Infect Chemother. 2019 Jun;51(2):130-141
https://doi.org/10.3947/ic.2019.51.2.130
pISSN 2093-2340·eISSN 2092-6448

ic Infection & Chemotherapy

Original Article

Comparison of *Escherichia coli* and *Klebsiella pneumoniae* Acute Pyelonephritis in Korean Patients

Miri Hyun, Ji Yeon Lee, Hyun ah Kim, and Seong Yeol Ryu

Department of Infectious Diseases, Keimyung University Dongsan Medical Center, Daegu, Korea

Received: Jan 16, 2019
Accepted: Apr 16, 2019

Corresponding Author:
Seong Yeol Ryu, MD
Department of Infectious Diseases, Dongsan Medical Center, Keimyung University School of Medicine, 1095 Dalgubeoldaero, Dalseo-gu, Daegu 42601, Korea.
Tel: +82-53-258-7722
Fax: +82-53-258-4990
E-mail: 121rsy@dsmc.or.kr

ORCID iDs
Miri Hyun
https://orcid.org/0000-0003-0062-342X
Seong Yeol Ryu
https://orcid.org/0000-0002-6023-8550

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

Author Contributions
Conceptualization: HMR. Data curation: LJY. Formal analysis: HMR, KHA. Methodology: HMR, LJY. Writing - review & editing: HMR, KHA, RSY.

ABSTRACT

Background: *Escherichia coli* and *Klebsiella pneumoniae* are two of the most common causes of urinary tract infection. The purpose of this study was to compare clinical characteristics and antimicrobial susceptibility of acute pyelonephritis (APN) between *E. coli* and *K. pneumoniae*.
Materials and Methods: We retrospectively reviewed medical records of patients with APN due to *E. coli* and *K. pneumoniae* between February 2014 and October 2017.
Results: A total 329 patients were enrolled; 258 cases of *E. coli* and 71 cases of *K. pneumoniae*. Among them, 219 cases were categorized into community-onset APN; 194 cases of *E. coli* and 25 cases of *K. pneumoniae*, and 110 patients were categorized into healthcare-associated APN; 64 cases of *E. coli* and 46 cases of *K. pneumoniae*. Catheter-associated APN was more frequently observed in *K. pneumoniae* in both community-onset and healthcare-associated APN. Neurogenic bladder, obstructive uropathy, urinary tract stone, bacteremia, and severe APN were more related to *E. coli* in healthcare-associated APN. In multivariate analysis, urinary catheter was more associated with *K. pneumoniae* (odds ratio [OR] 9.643, 95% confidence intervals [CI] 4.919-18.904, $P = 0.001$) and neurogenic bladder was more associated with *E. coli* (OR 3.765, 95% CI 1.112-12.772, $P = 0.033$). Extended-spectrum β-lactamase (ESBL) production was observed in 29.0% of *E. coli* in community-onset APN. Among ESBL, antimicrobial susceptibility of piperacillin/tazobactam was significantly higher in *E. coli* and ciprofloxacin was significantly higher in *K. pneumoniae*.
Conclusion: *K. pneumoniae* were more associated with urinary catheter while *E. coli* tended to be more associated with urogenital problems. ESBL positivity showed no significance in healthcare-associated APN. In community-onset APN, ESBL producing *E. coli* was more observed than *K. pneumoniae*.

Keywords: Urinary tract infection; *Escherichia coli*; *Klebsiella pneumoniae*

INTRODUCTION

Urinary tract infections (UTIs) are one of the most common bacterial infections and are caused by both Gram-negative and Gram-positive bacterium [1]. Also, UTIs are one of the major healthcare-associated infections (HAIs) [2] and account for up to 32% of all HAIs [3]. HAIs are a major concern for patient safety and can result in prolonged hospital stay,

increased morbidity and mortality, increased antimicrobial resistance, and excess financial burden [4]. UTIs are mostly complicated with various predisposing factors [5]. In more than 80% of the cases, they are related to the use of urologic devices including foley catheters [6], and according to risk factors and clinical settings, there are several described uropathogens [7]. *E. coli* is reported as the most common pathogen of UTIs, followed by the second most common, *K. pneumonia* [8]. In a multicenter study of bacteremic UTIs performed in Korea, the proportions of *E. coli* and *K. pneumoniae* infections were 71.8% in healthcare-associated UTIs and 89.9% in community-onset UTIs [8, 9]. Although several studies have described the characteristics of uropathogenic *E. coli* and *K. pneumoniae* individually [10, 11], there are only few studies comparing clinical characteristics between these two pathogens, especially studies comparing them in UTIs. Also, increased antimicrobial resistance in *Enterobacteriaceae* is a global concern [12-14]. The aim of this study was to compare the predisposing factors, clinical characteristics, treatment outcomes, and antimicrobial susceptibility profiles between acute pyelonephritis (APN) caused by *E. coli* and *K. pneumoniae*.

MATERIALS AND METHODS

1. Study subjects

Patients with monomicrobial APN who were admitted at Keimyung University Dongsan Medical Center between January 2014 to December 2017 with *E. coli* or *K. pneumoniae* isolated from clinical specimens were enrolled in this study. They were divided into two groups, labeled as *E. coli* and *K. pneumoniae*. Asymptomatic bacteriuria was excluded.

APN was defined as one or more of the followings: 1) the presence of fever (body temperature above 38°C), pyuria and bacteriuria with urinary symptoms, flank pain, and tenderness of costovertebral angle, 2) although there were no specific symptoms or signs of UTI, APN was identified in the radiologic findings with fever or leukocytosis, and there was no other focus of infection [15]. Obstructive uropathy included benign prostate hypertrophy (BPH) and uterine prolapse. Severe APN was determined as severe sepsis or shock due to APN. Recurrent UTI was defined as defined as ≥3 microbiologically documented episodes of symptomatic UTI during the last year or 2 episodes during the last 6 months. HAI was defined as a nosocomial infection (clinical symptoms of infection occurred 48 hours after hospital admission) or community onset infections with healthcare-associated risk factors, such as hospitalization within 90 days, received dialysis, taken intravenous medication in outpatient clinics, or resided in long-term care facilities. An invasive procedure was considered a medical procedure that invades the body, usually puncturing the skin and inserting prosthesis or aspirating, such as percutaneous needle aspiration, percutaneous nephrostomy, or percutaneous pus drainage. Patients who were under 18 years old or transferred to other hospitals during treatment were excluded.

Medical records, including epidemiology, underlying diseases, predisposing factors, previous antibiotic use, clinical characteristics, antimicrobial susceptibility profile, and treatment outcomes, were retrospectively analyzed. Severity of comorbidity was classified based on McCabe and Jackson score system; nonfatal underlying disease, ultimately fatal disease, and rapidly fatal disease. Diabetes or genitourinary, and gastrointestinal diseases were included in nonfatal diseases. Ultimately fatal diseases were defined as estimated to become fatal within 4 years, such as aplastic anemia, chronic leukemia, lymphomas, metastatic carcinomas, and severe heart failure. Acute leukemia or blastic relapse of chronic

https://doi.org/10.3947/ic.2019.51.2.130

leukemia were included in rapidly fatal disease [16]. Empirical antibiotic treatment and antibiotic adequacy were compared and analyzed between the two groups. The treatment outcomes were evaluated by the defervescence within 72 hours after empirical antibiotics, 30-day mortality, infection-related 30-day mortality, acute kidney injury, need for invasive procedure, and recurrence of UTI within 3 months. Infection-related 30-day mortality was defined as patients expired due to UTI or complications of UTI within 30 days. If the patients were discharged from hospital after admission within 30 days, we followed up the patients over 1 months at outpatient clinic. Acute kidney injury was defined as an increase in serum creatinine by >0.3 mg/dL within 48 hours, or an increase in serum creatinine to >1.5 times the baseline, or urine volume <0.5 mL/kg/hour for 6 hours.

Clinical specimens, such as blood, urine, and pus were obtained for identification of microorganisms. *E. coli* or *K. pneumoniae* isolation was performed using a Vitek system (BioMerieux, Lyon, France). Antimicrobial susceptibility profile was determined by the interpretation of the breakpoints recommended by the Clinical and Laboratory Standards Institute (CLSI) [17]. The study was approved by the Institutional Review Board of Dongsan Medical Center (IRB 2015-11-043).

2. Statistical methods

Statistical analysis was performed using SPSS version 21.0 (IBM Co., Armonk, NY, USA). Categorical variables were compared using the Pearson chi-square test or Fisher exact test. Continuous variables were compared using the Mann-Whitney *U* test or Student *t* test. Binary logistic regression was used to identify variables significantly associated with *K. pneumoniae* infection compared to *E. coli*. Statistical significance was defined as *P* values <0.05.

RESULTS

A total of 341 patients were diagnosed with APN, with *E. coli* or *K. pneumoniae* isolation in clinical specimens during the study period; 266/341 were cases of *E. coli* and 75/341 of *K. pneumoniae*. Eight patients with *E. coli* and four patients with *K. pneumoniae* infections were excluded because they were transferred to another hospital during treatment, attaining of a total of 329 patients with APN; 258/329 were cases of *E. coli* and 71/329 were cases of *K. pneumoniae*. Among them, 219 patients were classified into community-onset APN; 194/219 cases of *E. coli* and 25/219 cases of *K. pneumoniae* infections and 110 patients were classified into healthcare-associated APN; 64/110 cases of *E. coli* and 46/110 cases of *K. pneumoniae* infections (**Fig. 1**).

1. Baseline epidemiology, predisposing factors, and clinical characteristics between *Escherichia coli* and *Klebsiella pneumoniae*

The demographics, category of infections, underlying diseases, and predisposing factors of the two groups are shown in **Table 1**. Mean age was higher in *E. coli* group than in *K. pneumoniae*. Males were more observed in *K. pneumoniae* group. In category of infection, community-onset APN was more observed in *E. coli*, whereas healthcare-associated APN was more observed in *K. pneumoniae*. Underlying diseases except neurologic diseases and solid organ transplantations showed no differences between the two groups. Urinary tract stone, recurrent UTI and bacteremia were more associated with *E. coli*. Urinary catheter use and complicated APN were more associated with *K. pneumoniae*.

https://doi.org/10.3947/ic.2019.51.2.130

ic Infection & Chemotherapy

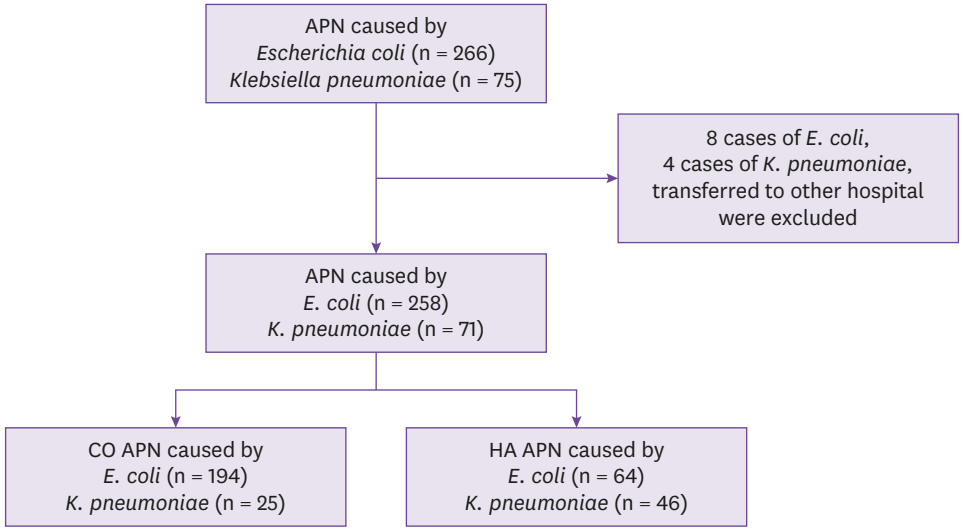

Figure 1. Flow chart showing the number of patients enrollment in this study.
APN, acute pyelonephritis; CO, community-onset; HA, healthcare-associated.

Table 1. Comparison of baseline characteristics, predisposing factors, clinical characteristics, and treatment outcome of acute pyelonephritis between *Escherichia coli* and *Klebsiella pneumoniae*

Variable	*E. coli* (n = 258) N (%)	*K. pneumoniae* (n = 71) N (%)	*P* value
Age (years)	69.59 ± 14.26	65.85 ± 14.98	0.054
Male	45 (17.4%)	23 (31.0%)	0.012
Category of infection			0.001
Community-onset	194 (75.2%)	25 (35.2%)	
Healthcare-associated	64 (24.8%)	46 (64.8%)	
Underlying diseases			
Solid tumor	37 (14.3%)	14 (19.7%)	0.268
Diabetes mellitus	104 (40.3%)	32 (45.1%)	0.471
Chronic liver disease	36 (14.0%)	6 (8.5%)	0.219
Chronic renal disease	9 (3.5%)	7 (9.9%)	0.054
Chronic lung disease	30 (11.6%)	4 (5.6%)	0.142
Neurologic disease	90 (34.9%)	38 (53.5%)	0.004
Hematologic malignancy	0 (0.0%)	1 (1.3%)	0.225
Solid organ transplantation	0 (0.0%)	4 (5.3%)	0.002
Predisposing factors			
Neurogenic bladder	22 (8.5%)	5 (7.0%)	0.686
Obstructive uropathy	23 (8.9%)	2 (2.8%)	0.086
Recurrent UTI	27 (10.5%)	0 (0.0%)	0.004
Urinary catheter	29 (11.2%)	36 (50.7%)	0.001
Hydronephrosis	27 (10.5%)	7 (9.9%)	0.882
Urinary tract stone	29 (11.2%)	2 (2.8%)	0.031
Prior antibiotics within 3 months	57 (22.1%)	20 (28.2%)	0.284
Clinical characteristics			
Severe UTI	172 (66.7%)	50 (70.4%)	0.550
Bacteremia	161 (62.4%)	25 (35.2%)	0.001
Complicated APN	39 (15.1%)	48 (67.6%)	0.001
Acute kidney injury	39 (15.1%)	14 (19.7%)	0.350
Treatment outcome			
Defervescence within 72 hours	197 (76.4%)	58 (81.7%)	0.341
30-day mortality	4 (1.6%)	11 (14.7%)	0.001
Hospital stay after infection (days)	14.38 ± 9.82	19.69 ± 21.63	0.047
Relapse within 3 months	20 (7.8%)	6 (8.0%)	0.944

UTI, urinary tract infection; APN, acute pyelonephritis.

https://doi.org/10.3947/ic.2019.51.2.130

2. Comparison of baseline epidemiology and clinical characteristics between *Escherichia coli* and *Klebsiella pneumoniae* healthcare-associated APN

The baseline characteristics, category of infections, predisposing factors, and clinical characteristics in healthcare-associated APN were shown in **Table 2**. In category of infection, community-onset infections with healthcare-associated risk factors and nosocomial infections were 52 cases (81.2%), 12 cases (18.8%) in *E. coli* group and 16 cases (30.4%), 32 cases (69.6%) in *K. pneumoniae* group, respectively. Hospital stays before infection were 0.02 days in *E. coli* group and 27.80 days in *K. pneumoniae* ($P = 0.005$). There were no significant differences in underlying systemic diseases between the two groups. Ultimately fatal diseases were more observed in *K. pneumoniae* group. Prior usage of antibiotics within 3 months was not different between the two groups. There were no significant differences in the kinds of previously used antibiotic; piperacillin/tazobactam (15.8% *vs.* 35.0%, $P = 0.111$), third cephalosporin (60.5% *vs.* 40.0%, $P = 0.136$), fluoroquinolone (44.7% *vs.* 40.0%, $P = 0.729$) and carbapenem (15.8% *vs.* 30.0%, $P = 0.307$). Recurrent UTI was more frequently observed in *E. coli* together with neurogenic bladder, and obstructive uropathy. Urinary catheter use was more associated to *K. pneumoniae* infection. Presence of urinary tract stone was associated to *E. coli* and the same was observed for hydronephrosis without significance. Abscess formation showed no significant differences between the two groups. Renal abscesses were combined in five cases in *E. coli* group (7.8%) and three in *K. pneumoniae* group (6.5%).

Table 2. Comparison of clinical characteristics and treatment outcomes between *Escherichia coli* and *K. pneumoniae* healthcare-associated acute pyelonephritis

	E. coli (n = 64)	*K. pneumoniae* (n = 46)	*P* value
Age (years)	74.22 ± 12.24	65.76 ± 14.73	0.001
Male	21 (32.8%)	12 (26.1%)	0.448
Category of infection			0.001
Community-onset	52 (81.2%)	16 (30.4%)	
Nosocomial	12 (18.8%)	32 (69.6%)	
Severity of comorbidity			0.018
McCabe and Jackson			
Nonfatal disease	59 (92.2%)	35 (76.1%)	
Ultimately fatal disease	5 (7.8%)	11 (23.9%)	
Rapidly fatal disease	0 (0.0%)	0 (0.0%)	
Predisposing factors			
Neutropenia	0 (0.0%)	1 (2.0%)	0.439
Neurogenic bladder	12 (18.8%)	2 (4.3%)	0.025
Obstructive uropathy	10 (15.6%)	1 (2.2%)	0.024
Recurrent UTI	17 (26.6%)	0 (0.0%)	0.001
Urinary catheter	16 (25.0%)	25 (54.3%)	0.002
Hydronephrosis	9 (14.1%)	2 (4.3%)	0.116
Urinary tract stone	9 (14.1%)	0 (0.0%)	0.010
Prior antibiotics within 3 months	38 (59.4%)	20 (43.5%)	0.100
Hospital stays before infection (days)	0.02 ± 0.13	27.80 ± 77.46	0.005
Clinical characteristics			
Severe APN	34 (53.1%)	10 (21.7%)	0.001
Bacteremia	44 (68.8%)	11 (23.9%)	0.001
Complicated APN	19 (29.7%)	31 (67.4%)	0.001
Acute kidney injury	9 (14.1%)	8 (17.4%)	0.634
Treatment outcomes			
Defervescence within 72 hours	14 (21.9%)	9 (19.6%)	0.769
Thirty-day mortality	3 (4.7%)	9 (19.6%)	0.014
Infection related 30-day mortality	2 (3.1%)	1 (2.6%)	0.999
Hospital stay after infection (days)	20.19 ± 13.97	26.14 ± 26.37	0.124
Relapse within 3 months	10 (15.6%)	2 (4.3%)	0.061

UTI, urinary tract infection; APN, acute pyelonephritis.

https://doi.org/10.3947/ic.2019.51.2.130

Prostatic abscesses were combined in two cases in *E. coli* group (3.1%). Finally, severe APN and bacteremic APN were more associated with *E. coli* infection (**Table 2**).

In multivariate analysis, urinary catheter use was more associated with *K. pneumoniae* than *E. coli* infection (**Table 3**). Age over 65 years (odds ratio [OR] 2.112, 95% confidence intervals [CI] 1.142-3.906, $P = 0.017$) and neurogenic bladder (OR 3.765, 95% CI 1.112-12.772, $P = 0.033$) were more associated with *E. coli* infection.

3. Comparison of antimicrobial susceptibility rates between *Escherichia coli* and *Klebsiella pneumoniae*

Comparisons of antimicrobial susceptibility rates between *E. coli* and *K. pneumoniae* were shown in **Table 4**.

In total cases, ESBL positivity was no significant differences between *E. coli* and *K. pneumoniae* group. Piperacillin/tazobactam and tigecycline were more sensitive to *E. coli* than *K. pneumoniae*. Whereas, ciprofloxacin and gentamicin were more sensitive to *K. pneumoniae* than *E. coli*.

In community-onset APN, ESBL positivity were observed in 29.0% of *E. coli* and 8.0% of *K. pneumoniae*. Amoxicillin/clavulanate, aztreonam, cefazolin, ceftazidime, cefepime, and ciprofloxacin were more sensitive to *E. coli* than *K. pneumoniae*. Piperacillin/tazobactam showed similar antimicrobial susceptibility rate, 93.3% in *E. coli* and 96.0% in *K. pneumoniae*.

In healthcare-associated APN, *K. pneumoniae* group was more sensitive to ciprofloxacin and gentamicin while *E. coli* group was more sensitive to piperacillin/tazobactam and tigecycline.

Table 3. Predisposing factors associated with *Klebsiella pneumoniae* compared to *Escherichia coli* in acute pyelonephritis

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age > 65 years	0.519 (0.302–0.891)	0.017	0.473 (0.256–0.875)	0.017
Male	2.125 (1.170–3.861)	0.013	1.705 (0.841–3.456)	0.139
Diabetes mellitus	1.215 (0.715–2.063)	0.471		
Urinary catheter	8.122 (4.436–14.870)	0.001	9.643 (4.919–18.904)	0.001
Neurogenic bladder	0.813 (0.296–2.228)	0.687	0.266 (0.078–0.901)	0.033
Obstructive uropathy	0.296 (0.068–1.288)	0.105		
Urinary tract stone	0.229 (0.053–0.984)	0.047	0.214 (0.045–1.010)	0.052

CI, confidence interval.

Table 4. Comparison of antimicrobial susceptibility between *Escherichia coli* and *Klebsiella pneumoniae*

	Total (n = 329)			Community-onset APN (n = 219)			Healthcare-associated APN (n = 110)		
	E. coli (n = 258) N (%)	*K. pneumoniae* (n = 71) N (%)	*P* value	*E. coli* (n = 194) N (%)	*K. pneumoniae* (n = 25) N (%)	*P* value	*E. coli* (n = 64) N (%)	*K. pneumoniae* (n = 46) N (%)	*P* value
Amikacin	255 (99.2%)	67 (94.4%)	0.021	193 (100.0%)	25 (100.0%)	-	62 (96.9%)	42 (91.3%)	0.234
Amoxicillin/clavulanate	154 (59.9%)	48 (67.6%)	0.239	129 (66.8%)	24 (96.0%)	0.003	25 (39.1%)	24 (52.2%)	0.172
Aztreonam	153 (59.5%)	38 (53.5%)	0.363	137 (71.0%)	23 (92.0%)	0.025	16 (25.0%)	15 (32.6%)	0.382
Cefazolin	140 (54.5%)	36 (50.7%)	0.573	126 (65.3%)	23 (92.0%)	0.007	14 (21.9%)	13 (28.3%)	0.443
Cefotaxime	148 (57.6%)	38 (53.5%)	0.540	133 (68.9%)	23 (92.0%)	0.025	15 (23.4%)	15 (32.6%)	0.287
Cefepime	153 (59.5%)	39 (54.9%)	0.486	137 (71.0%)	23 (92.0%)	0.025	16 (25.0%)	16 (34.8%)	0.265
Ciprofloxacin	144 (56.0%)	50 (70.4%)	0.029	130 (67.4%)	24 (96.0%)	0.003	14 (21.9%)	26 (56.5%)	0.001
Gentamicin	170 (66.1%)	57 (80.3%)	0.022	139 (72.0%)	22 (88.0%)	0.087	31 (48.4%)	35 (76.1%)	0.004
Piperacillin/tazobactam	232 (90.3%)	53 (74.6%)	0.001	180 (93.3%)	24 (96.0%)	0.999	52 (81.2%)	29 (63.0%)	0.033
Tigecycline	257 (100.0%)	64 (90.1%)	0.001	193 (100.0%)	24 (96.0%)	0.115	64 (100.0%)	40 (87.0%)	0.004
TMP/SMX	155 (60.3%)	46 (64.8%)	0.493	127 (65.8%)	22 (88.0%)	0.025	28 (43.8%)	24 (52.2%)	0.383
ESBL positivity	104 (40.5%)	32 (45.1%)	0.486	56 (29.0%)	2 (8.0%)	0.025	48 (75.0%)	30 (65.2%)	0.265

APN, acute pyelonephritis; TMP/SMX, trimethoprim/sulfamethoxazole; ESBL, extended-spectrum β-lactamase.

https://doi.org/10.3947/ic.2019.51.2.130

Table 5. Comparison of antimicrobial susceptibility between extended spectrum-β lactamase producing *Escherichia coli* and *Klebsiella pneumoniae* in healthcare-associated acute pyelonephritis

	E. coli (n = 48) N (%)	*K. pneumoniae* (n = 30) N (%)	*P* value
Amikacin	46 (95.8%)	27 (90.0%)	0.367
Gentamicin	16 (33.3%)	20 (66.7%)	0.004
Ciprofloxacin	5 (10.4%)	11 (36.7%)	0.005
Cefepime	0 (0.0%)	0 (0.0%)	-
Piperacillin/tazobactam	36 (75.0%)	14 (46.7%)	0.011
Trimethoprim/sulfamethoxazole	17 (35.4%)	10 (33.3%)	0.851

ESBL productions were observed in 48 cases of *E. coli* (75.0%) and 30 cases of *K. pneumoniae* (65.2%) infection. Among the pathogens confirmed as ESBL-producing, *E. coli* was more susceptible to piperacillin/tazobactam (75.0% *vs.* 46.7%, $P = 0.011$) and *K. pneumoniae* to ciprofloxacin (10.4% *vs.* 36.7%, $P = 0.005$). Susceptibility to trimethoprim/sulfamethoxazole showed no significant differences between the two groups (35.4% *vs.* 33.3%, $P = 0.851$) (**Table 5**).

In subgroup analysis of 104 cases of APN with ESBL producing *E. coli*, percentages of community-onset APN, community-onset APN with healthcare associated risk factors, and nosocomial APN were 53.8%, 37.5%, 8.7%, respectively. In 32 cases of APN with ESBL producing *K. pneumoniae*, the percentages were 6.2%, 21.9%, and 71.9%, respectively ($P = 0.001$).

4. Comparisons of empirical antibiotics, antibiotic adequacy, and treatment outcomes between the two groups

In community-onset APN, 3rd-generation cephalosporins were the most commonly used empirical antibiotics in both groups (90.2% *vs.* 80.0%, $P = 0.164$), followed by carbapenem (6.2% *vs.* 12.0%, $P = 0.389$). One hundred thirty-seven cases of *E. coli* and 24 cases of *K. pneumoniae* were treated using concordant antibiotics. The adequacy of empirical antibiotics showed 70.6% in *E.coli* and 96.0% in *K. pneumoniae* group ($P = 0.007$).

No significant differences between the two groups were observed in the cases with defervescence within 72 hours (75.8% *vs.* 84.0%, $P = 0.360$) and acute kidney injury (15.5% *vs.* 24.0%, $P = 0.263$). Hospital stay after infection was longer in *E. coli* than in *K. pneumoniae* group (12.46 days *vs.* 10.48 days, $P = 0.187$). Thirty-day mortality (0.5% *vs.* 4.0%, $P = 0.216$) and infection related 30-day mortality (0.0% *vs.* 6.2%, $P = 0.076$) showed no significant differences between the two groups. Relapsed UTI within 3 months was more commonly observed in *K. pneumoniae* when compared to *E. coli* group with no significance (5.2% *vs.* 12.0%, $P = 0.376$).

In healthcare-associated APN, 3rd-generation cephalosporins were the most commonly used empirical antibiotics in both groups (62.5% *vs.* 47.7%, $P = 0.128$), followed by carbapenem (28.1% *vs.* 27.3%, $P = 0.923$). Thirty-seven cases of *E. coli* (57.8%) were treated using concordant antibiotics and 27 cases using discordant antibiotics. Considering these 27 discordant cases, the treatment was modified to definitive antibiotics during hospitalization and 24/27 cases (88.8%) were modified within 72 hours. Thirty cases of *K. pneumoniae* (60%) were treated using concordant antibiotics, and 20 cases using discordant antibiotics. Among them, 18/20 (90.0%) cases were modified to definitive antibiotics and 15/20 cases (75.0%) were modified within 72 hours. Comparison of the adequacy of empirical antibiotics showed no significant differences between the two groups ($P = 0.617$). The duration of antimicrobial treatment was longer in the *E. coli* group than in the *K. pneumoniae* group (21.4 days *vs.* 15.6 days, $P = 0.003$).

https://doi.org/10.3947/ic.2019.51.2.130

Need for an invasive procedure was observed in 12.5% of *E. coli* cases and 4.0% of *K. pneumoniae* cases with no significance ($P = 0.182$). No significant differences between the two groups were observed in the cases with defervescence within 72 hours and acute kidney injury (**Table 5**). Hospital stay after infection was longer in *K. pneumoniae* than in *E. coli* group (20.2 days *vs.* 26.1 days, $P = 0.124$). Thirty-day mortality was significantly higher in *K. pneumoniae* group. However, infection-related 30-day mortality showed no significant difference between the two groups. Relapsed UTI within 3 months was more commonly observed in *E. coli* when compared to *K. pneumoniae* group with no significance (15.6% *vs.* 6.0%, $P = 0.109$).

Relapses within 3 months, infection related 30-day mortality, and defervescences within 72 hours showed no significant differences according to adequacy of empirical antibiotics.

DISCUSSION

E. coli and *K. pneumoniae* are two of the most common pathogens associated with high morbidity and mortality among Gram-negative bacilli, especially in UTI [18]. The etiologies of UTI were diverse according to regions and countries, and dependent on the severity of complications; *E. coli* was the most common, followed by *K. pneumonia* [6, 7, 19, 20]. Baizet et al. reported that *E. coli* was the most common pathogen in cystitis, pyelonephritis in females, and upper UTI in male. *K. pneumoniae* was the second most common pathogen in pyelonephritis in females and upper UTI in males [19]. Comparisons of clinical characteristics between *E. coli* and *K. pneumoniae* had been presented in many reports [19, 21]; however, comparative studies regarding the differences in antimicrobial resistance rates and predisposing factors between the two strains were rare. In this study, we compared clinical characteristics, treatment outcomes, and determined the antimicrobial susceptibility profiles of UTI between *E. coli* and *K. pneumoniae*.

K. pneumoniae was more associated with urinary catheter use in this study. In healthcare-associated UTI, most cases were associated with urinary catheter use [5-7]. Oh et al. reported that patients with catheter-associated UTI had diverse pathogens according to different kinds and indwelling duration of urinary catheter (intermittent, short-term, and long-term catheterization) [7]. Indeed, urinary catheters serve as common predisposing substrates of UTIs. Maharhan et al. reported that *E. coli* was the most common biofilm-forming bacteria in catheter-associated UTI [22]. Biofilm-forming mechanisms can be different according to the pathogen. Uropathogens, such as *K. pneumoniae* and *Proteus mirabilis* produce urease and form crystalline biofilms on urinary catheters. Urease production can break down the urea, release ammonia, and increase urine pH and calcium magnesium phosphate crystal formation within the biofilm matrix. Crystal formation can block the catheter and lead to bladder distension, urine leakage, and bladder reflux into the kidney [23]. Uropathogenic *E. coli* have different mechanisms for biofilm formation; several virulence factors, such as *a*-hemolysin, lipopolysaccharide, protease, adhesins, aerobactin, and fimbriae, have important roles in forming the biofilm. Among several virulence factors, type I fimbriae play an important role in the attachment to the mucosal epithelium, initiation of biofilm formation, and persistence in the bladder [24]. Besides, biofilm production can increase resistance to antibiotics and virulence [25]. Unlike previous studies, we determined that *K. pneumoniae* was more associated with urinary catheter use than *E. coli*. Further research will be necessary to determine whether there are differences between these two pathogens in biofilm formation.

https://doi.org/10.3947/ic.2019.51.2.130

Along with biofilm formation, residual urine after voiding is a risk factor for UTI. *E. coli* was significantly associated with neurogenic bladder in this study. The probability of UTI appearance can increase in proportion to the residual volume of urine. Residual urine volume greater than 100 mL resulted in a 4.9-fold increase in UTI occurrence compared to those with residual volume less than 100 mL [26]. Furthermore, increased intravesical pressure results in bladder ischemia and delayed immune response to uropathogens. Additionally, neurogenic bladder, especially in patients with spinal cord injury, might lead to immune dysfunctions, such as decreased proinflammatory and anti-inflammatory responses to uropathogens. Therefore, uropathogens, such as *E. coli* and *K. pneumoniae* may not be easily eradicated with antibiotics when invading urothelial cells during acute UTI and proliferating within the urothelium [27].

In addition, urinary tract stone and obstructive uropathy were more frequently observed in *E. coli* infection in this study. Obstructive uropathy, such as BPH in men and uterine prolapse in women, can cause a physiologic blockage of the urethra and bladder outlet resulting in urinary stasis. In the same way, ureteral obstruction caused by urinary tract stones can prompt urinary stasis and renal dysfunction. As a result, urinary stasis can induce adherence of bacteria and invasion to the urogenital epithelium [28]. Chen et al. reported that the four most common uropathogens isolated from patients with urinary stones were *E. coli*, *K. pneumoniae*, *P. mirabilis* and *Enterococcus faecalis* [29].

Megged et al. compared bacteremic UTI to non-bacteremic UTI. Patients with bacteremic UTI were more associated with male, higher creatinine levels, and underlying urologic conditions other than non-bacteremic UTI [30]. Oh et al. proposed a model to estimate the probability of bacteremia in UTI. Risk factors of bacteremia were diabetes mellitus, urinary tract stone, tenderness of costovertebral angle, azotemia, neutrophilia, and thrombocytopenia [31]. In the present study, bacteremic UTI was more associated with *E. coli*. Furthermore, *E. coli* was more associated with male sex, neurogenic bladder, and presence of urinary tract stone. These factors might lead to a higher incidence of bacteremia in *E. coli* infection.

Recently, antimicrobial resistance in Gram-negative bacteria has been gradually increasing worldwide [12]. In Bangladesh, antimicrobial resistance rates to third-generation cephalosporins in *Enterobacteriacea*e were over 50% in UTI, including community-onset and healthcare-associated infections [13]. In the present study, the proportions of ESBL production were 29.0% in *E. coli* and 8.0% in *K. pneumoniae* in community-onset APN. Also, over 30% of *E. coli* in community-onset APN were resistant to ciprofloxacin. Ciprofloxacin or 3rd generation cephalosporin is recommended as empirical antibiotics for community-onset APN. In a report of community-onset UTI conducted in United Arab Emirates, 76% of *E. coli* and *K. pneumoniae* were ESBL producers [14]. Based on the present and previous study results, antibiotic resistance in community can be a global concern in the near future. Besides, 60-70% isolates of *E. coli* and *K. pneumoniae* in healthcare-associated UTI were resistant to third- and fourth-generation cephalosporins in the present study. In addition, in a report conducted in Turkey, ESBL production was detected in 82.8% of *K. pneumoniae* and 72.9% of *E. coli* cases in pediatric patients with nosocomial UTI [32]. Extended-spectrum cephalosporins, such as ceftazidime or cefepime, were recommended as empirical antibiotics for healthcare-associated UTI [33]. Based on present and previous study results about antimicrobial resistance of *Enterobacteriaceae*, we think that it is difficult to recommend third- or fourth-generation cephalosporins as an empirical antibiotic in healthcare-associated UTI because of higher resistance development. Instead, piperacillin/tazobactam, carbapenem, and amikacin were relatively effective in both bacteria.

https://doi.org/10.3947/ic.2019.51.2.130

A study by Scheurman et al. reported that acquisitions of ESBL-producing *Enterobacteriaceae* bloodstream infections were more observed in nosocomial and community-onset healthcare-associated infections [34]. Subgroup analysis of our study shows that ESBL-producing *E. coli* was relatively high in community-onset APN than *K. pneumoniae*. The discrepancy of these two studies might be due to difference of sources of bacteremia and composition of community and healthcare-associated infections. Also, resistance of these bacteria has been changed over the times from the mentioned study. For these reasons, high ESBL positivity of *E. coli* in community-onset APN might be presented in our study.

There are several limitations to this study. First, this study was retrospective and relied on microbiological culture results, which may introduce bias in the data interpretation. Second, we had to rely only on medical records. Third, we could not identify the different kinds of urinary catheters and duration of indwelling catheters. Additionally, it was difficult to evaluate urinary function or identify the subjective symptoms of discomfort during urination in all patients. Fourth, we should acknowledge that patients included in this study were in a tertiary hospital and might be in a more severe state than those in a primary medical center.

Despite these limitations, we found the characteristics of predisposing factors, clinical manifestations, and antimicrobial susceptibility of *E. coli* and *K. pneumoniae* in healthcare-associated UTI in a tertiary hospital setting in South Korea. Common causative pathogens of healthcare-associated UTI can be diverse according to region and country. Additionally, antimicrobial susceptibility can be different according to local antimicrobial resistance pattern and history of previous antibiotics use. Therefore, further multicenter studies regarding antimicrobial susceptibility and clinical characteristics of uropathogens in healthcare-associated UTI will be needed to identify the epidemiology of uropathogens and antimicrobial susceptibility in our country.

In conclusions, *K. pneumoniae* was more associated with urinary catheter use, and *E. coli* was more associated with an anatomical or functional urologic problem. *E. coli* was more associated with bacteremic UTI and severe UTI. Antimicrobial susceptibility test revealed that ESBL producing *E. coli* were more observed than *K. pneumoniae* in community-onset APN and antimicrobial resistant rates of third- and fourth-generation cephalosporins were high in both *E. coli* and *K. pneumoniae* in healthcare-associated APN.

ACKNOWLEGMENTS

We are grateful to Eun-Sil Park for contributions to data collection.

REFERENCES

1. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol 2015;13:269-84.
PUBMED | CROSSREF
2. Magill SS, Hellinger W, Cohen J, Kay R, Bailey C, Boland B, Carey D, de Guzman J, Dominguez K, Edwards J, Goraczewski L, Horan T, Miller M, Phelps M, Saltford R, Seibert J, Smith B, Starling P, Viergutz B, Walsh K, Rathore M, Guzman N, Fridkin S. Prevalence of healthcare-associated infections in acute care hospitals in Jacksonville, Florida. Infect Control Hosp Epidemiol 2012;33:283-91.
PUBMED | CROSSREF

3. Ali S, Birhane M, Bekele S, Kibru G, Teshager L, Yilma Y, Ahmed Y, Fentahun N, Assefa H, Gashaw M, Gudina EK. Healthcare associated infection and its risk factors among patients admitted to a tertiary hospital in Ethiopia: longitudinal study. Antimicrob Resist Infect Control 2018;7:2.
PUBMED | CROSSREF
4. Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, Donaldson L, Pittet D. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. Lancet 2011;377:228-41.
PUBMED | CROSSREF
5. Wagenlehner FM, Cek M, Naber KG, Kiyota H, Bjerklund-Johansen TE. Epidemiology, treatment and prevention of healthcare-associated urinary tract infections. World J Urol 2012;30:59-67.
PUBMED | CROSSREF
6. Vásquez V, Ampuero D, Padilla B. Urinary tract infections in inpatients: that challenge. Rev Esp Quimioter 2017;30 (Suppl 1):39-41.
PUBMED
7. Oh WS, Hur JA, Kim ES, Park KH, Choi HK, Moon C, Kim BN. Factors associated with specific uropathogens in catheter-associated urinary tract infection: developing a clinical prediction model. J Int Med Res 2014;42:1335-47.
PUBMED | CROSSREF
8. Kang CI, Chung DR, Son JS, Ko KS, Peck KR, Song JH; Korean Network for Study of Infectious Diseases. Clinical significance of nosocomial acquisition in urinary tract-related bacteremia caused by gram-negative bacilli. Am J Infect Control 2011;39:135-40.
PUBMED | CROSSREF
9. Chiang CH, Pan SC, Yang TS, Matsuda K, Kim HB, Choi YH, Hori S, Wang JT, Sheng WH, Chen YC, Chang FY, Chang SC. Healthcare-associated infections in intensive care units in Taiwan, South Korea, and Japan: recent trends based on national surveillance reports. Antimicrob Resist Infect Control 2018;7:129.
PUBMED | CROSSREF
10. Olesen B, Kolmos HJ, Orskov F, Orskov I. A comparative study of nosocomial and community-acquired strains of Escherichia coli causing bacteraemia in a Danish University Hospital. J Hosp Infect 1995;31:295-304.
PUBMED | CROSSREF
11. Tsay RW, Siu LK, Fung CP, Chang FY. Characteristics of bacteremia between community-acquired and nosocomial Klebsiella pneumoniae infection: risk factor for mortality and the impact of capsular serotypes as a herald for community-acquired infection. Arch Intern Med 2002;162:1021-7.
PUBMED | CROSSREF
12. Kreger BE, Craven DE, Carling PC, McCabe WR. Gram-negative bacteremia. III. Reassessment of etiology, epidemiology and ecology in 612 patients. Am J Med 1980;68:332-43.
PUBMED | CROSSREF
13. Haque R, Akter ML, Salam MA. Prevalence and susceptibility of uropathogens: a recent report from a teaching hospital in Bangladesh. BMC Res Notes 2015;8:416.
PUBMED | CROSSREF
14. Ranjan Dash N, Albataineh MT, Alhourani N, Khoudeir AM, Ghanim M, Wasim M, Mahmoud I. Community-acquired urinary tract infections due to extended-spectrum β -lactamase-producing organisms in United Arab Emirates. Travel Med Infect Dis 2018;22:46-50.
PUBMED | CROSSREF
15. Kunin CM. Definition of acute pyelonephritis vs the urosepsis syndrome. Arch Intern Med 2003;163:2393; author reply 2393-4.
PUBMED | CROSSREF
16. McCabe WR, Jackson GG. Gram-negative bacteremia.I. Etiology and ecology. Arch Intern Med 1962;110:847-55.
CROSSREF
17. Clinical and Laboratory Standards Institute (CLSI). M100-S25 performance standards for antimicrobial susceptibility testing; Twenty-fifth informational supplement. Wayne, PA: CLSI; 2015.
18. Uslan DZ, Crane SJ, Steckelberg JM, Cockerill FR 3rd, St Sauver JL, Wilson WR, Baddour LM. Age- and sex-associated trends in bloodstream infection: a population-based study in Olmsted County, Minnesota. Arch Intern Med 2007;167:834-9.
PUBMED | CROSSREF
19. Baizet C, Ouar-Epelboin S, Walter G, Mosnier E, Moreau B, Djossou F, Epelboin L. Decreased antibiotic susceptibility of Enterobacteriaceae causing community-acquired urinary tract infections in French Amazonia. Med Mal Infect 2019;49:63-8.
PUBMED | CROSSREF

20. Johansen TE, Cek M, Naber KG, Stratchounski L, Svendsen MV, Tenke P; PEP and PEAP-study investigators; Board of the European Society of Infections in Urology. Hospital acquired urinary tract infections in urology departments: pathogens, susceptibility and use of antibiotics. Data from the PEP and PEAP-studies. Int J Antimicrob Agents 2006;28 (Suppl 1):S91-107.
PUBMED | CROSSREF

21. Chen SC, Wu WY, Yeh CH, Lai KC, Cheng KS, Jeng LB, Wang PH, Lin DB, Chen CC, Lee MC, Bell WR. Comparison of *Escherichia coli* and *Klebsiella pneumoniae* liver abscesses. Am J Med Sci 2007;334:97-105.
PUBMED | CROSSREF

22. Maharjan G, Khadka P, Siddhi Shilpakar G, Chapagain G, Dhungana GR. Catheter-associated urinary tract infection and obstinate biofilm producers. Can J Infect Dis Med Microbiol 2018;2018:7624857.
PUBMED | CROSSREF

23. Stickler D, Morris N, Moreno MC, Sabbuba N. Studies on the formation of crystalline bacterial biofilms on urethral catheters. Eur J Clin Microbiol Infect Dis 1998;17:649-52.
PUBMED | CROSSREF

24. Mulvey MA, Lopez-Boado YS, Wilson CL, Roth R, Parks WC, Heuser J, Hultgren SJ. Induction and evasion of host defenses by type 1-piliated uropathogenic *Escherichia coli*. Science 1998;282:1494-7.
PUBMED | CROSSREF

25. Mittal S, Sharma M, Chaudhary U. Biofilm and multidrug resistance in uropathogenic *Escherichia coli*. Pathog Glob Health 2015;109:26-9.
PUBMED | CROSSREF

26. Kim BR, Lim JH, Lee SA, Kim JH, Koh SE, Lee IS, Jung H, Lee J. The relation between postvoid residual and occurrence of urinary tract infection after stroke in rehabilitation unit. Ann Rehabil Med 2012;36:248-53.
PUBMED | CROSSREF

27. McKibben MJ, Seed P, Ross SS, Borawski KM. Urinary tract infection and neurogenic bladder. Urol Clin North Am 2015;42:527-36.
PUBMED | CROSSREF

28. Hickling DR, Sun TT, Wu XR. Anatomy and physiology of the urinary tract: relation to host defense and microbial infection. Microbiol Spectr 2015;3:UTI-0016-2012.
PUBMED | CROSSREF

29. Chen D, Zhang Y, Huang J, Liang X, Zeng T, Lan C, Duan X, Zhao Z, Zeng G, Tiselius HG, Lu X, Wu W. The analysis of microbial spectrum and antibiotic resistance of uropathogens isolated from patients with urinary stones. Int J Clin Pract 2018;72:e13205.
PUBMED | CROSSREF

30. Megged O. Bacteremic vs nonbacteremic urinary tract infection in children. Am J Emerg Med 2017;35:36-8.
PUBMED | CROSSREF

31. Oh WS, Kim YS, Yeom JS, Choi HK, Kwak YG, Jun JB, Park SY, Chung JW, Rhee JY, Kim BN. Developing a model to estimate the probability of bacteremia in women with community-onset febrile urinary tract infection. J Infect Dev Ctries 2016;10:1222-9.
PUBMED | CROSSREF

32. Devrim F, Serdaroğlu E, Çağlar İ, Oruç Y, Demiray N, Bayram N, Ağın H, Çalkavur S, Sorguç Y, Dinçel N, Ayhan Y, Yılmaz E, Devrim I. The emerging resistance in nosocomial urinary tract infections: from the pediatrics perspective. Mediterr J Hematol Infect Dis 2018;10:e2018055.
PUBMED | CROSSREF

33. Peleg AY, Hooper DC. Hospital-acquired infections due to gram-negative bacteria. N Engl J Med 2010;362:1804-13.
PUBMED | CROSSREF

34. Scheuerman O, Schechner V, Carmeli Y, Gutiérrez-Gutiérrez B, Calbo E, Almirante B, Viale PL, Oliver A, Ruiz-Garbajosa P, Gasch O, Gozalo M, Pitout J, Akova M, Peña C, Molina J, Hernández-Torres A, Venditti M, Prim N, Origüen J, Bou G, Tacconelli E, Tumbarello M, Hamprecht A, Karaiskos I, de la Calle C, Pérez F, Schwaber MJ, Bermejo J, Lowman W, Hsueh PR, Navarro-San Francisco C, Bonomo RA, Paterson DL, Pascual A, Rodríguez-Baño J; REIPI/ESGBIS/INCREMENT investigators. Comparison of predictors and mortality between bloodstream infections caused by ESBL-producing *Escherichia coli* and ESBL-producing *Klebsiella pneumoniae*. Infect Control Hosp Epidemiol 2018;39:660-7.
PUBMED | CROSSREF