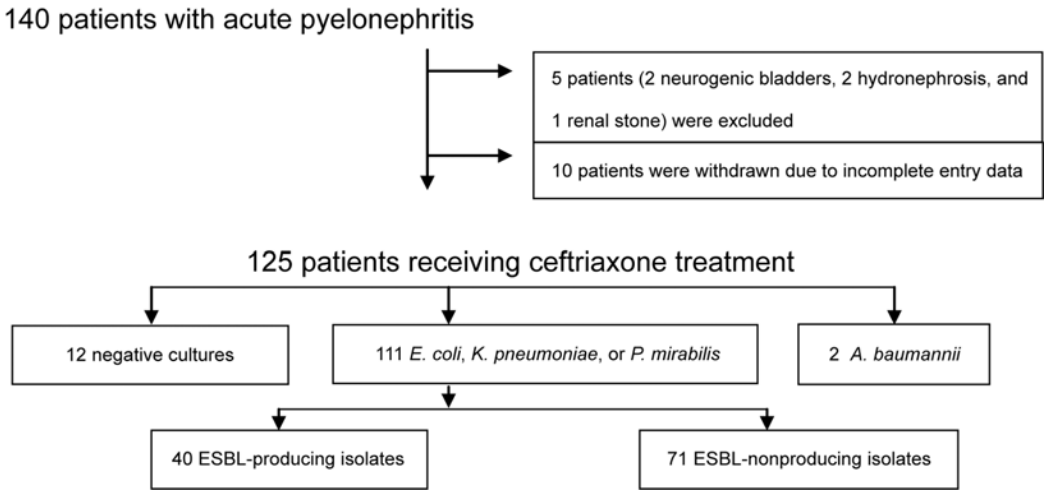

Fig. 1 Enrollment of the female patients with acute pyelonephritis

125 patients, there were 111 *E. coli, K. pneumoniae*, or *P. mirabilis*, 2 *A. baumannii*, and 12 negative cultures. Overall, 111 patients with *E. coli, K. pneumoniae*, or *P. mirabilis* infection (18 *E. coli*, 1 *K. pneumoniae*, and 1 *P. mirabilis* positive blood cultures) were included in the analysis. Of these, 40 patients (36.03%) had ESBL-producing isolates (35 *E. coli*, 4 *K. pneumoniae*, and 1 *P. mirabilis*).

Demographic and clinical characteristics

There were no significant differences in demographic characteristics between the ESBL-producing and ESBL-nonproducing groups except the higher rates of previous antibiotic use, hospitalization, UTI, and cerebrovascular diseases in the ESBL-producing group (Table 1). However, in the multivariate analysis, previous antibiotic use and UTI were only the risk factors for ESBL-producing *E. coli, K. pneumoniae*, or *P. mirabilis* infections (p = 0.001). Regarding clinical and laboratory data, there were no differences between the two groups except the lower frequency of costovertebral angle tenderness in the ESBL-producing group (p = 0.001), probably due to the higher number of patients with cerebrovascular disease in this group.

Antimicrobial susceptibility

The rate of resistance to each antibiotic determined by the disk diffusion method was significantly higher in the ESBL-producing isolates than in the ESBL-nonproducing isolates, except trimethoprim/sulfamethoxazole (Table 2). Both ESBL-producing and ESBL-nonproducing isolates were susceptible to meropenem and imipenem. In addition, all ESBL-nonproducing isolates were susceptible to ceftriaxone, ceftazidime, cefepime, meropenem, and imipenem. The multidrug resistance (MDR) pattern (more than two

Table 1. A comparison of variables between patients with ESBL-producing and ESBL-nonproducing *E. coli, K. pneumoniae*, or *P. mirabilis*

Variable	ESBL-producing isolates (n = 40)[a]	ESBL-nonproducing isolates (n = 71)[a]	p-value
Mean age (years)	72.2	61.4	NS
Mean fever duration before diagnosis (days)	1.7	1.9	NS
Underlying diseases			
Diabetes mellitus	18 (45)	27 (38.03)	0.47
Cerebrovascular disease	14 (35)	9 (12.7)	0.005
Past medical history			
Previous antibiotic use within 1 month	12 (30)	4 (5.6)	0.0004
Previous hospitalization within 3 months	10 (25)	4 (5.6)	0.003
Previous UTI within 6 months	13 (32.5)	5 (7)	0.0005
Signs and symptoms			
Fever	19 (47.5)	47 (66.2)	0.054
Chills	17 (42.5)	44 (61.9)	0.05
Vomiting	13 (32.5)	32 (45.1)	0.195
Dysuria	15 (37.5)	42 (59.2)	0.0284
Costoverterbral angle tenderness	5 (12.5)	35 (49.3)	0.0001
Vital signs			
Mean body temperature (°C)	38.4	38.7	NS
Mean systolic BP (mmHg)	124.0	121.9	NS
Mean diastolic BP (mmHg)	73.9	74.5	NS
Laboratory data			
Mean hematocrit (%)	33.1	34.5	NS
Mean WBC (cells/mm^3)	10,211.7	11,871.5	NS
Mean WBC in urine (cells/HPF)	67.5	77.7	NS
Mean creatinine (mg/dL)	1.3	1.1	NS
Mean blood sugar (mg/dL)	137.3	139.1	NS

ESBL: extended-spectrum beta-lactamase, UTI: urinary tract infection, BP: blood pressure, WBC: white blood cells, HPF: high-power field, NS: not significant

[a] Data in each variable represent the number and percentage (in parenthesis), unless otherwise indicated

Table 2. A comparison of antibiotic resistance patterns between the ESBL-producing and ESBL-nonproducing *E. coli*, *K. pneumoniae*, or *P. mirabilis*

Variable	ESBL-producing isolates (n = 40)[a]	ESBL-nonproducing isolates (n = 71)[a]	p-value
Gentamicin	25 (62.5)	7 (9.9)	<0.0001
Amikacin	6 (15)	1 (1.4)	0.0046
Trimethoprim/sulfamethoxazole	29 (72.5)	30 (42.3)	0.0918
Ciprofloxacin	33 (82.5)	13 (18.3)	<0.0001
Ampicillin	40 (100)	48 (67.6)	0.0005
Ceftriaxone	39 (97.5)	0	<0.0001
Ceftazidime	25 (62.5)	0	<0.0001
Cefepime	20 (50)	0	<0.0001
Amoxicillin/clavulanate	25 (62.5)	14 (19.7)	<0.0001
Cefoperazone/sulbactam	12 (30)	2 (2.8)	0.0003
Meropenem	0	0	-
Imipenem	0	0	-
Classes of antibiotics			
Resistance to ≤ 2 classes	0	42 (59.2)	<0.0001
Resistance to ≥ 3 classes	40 (100)	22 (30.9)	<0.0001

Data in parenthesis represent the percentage, unless otherwise indicated

Table 3. A comparison of baseline clinical severity and outcomes at 72 hours of treatment between ESBL-producing and ESBL-nonproducing *E. coli*, *K. pneumoniae*, or *P. mirabilis*

Parameter	ESBL-producing isolates (n = 40)[a]	ESBL-nonproducing isolates (n = 71)[a]	p-value
Clinical severity			
Mild severity	26 (65)	36 (50.7)	0.15
Moderate severity	14 (35)	35 (49.3)	0.15
Clinical outcome			
Poor	14 (35)	5 (7)	0.0002
Chills	0 (0)	0 (0)	-
Nausea and vomiting	1 (2.5)	3 (4.2)	0.64
Costovertebral-angle tenderness	0 (0)	3 (4.2)	0.19
Microbiological outcome			
Poor	13 (32.5)	0 (0)	<0.0001
Urine WBC > 10 cells/HPF	4 (10)	6 (8.5)	0.69

ESBL: extended-spectrum beta-lactamase, SD: standard deviation, WBC: white blood cells, HPF: high-power field
[a] Data in parenthesis represent the percentage, unless otherwise indicated

classes of antibiotics) was observed in 40 of 40 (100%) and 22 of 71 (30.9%) of the ESBL-producing and ESBL-nonproducing isolates, respectively.

Outcomes

In the present study, there were no patients with marked severity due to the exclusion criteria. There was no significant difference of the clinical severity between the two groups (Table 3). 14 of 40 (35%) ESBL-producing and 35 of 71 (49.3%) of ESBL-nonproducing group had moderate clinical severity.

Clinical outcome

The poor clinical outcome was observed in 14 of 40 patients (35%) and 5 of 71 patients (7%) in the ESBL-producing and ESBL-nonproducing groups,

respectively (Table 3). This was statistically different ($p = 0.0002$). No patient died within 72 hours of the antibiotic treatment.

Microbiological outcome

The poor microbiological outcome was also observed in 13 of 40 (32.5%) and 0 of 71 (0%) in the ESBL-producing and ESBL-nonproducing groups, respectively. This difference was statistically significant ($p < 0.0001$). There were no patients with superinfection during the present study period.

Forty-six patients remained for analysis at the end of treatment of acute pyelonephritis. These included 17 (42.5%) in the ESBL-producing and 29 (40.8%) in the ESBL-nonproducing groups. The overall 14-day mortality rate was 5.9% (1 of 17) in the ESBL-producing group and 0% in the ESBL-nonproducing group ($p = 0.18$). Ceftriaxone was switched to oral ciprofloxacin in all 29 patients in the ESBL-nonproducing group with good clinical and microbiological outcomes at the end of treatment. Of 17 patients in the ESBL-producing group, 6 or 6 were switched to oral ciprofloxacin or carbapenem, respectively, and five with good clinical outcome and infected with susceptible strain of bacteria still continued ceftriaxone or switched to ceftazidime treatment, after obtaining the susceptibility results at about 72 hours of ceftriaxone treatment. The poor clinical and microbiological outcomes were noted in all five patients with ceftriaxone or ceftazidime treatment. Of these five patients, four and one were switched to carbapenem due to a relapse of UTI and nosocomial pneumonia, respectively at about 4-6 days of treatment when the result of ESBL-production was also obtained. The only one patient who died was a 69-year-old female with HT and gout. After 72 hours of ceftriaxone treatment for acute pyelonephritis caused by ESBL-producing *E. coli*, fever was resolved and urine culture was negative. After six days of treatment, she developed nosocomial pneumonia caused by *A. baumannii*, and ceftriaxone was changed to imipenem. The patient did not improve, and eventually died after four days of imipenem treatment.

Discussion

Past attempts to identify the risk factors for infections caused by ESBL-producing organisms have resulted in different conclusions. These included a prolonged hospital stay[21,22], a prolonged intensive care unit stay[23,24], a use of invasive procedures including central venous or arterial catheter[16,23-26], ventilator[24-27], hemodialysis[28], urinary catheter[16,22-25], a previous use of oxyimino beta-lactams[15,23,29-32] or any antibiotics[6,26,33]. In the present study, previous UTI and antibiotic use within six months were only the independent risk factors for these infections.

In the present study, the MDR pattern was observed in all isolates with ESBL-production, compared to only one-third of those without ESBL-production. These MDR isolates were significantly associated with resistance to other nonbeta-lactam antibiotics including gentamicin (62.5%), ciprofloxacin (82.5%), and trimethoprim/sulfamethoxazole (72.5%). The high rate of ciprofloxacin resistance associated with ESBL-production is very surprising as the quinolone resistance is chromosome-mediated and is rarely plasmid-mediated. This probably indicates the selection of ciprofloxacin-resistant isolates by the pressure use of quinolones within our hospital where the ESBL-producing organisms were also prevalent, or the two resistance genes are transferred on the same plasmid as recently described[34].

In the present study, the mortality rate in the ESBL-producing group was 0 and 5.9% at 72 hours and 14 days of treatment, and was lower than that reported by previous studies[15,16,26,33,35-38]. This is likely due to the inclusion of only acute pyelonephritis with mild and moderate severity in the present study. There was no significant difference in the mortality rate between the ESBL-producing and ESBL-nonproducing groups in the present study. There is a conflicting result of the mortality rate in the literature, probably due to differences in the study design, inclusion and exclusion criteria, and operational definitions among those studies. Schiappa et al reported the similar mortality in patients with bacteremia caused by ESBL-producing and ESBL-nonproducing *E. coli* and *K. pneumoniae* if an appropriate antibiotic was given[15]. This is in consistent with that reported by Menashe et al [26] as well as Lautenbach and colleagues[33]. In contrast, Kim et al described the higher mortality rate in the pediatric patients with ESBL-producing *E. coli* or *K. pneumoniae* bacteremia, compared to those without ESBL-production[36].

In the present study, there were significant differences in both clinical and microbiological outcomes at 72 hours of empirical ceftriaxone treatment before obtaining the susceptibility results between the ESBL-producing and ESBL-nonproducing groups, even though the authors included only patients with mild and moderate severity of infection and theoretically the high levels of cephalosporins in the urine may be sufficient to kill the organisms with or without

ESBL-production. This is in contrast with a retrospective study by Lautenbach et al that showed the clinical response at 72 hours of treatment in the infections (51.5% UTI) caused by ESBL-producing and ESBL-nonproducing isolates was not significantly different (75.8% and 83.3%, p = 0.08)[33]. However, no data of the types of antibiotic treatment was shown in their study. In contrast, Kang et al conducted a retrospective study in patients with *K. pneumoniae* bacteremia[37]. The clinical outcome at 72 hours of treatment in the ESBL-producing group was poorer than that of the ESBL-nonproducing group (13.3% and 36.7%, p = 0.003). In addition, the poor microbiological outcome was observed in patients infected with ESBL-producing isolates, compared to those without ESBL-production. However, UTI was the primary site of infections in only 6.7% of patients in their study.

In the present study, the clinical and microbiological outcomes at 14 days of treatment were not evaluated because most patients were lost to follow-up and switched to other antibiotics. Thus, it is impossible to compare the outcomes between the two treatment groups at this period. However, due to a longer duration of determination of ESBL-production (about 4-6 days), all except one patient who continued ceftriaxone or switched to ceftazidime treatment had a relapse of acute pyelonephritis. This is in contrast with previous studies with a small number of patients[4,12]. Emory et al conducted a retrospective study in patients with the Enterobacteriaceae infections. Four of four patients with UTI caused by ESBL-producing organisms were cured with the expanded-spectrum cephalosporins[4]. Brun-Buisson et al demonstrated that cefotaxime treatment was effective in uncomplicated urinary tract infection caused by ESBL-producing *K. pneumoniae*, but failed in major infections of other sites[12]. In contrast, some studies showed that cephalosporin treatment of infections caused by ESBL-producing isolates has been associated with more failure than those caused by ESBL-nonproducing isolates[8,15,16,37].

Paterson et al published a prospective observational study of the treatment outcome in patients with serious infections due to ESBL-producing *E. coli* or *K. pneumoniae*[8]. The outcome of patients who received cephalosporins treatment was more favorable when the minimal inhibitory concentration (MIC) for the infecting organism was $\leq$ 2 μg/mL rather than when it was $\geq$ 8 μg/mL. The treatment failure was observed in all four patients with the MIC of the intermediate range (16-32 μg/mL) and 15 of 28 (54%) with the MIC of the susceptibility range (< 8 μg/mL). In addition, carbapenem treatment for ESBL-producing infections has been associated with the best outcomes in terms of survival and bacteriologic clearance in several studies[8,14,17,37-41]. Unfortunately, no data of the MIC of all isolates was available in the present study. Much controversy exists whether which parameter, *in vitro* MIC or resistant mechanism, correlates well with the clinical outcome of treatment of infections caused by ESBL-producing isolates. In addition, it would be better if the types of ESBLs in the present study could be determined since the outcomes may be different. CTX-M is mostly prevalent among the ESBL-producing strains in our hospitals (unpublished data). Several factors, including the inoculum effect, the site and severity of infection, as well as the pharmacokinetic and pharmacodynamic targets of each cephalosporin antibiotic, may also influence the treatment outcomes. Regarding ethical issue in the present study, due to a lack of data of the frequency of ESBL-production in Enterobacteriacae in Thailand, every guideline recommends third-generation cephalosporin for empirical treatment of acute pyelonephritis caused by Gram-negative or unknown bacteria before obtaining the microbiological results. Based on the results of the present study, the authors believe that there would be a revision of the guidelines to include both the available local susceptibility data and attributable risks for ESBL-producing organism before making the decision to select the appropriate empirical antibiotic for the treatment of acute pyelonephritis. In addition, it would be very interesting to conduct a randomized controlled study comparing the outcomes between empirical treatment with carbapenem versus third- or fourth-generation cephalosporin with switching to carbapenem after obtaining the susceptibility results in acute pyelonephritis caused by ESBL-producing organism. This would be of much benefit for physicians who take care of patients with acute pyelonephritis.

In conclusion, to the authors' knowledge, this is the first prospective study to evaluate the outcomes of empirical ceftriaxone treatment in acute pyelonephritis caused by ESBL-producing Enterobacteriaceae. The present study confirms that acute pyelonephritis in the female patients caused by ESBL-producing strains could not be treated with ceftriaxone.

Acknowledgements

The present study was supported by Ratchadapiseksompotch Fund, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

The authors' wish to thank Dr Jirachai Waiwarawooth from the Department of Medicine, Chonburi Hospital. We also wish to thank the Departments of Microbiology of Chulalongkorn University, Chonburi Hospital, Taksin Hospital, and Charoenkrung-Pracharuk Hospital, for their assistance with the present study.

Potential conflicts of interest

All authors have no conflicts of interest.

References

1. Knothe H, Shah P, Krcmery V, Antal M, Mitsuhashi S. Transferable resistance to cefotaxime, cefoxitin, cefamandole and cefuroxime in clinical isolates of *Klebsiella pneumoniae* and Serratia marcescens. Infection 1983; 11: 315-7.
2. Livermore DM. Beta-lactamase-mediated resistance and opportunities for its control. J Antimicrob Chemother 1998; 41(Suppl D): 25-41.
3. Pitout JD, Sanders CC, Sanders WE Jr. Antimicrobial resistance with focus on beta-lactam resistance in gram-negative bacilli. Am J Med 1997; 103: 51-9.
4. Emery CL, Weymouth LA. Detection and clinical significance of extended-spectrum beta-lactamases in a tertiary-care medical center. J Clin Microbiol 1997; 35: 2061-7.
5. Quinn JP. Clinical significance of extended-spectrum beta-lactamases. Eur J Clin Microbiol Infect Dis 1994; 13(Suppl 1): S39-42.
6. Bradford PA. Extended-spectrum beta-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. Clin Microbiol Rev 2001; 14: 933-51.
7. National Nosocomial Infections Surveillance System. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 to June 2002, issued August 2002 Am J Infect Control 2002; 30: 458-75.
8. Paterson DL, Ko WC, Von Gottberg A, Mohapatra S, Casellas JM, Goossens H, et al. Antibiotic therapy for *Klebsiella pneumoniae* bacteremia: implications of production of extended-spectrum beta-lactamases. Clin Infect Dis 2004; 39: 31-7.
9. Winokur PL, Canton R, Casellas JM, Legakis N. Variations in the prevalence of strains expressing an extended-spectrum beta-lactamase phenotype and characterization of isolates from Europe, the Americas, and the Western Pacific region. Clin Infect Dis 2001; 32(Suppl 2): S94-103.
10. Bell JM, Turnidge JD, Gales AC, Pfaller MA, Jones RN. Prevalence of extended spectrum beta-lactamase (ESBL)-producing clinical isolates in the Asia-Pacific region and South Africa: regional results from SENTRY Antimicrobial Surveillance Program (1998-99). Diagn Microbiol Infect Dis 2002; 42: 193-8.
11. Paterson DL, Ko WC, Von Gottberg A, Casellas JM, Mulazimoglu L, Klugman KP, et al. Outcome of cephalosporin treatment for serious infections due to apparently susceptible organisms producing extended-spectrum beta-lactamases: implications for the clinical microbiology laboratory. J Clin Microbiol 2001; 39: 2206-12.
12. Brun-Buisson C, Legrand P, Philippon A, Montravers F, Ansquer M, Duval J. Transferable enzymatic resistance to third-generation cephalosporins during nosocomial outbreak of multiresistant *Klebsiella pneumoniae*. Lancet 1987; 2: 302-6.
13. Meyer KS, Urban C, Eagan JA, Berger BJ, Rahal JJ. Nosocomial outbreak of Klebsiella infection resistant to late-generation cephalosporins. Ann Intern Med 1993; 119: 353-8.
14. Paterson DL. Recommendation for treatment of severe infections caused by Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs). Clin Microbiol Infect 2000; 6: 460-3.
15. Schiappa DA, Hayden MK, Matushek MG, Hashemi FN, Sullivan J, Smith KY, et al. Ceftazidime-resistant *Klebsiella pneumoniae* and *Escherichia coli* bloodstream infection: a case-control and molecular epidemiologic investigation. J Infect Dis 1996; 174: 529-36.
16. Kim YK, Pai H, Lee HJ, Park SE, Choi EH, Kim J, et al. Bloodstream infections by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in children: epidemiology and clinical outcome. Antimicrob Agents Chemother 2002; 46: 1481-91.
17. Cunha BA. Pseudomonas aeruginosa: resistance and therapy. Semin Respir Infect 2002; 17: 231-9.
18. Bradford PA, Urban C, Mariano N, Projan SJ, Rahal JJ, Bush K. Imipenem resistance in *Klebsiella pneumoniae* is associated with the combination of ACT-1, a plasmid-mediated AmpC beta-lactamase, and the foss of an outer membrane protein. Antimicrob Agents Chemother 1997; 41: 563-9.
19. Ahmad M, Urban C, Mariano N, Bradford PA, Calcagni E, Projan SJ, et al. Clinical characteristics and molecular epidemiology associated with

imipenem-resistant *Klebsiella pneumoniae*. Clin Infect Dis 1999; 29: 352-5.
20. National Committee for Clinical Laboratory Standards. Performance Standard for Antimicrobial Susceptibility Testing: Fourteenth Information Supplement M100-S14. Wayne, PA: National Committee for Clinical Laboratory Standards; 2004: 32-5.
21. Safdar N, Maki DG. The commonality of risk factors for nosocomial colonization and infection with antimicrobial-resistant *Staphylococcus aureus*, enterococcus, gram-negative bacilli, *Clostridium difficile*, and *Candida*. Ann Intern Med 2002; 136: 834-44.
22. Mangeney N, Niel P, Paul G, Faubert E, Hue S, Dupeyron C, et al. A 5-year epidemiological study of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* isolates in a medium- and long-stay neurological unit. J Appl Microbiol 2000; 88: 504-11.
23. Lucet JC, Chevret S, Decre D, Vanjak D, Macrez A, Bedos JP, et al. Outbreak of multiply resistant enterobacteriaceae in an intensive care unit: epidemiology and risk factors for acquisition. Clin Infect Dis 1996; 22: 430-6.
24. De Champs C, Rouby D, Guelon D, Sirot J, Sirot D, Beytout D, et al. A case-control study of an outbreak of infections caused by *Klebsiella pneumoniae* strains producing CTX-1 (TEM-3) beta-lactamase. J Hosp Infect 1991; 18: 5-13.
25. Pena C, Pujol M, Ricart A, Ardanuy C, Ayats J, Linares J, et al. Risk factors for faecal carriage of *Klebsiella pneumoniae* producing extended spectrum beta-lactamase (ESBL-KP) in the intensive care unit. J Hosp Infect 1997; 35: 9-16.
26. Menashe G, Borer A, Yagupsky P, Peled N, Gilad J, Fraser D, et al. Clinical significance and impact on mortality of extended-spectrum beta lactamase-producing Enterobacteriaceae isolates in nosocomial bacteremia. Scand J Infect Dis 2001; 33: 188-93.
27. Piroth L, Aube H, Doise JM, Vincent-Martin M. Spread of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*: are beta-lactamase inhibitors of therapeutic value? Clin Infect Dis 1998; 27: 76-80.
28. D'Agata E, Venkataraman L, DeGirolami P, Weigel L, Samore M, Tenover F. The molecular and clinical epidemiology of enterobacteriaceae-producing extended-spectrum beta-lactamase in a tertiary care hospital. J Infect 1998; 36: 279-85.
29. Pena C, Pujol M, Ardanuy C, Ricart A, Pallares R, Linares J, et al. Epidemiology and successful control of a large outbreak due to *Klebsiella pneumoniae* producing extended-spectrum beta-lactamases. Antimicrob Agents Chemother 1998; 42: 53-8.
30. Paterson DL, Ko WC, Von Gottberg A, Mohapatra S, Casellas JM, Goossens H, et al. International prospective study of *Klebsiella pneumoniae* bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial Infections. Ann Intern Med 2004; 140: 26-32.
31. Du B, Long Y, Liu H, Chen D, Liu D, Xu Y, et al. Extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* bloodstream infection: risk factors and clinical outcome. Intensive Care Med 2002; 28: 1718-23.
32. Lin MF, Huang ML, Lai SH. Risk factors in the acquisition of extended-spectrum beta-lactamase *Klebsiella pneumoniae*: a case-control study in a district teaching hospital in Taiwan. J Hosp Infect 2003; 53: 39-45.
33. Lautenbach E, Patel JB, Bilker WB, Edelstein PH, Fishman NO. Extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: risk factors for infection and impact of resistance on outcomes. Clin Infect Dis 2001; 32: 1162-71.
34. Martinez-Martinez L, Pascual A, Jacoby GA. Quinolone resistance from a transferable plasmid. Lancet 1998; 351: 797-9.
35. Ho PL, Chan WM, Tsang KW, Wong SS, Young K. Bacteremia caused by *Escherichia coli* producing extended-spectrum beta-lactamase: a case-control study of risk factors and outcomes. Scand J Infect Dis 2002; 34: 567-73.
36. Kim BN, Woo JH, Kim MN, Ryu J, Kim YS. Clinical implications of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* bacteraemia. J Hosp Infect 2002; 52: 99-106.
37. Kang CI, Kim SH, Kim DM, Park WB, Lee KD, Kim HB, et al. Risk factors for and clinical outcomes of bloodstream infections caused by extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*. Infect Control Hosp Epidemiol 2004; 25: 860-7.
38. Ramphal R, Ambrose PG. Extended-spectrum beta-lactamases and clinical outcomes: current data. Clin Infect Dis 2006; 42(Suppl 4): S164-S172.
39. Wong-Beringer A. Therapeutic challenges associated with extended-spectrum, beta-lactamase-producing *Escherichia coli* and *Klebsiella*

pneumoniae. Pharmacotherapy 2001; 21: 583-92.
40. Zanetti G, Bally F, Greub G, Garbino J, Kinge T, Lew D, et al. Cefepime versus imipenem-cilastatin for treatment of nosocomial pneumonia in intensive care unit patients: a multicenter, evaluator-blind, prospective, randomized study. Antimicrob Agents Chemother 2003; 47: 3442-7.
41. Burgess DS, Hall RG, Lewis JS, Jorgensen JH, Patterson JE. Clinical and microbiologic analysis of a hospital's extended-spectrum beta-lactamase-producing isolates over a 2-year period. Pharmacotherapy 2003; 23: 1232-7.

การศึกษาแบบไปข้างหน้าและเปรียบเทียบของการรักษาด้วย ceftriaxone ในการติดเชื้อที่กรวยไตแบบเฉียบพลันและเกิดโดยแบคทีเรียที่สร้างเอนไซม์ extended-spectrum beta-lactamase

ชุษณา สวนกระต่าย, กมลวรรณ จุติวรกุล, สุพรรณี จิรจริยาเวช

***ภูมิหลัง**: มีข้อถกเถียงในการรักษาด้วย cephalosporin ว่าจะเหมาะสมหรือไม่ สำหรับการติดเชื้อที่เกิดโดยแบคทีเรียที่สร้างเอนไซม์ extended-spectrum beta-lactamase (ESBL) เนื่องจากไม่มีการศึกษาที่เป็น randomized controlled มาก่อนการศึกษานี้จึงมีวัตถุประสงค์จะวิเคราะห์ผลการรักษาด้วย ceftriaxone ในการติดเชื้อที่กรวยไตแบบเฉียบพลันและเกิดโดย Escherichia coli, Klebsiella pneumoniae และ Proteus mirabilis ที่สร้างเอนไซม์ ESBL*

***วัสดุและวิธีการ**: เป็นการศึกษาแบบไปข้างหน้า และเปรียบเทียบในผู้ป่วยหญิงที่รับไว้ในโรงพยาบาล เนื่องจากการติดเชื้อที่กรวยไตแบบเฉียบพลัน และเกิดโดย E. coli, K. pneumoniae และ P. mirabilis ที่สร้าง และไม่สร้างเอนไซม์ ESBL ใน 4 โรงพยาบาลของประเทศไทยระหว่างปี พ.ศ. 2547-2549 ผลการรักษาทางคลินิก และจุลชีววิทยาได้รับการวิเคราะห์ที่ 72 ชั่วโมงหลังการให้การรักษาด้วย ceftriaxone*

***ผลการศึกษา**: มีผู้ป่วย 111 ราย มีอายุเฉลี่ย 65.29 ปี ไม่มีความแตกต่างในลักษณะทางระบาดวิทยาคลินิก และผลการตรวจทางห้องปฏิบัติการ ระหว่างกลุ่มที่สร้าง และไม่สร้างเอนไซม์ ESBL ยกเว้นประวัติการใช้ยาปฏิชีวนะ และการติดเชื้อของทางเดินปัสสาวะในอัตราสูงกว่า และการตรวจร่างกายมีการเจ็บของบั้นเอว ในอัตราต่ำกว่าในกลุ่มสร้างเอนไซม์ ESBL การตอบสนองทางคลินิก (ร้อยละ 65 และร้อยละ 93) และการตอบสนองทางจุลชีววิทยา (ร้อยละ 67.5 และร้อยละ 100) ที่ 72 ชั่วโมงหลังการรักษาด้วย ceftriaxone มีอัตราต่ำกว่าในกลุ่มสร้างเอนไซม์ ESBL เมื่อเทียบกับกลุ่มไม่สร้างเอนไซม์ ESBL ($p < 0.0002$)*

***สรุป**: จากความรู้จนถึงปัจจุบัน การศึกษานี้เป็นการศึกษาแรกที่เป็นแบบไปข้างหน้าและเปรียบเทียบเพื่อวิเคราะห์ผลการรักษาด้วย ceftriaxone ในการติดเชื้อที่กรวยไตแบบเฉียบพลันและเกิดโดย Enterobacteriaceae ที่สร้างเอนไซม์ ESBL การศึกษานี้ให้ข้อสรุปว่าไม่ควรใช้ ceftriaxone ในการรักษาการติดเชื้อที่กรวยไตแบบเฉียบพลันในผู้หญิง*