ORIGINAL ARTICLE

Korean J Intern Med 2015;30:372-383
http://dx.doi.org/10.3904/kjim.2015.30.3.372

KJIM

A comparison of the clinical characteristics of elderly and non-elderly women with community-onset, non-obstructive acute pyelonephritis

U-Im Chang, Hyung Wook Kim, Yong-sun Noh, and Seong-Heon Wie

Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Received: November 1, 2014
Revised : November 28, 2014
Accepted: December 2, 2014

Correspondence to
Seong-Heon Wie, M.D.
Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, 93 Jungbu-daero, Paldal-gu, Suwon 442-723, Korea
Tel: +82-31-249-8169
Fax: +82-31-253-8898
E-mail: wiesh@chol.com

Background/Aims: Acute pyelonephritis (APN) is the most common cause of community-onset bacteremia in hospitalized elderly patients. The objectives of this study were to investigate the differences in the clinical and microbiological data of hospitalized elderly and non-elderly women with community-onset APN.

Methods: Women with community-onset APN as a discharge diagnosis were identified from January 2004 to December 2013 using an electronic medical records system. We compared the clinical and microbiologic data in elderly and non-elderly women with community-onset APN due to Enterobacteriaceae.

Results: Of the 1,134 women with community-onset APN caused by Enterobacteriaceae, 443 were elderly and 691 were non-elderly women. The elderly group had a lower frequency of upper and lower urinary tract symptoms/signs than the non-elderly. The incidence of bacteremia, extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, patients with a C-reactive protein (CRP) level ≥ 15 mg/dL, and patients with a leukocyte count ≥ 15,000/mm^3 in the blood, were significantly higher in the elderly group than in the non-elderly group. The proportion of patients requiring hospitalization for 10 days or more was significantly higher in the elderly group compared to the non-elderly group (51.5% vs. 26.2%, $p < 0.001$). The clinical cure rates at 4 to 14 days after the end of therapy were 98.3% (338/344) and 97.4% (519/533) in the elderly and non-elderly groups, respectively ($p = 0.393$).

Conclusions: Elderly women with APN exhibit higher serum CRP levels, a higher frequency of bacteremia, a higher proportion of ESBL-producing uropathogens, and require a longer hospitalization than non-elderly women, although these patients may not complain of typical urinary symptoms.

Keywords: Pyelonephritis; Aged; Non-elderly; Enterobacteriaceae

INTRODUCTION

The proportion of people age 65 and older is expected to increase in the Republic of Korea (ROK), and the increasing proportion of elderly persons will have a great impact on the healthcare system. Acute pyelonephritis (APN) is the most common cause of community-acquired bacteremia in hospitalized elderly patients [1,2]. Although most bacteriuria in the elderly is asymptomatic or accompanied by mild urinary tract infection (UTI) symptoms, a mild UTI can develop into severe and life-threatening sepsis. Many comorbid conditions and

pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

decreased immune and physiologic functions can make the elderly susceptible to UTIs. Thus, many comorbid conditions are considered to be complicating factors and include the functional or structural abnormalities of the urinary tract.

UTI symptoms or signs of infection can be atypical and vague in the elderly, even in an upper urinary tract infection such as APN. Since the clinical manifestation of community-onset APN can be different between elderly and non-elderly patients, a different approach for the diagnosis and management of the elderly may be required. The basic data necessary in order to establish diagnostic and therapeutic guidelines for elderly patients with APN include: clinical presentation, microbiology, and clinical outcomes.

Advanced age is considered to be a complicating factor of APN, without reference to the presence of other complicating factors [3]. At the initial presentation of community-onset APN, gender, menopause status, and a history of comorbid conditions can be used for the classification or stratification of APN without the need to conduct other costly examinations for the identification of complicating factors. Advanced age is one of the risk factors easily identified during the initial presentation of APN, and can be used for classifying the APN, or predicting the prognosis of patients with APN [3-5]. However, there have been few clinical studies comparing the clinical manifestation, microbiology, and clinical outcomes of elderly or non-elderly women with community-onset APN in the ROK. Therfore, a different approach for diagnosing and treating the elderly APN group may be required [6-8].

The objective of this study was to investigate differences in the clinical and microbiological data of elderly and non-elderly women with community-onset APN who were hospitalized at a university hospital in the ROK from January 2004 to December 2013.

METHODS

Study design

The current work was a retrospective study of patients with community-onset non-obstructive APN due to Enterobacteriaceae, conducted at the St. Vincent's Hospital, College of Medicine, The Catholic University of Korea in Suwon, South Korea, from January 2004 to December 2013. The study protocol was approved by the Institutional Review Board (IRB) of the St. Vincent's Hospital. The IRB waived the requirement to document informed consent for all subjects in this study.

Patient population

Women aged ≥ 18-year-old with community-onset non-obstructive APN due to Enterobacteriaceae and who were hospitalized at St. Vincent's Hospital were eligible for inclusion in this study. The clinical and demographic data were collected retrospectively using an electronic medical records system. Clinical symptoms, comorbid conditions, microbial pathogens, laboratory findings, and antimicrobial regimens were analyzed by reviewing the electronic medical records of women who were diagnosed with APN as a discharge diagnosis found in the hospital discharge database between January 2004 and December 2013. APN was defined by the presence of a fever (body temperature ≥ 38.0°C), pyuria on urinalysis (≥ 5 to 9 leukocytes/high power field), and bacteriuria with a colony count of ≥ 100,000 colony-forming units (CFU)/mL for clean voided urine [9,10]. Patients with the following conditions were excluded from the study: (1) a catheter-associated UTI; (2) an obstructive APN that demanded interventional managements, such as catheterization, percutaneous nephrostomy, or surgical treatment; or (3) APN occurring 48 hours or more after hospital admission. The following were considered as complicating factors: non-obstructive renal stone, underactive bladder, polycystic kidney disease, vesicoureteral reflux, diabetes mellitus, cerebrovascular disorder, chronic liver disease, chronic renal disease, congestive heart failure, connective tissue disorder, malignancy, and pregnancy [11,12]. Underactive bladder was diagnosed by urologists and women with underactive bladder requiring catheterization or urological interventional procedures were excluded in this study. Finally, this study solely included and analyzed urine culture-confirmed cases of community-onset non-obstructive APN caused by Enterobacteriaceae in women ≥ 18-years-old who were hospitalized and initially treated with an intravenous antimicrobial agent.

Data collection

The study collected and analyzed baseline demograph-

ic characteristics, medical history, underlying diseases, urinary tract symptoms, physical examination findings, laboratory findings, the duration of antibiotic therapy, microbiological data, defervescent time, duration of hospital stay, and mortality by reviewing the electronic medical records of the study participants. Clinical assessments including clinical symptoms, body temperature, and laboratory findings were performed at the time of admission, after 72 hours of antimicrobial treatment, and at the 4 to 14 day follow-up visit after the end of therapy (EOT).

Definitions and clinical outcome assessments

The study compared the time to defervescence after antimicrobial therapy was initiated, the duration of the hospital stay, the rate of early clinical success, and clinical cure between elderly and non-elderly women with community-onset APN. Elderly was defined as the age of 65 years or above. Women under 65 were defined as non-elderly.

Early clinical success was defined as defervescence within 72 hours after the start of the initial antimicrobial treatment. A clinical cure was defined as defervescence and the absence of UTI symptoms or signs at the 4 to 14 day follow-up visit after the EOT. Clinical failure was defined as the persistence or recurrence of pretherapy urinary tract signs and symptoms within the 4 to 14 day follow-up after completion of antimicrobial therapy [13,14].

Defervescence was defined as the afebrile state of the body temperature (tympanic) at or below 37.0°C for 24 hours or longer [10]. The time to defervescence was defined as the time period after beginning an intravenous antimicrobial agent until defervescence.

Initial intravenous antibiotics were considered concordant if the *in vitro* susceptibility testing revealed that the initial antibiotics were active against the causative uropathogens.

Microbiological data and outcome assessments

Urine and blood cultures were conducted to detect the causative uropathogens and identify the *in vitro* susceptibility of the uropathogens in women with febrile APN at the time of admission. The etiological agents were confirmed by the presence of any micro-organisms with a colony count of ≥ 10^5 CFU/mL in urine cultures or the isolation of micro-organisms from blood specimens of patients with APN. Species and antibiotic susceptibility patterns of urinary tract pathogens were identified and revealed using a semiautomated microbiology system (VITEK, bioMerieux, Hazelwood, MO, USA; or Microscan, DADE Behring, West Sacramento, CA, USA) [15]. A microbiological cure was defined as the eradication of all uropathogens or a reduction of the urine pathogen population from ≥ 10^5 CFU/mL to < 10^4 CFU/mL, with no pathogenic micro-organism present in the blood.

Statistical methods

The results are presented as the number of patients (percentage of total) or median (interquartile range [IQR], 1Q to 3Q), or mean ± standard deviation. We used Fisher exact test or the Pearson chi-square test to compare categorical variables. Continuous variables were assessed and analyzed using the Mann-Whitney test or an independent *t* test. We conducted a multivariate analysis using logistic regression to estimate the influence of independent variables on a longer hospitalization (≥ 10 days) and early clinical failure in APN patients initially treated with intravenous antimicrobial agents. Variables with a $p < 0.1$ in the univariate analyses were included in the multivariate analyses. We used SPSS version 21.0 (IBM Co., Armonk, NY, USA) to analyze the resultant data. All statistical tests were two-tailed, and *p* values of less than 0.05 indicated a statistically significant difference.

RESULTS

Demographic and clinical characteristics

A total of 2,496 patients with community-onset APN were screened and identified from the electronic data from January 2004 to December 2013. From these, 1,134 patients with community-onset non-obstructive APN resulting from Enterobacteriaceae infection, who were hospitalized and received initial antibiotic treatment as an intravenous antimicrobial agent, were analyzed (Fig. 1). Of these 1,134 patients, 443 were classified as elderly, and 691 were considered non-elderly women. For the initial antibiotic treatment, 526 patients (46.4%) received cefuroxime, 373 patients (32.9%) gentamicin, and 235 patients (20.7%) cefotaxime. Table 1 shows a comparison of the baseline demographics, clinical characteristics,

http://dx.doi.org/10.3904/kjim.2015.30.3.372

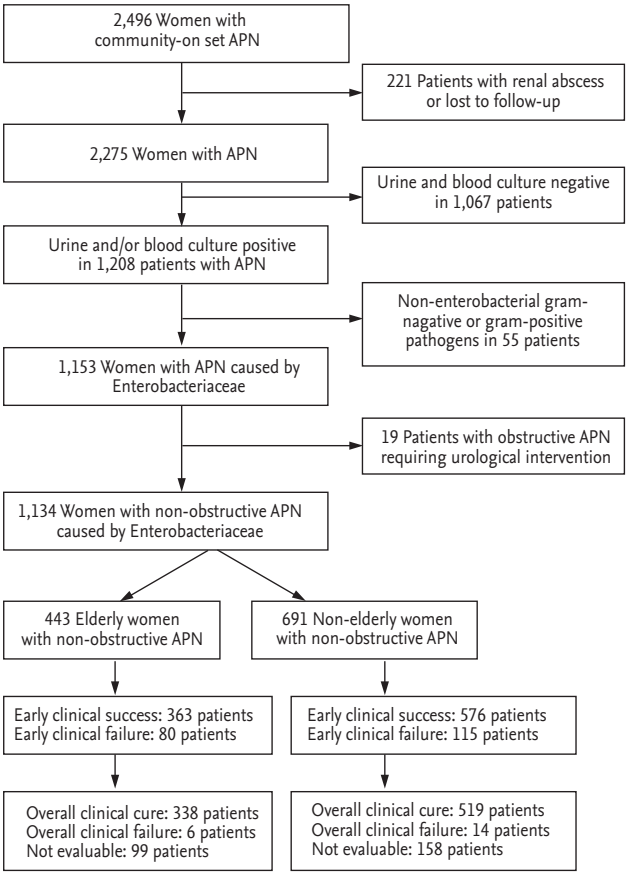

Figure 1. A schematic diagram of the study design and subject enrollment. APN, acute pyelonephritis.

comorbid conditions, and laboratory findings in the elderly and non-elderly groups. The median ages of the elderly and non-elderly groups were 73 years (IQR, 69 to 78) and 44 years (IQR, 31 to 53), respectively ($p < 0.001$) (Table 1). The initial body temperature, the frequency of costovertebral angle tenderness, flank pain, and lower UTI symptoms were significantly lower in the elderly group than in the non-elderly group. The elderly group also showed a significantly higher proportion of bacteremia, extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, patients with a C-reactive protein (CRP) level ≥ 15 mg/dL, and patients with a leukocyte count ≥ 15,000/mm^3 in the blood (Table 1). A history of a previous occurrence of a UTI and the frequency of antibiotic usage within 12 months prior to the hospital visit were markedly increased in the non-elderly group (Table 1).

Microbiological data

Of the 1,134 cases enrolled in the study, *Escherichia coli* was the predominant uropathogen (1,069 patients, 94.3%) and non-*E. coli* Enterobacteriaceae were isolated from 65 patients (5.7%). The non-*E. coli* isolates included 31 *Klebsiella pneumoniae*, eight *Enterobacter aerogenes*, seven *Enterobacter cloacae*, seven *Proteus mirabilis*, five *Citrobacter koseri*, four *Citrobacter freundii*, two *Klebsiella oxytoca*, and one *Klebsiella ozanae*. The results of the antibacterial susceptibility testing of the 1,143 Enterobacteriaceae isolates are described in Table 2. The susceptibility of Enterobacteriaceae to amikacin, ampicillin, amoxicillin/clavulanate, cefuroxime, fluoroquinolone, gentamicin, tobramycin, piperacillin/tazobactam, and trimethoprim/sulfamethoxazole were not significantly different between the elderly and non-elderly groups.

In the elderly versus non-elderly groups, the susceptibility of Enterobacteriaceae to cefotaxime (91.4% vs. 94.9%, $p = 0.019$), ceftazidime (94.1% vs. 97.4%, $p = 0.007$), and cefepime (92.8% vs. 96.3%, $p = 0.024$) was significantly higher in the non-elderly group. In addition, the proportion of ESBL-producing Enterobacteriaceae was significantly higher in the elderly group (9.0% vs. 5.5%, $p = 0.022$).

Comparison of clinical outcomes between the elderly and non-elderly groups

The current study compared clinical outcomes of patients in the elderly and non-elderly groups (Table 3). The duration of the initial intravenous antibiotic treatment was 7 days (IQR, 5 to 7) and 6 days (IQR, 5 to 7), respectively, in the elderly and non-elderly group ($p < 0.001$). The proportions of the initial concordant intravenous antimicrobial therapy were determined not to be significant ($p = 0.178$). Of the 1,134 patients enrolled in the study, 877 (77.3%) and 553 (48.8%), respectively, had a clinical and microbiological follow-up after 4 to 14 days after the completion of antibiotic therapy.

Thirty-two (7.2%) of the 443 patients in the elderly group and 53 (7.7%) of the 691 patients in the non-elderly group had their course of treatment changed to an alternative intravenous therapy. The defervescence rates were 12.0% (53/443) versus 10.0% (69/691) at 24 hours, 44.9% (199/443) versus 46.7% (323/691) at 48 hours, 81.9% (363/443) versus 83.4% (576/691) at 72 hours, 91.4% (405/443) versus 92.3% (638/691) at 96 hours, and 95.7% (424/443)

Table 1. Clinical characteristics and laboratory findings of elderly and non-elderly women with community-onset non-obstructive acute pyelonephritis caused by Enterobacteriaceae

Characteristic	Elderly women with APN (n = 443)	Non-elderly women with APN (n = 691)	*p* value
Age, yr	73.0 (69.0–78.0)	44.0 (31.0–53.0)	< 0.001[a]
Clinical feature			
Body temperature, °C	38.5 (38.1–39.2)	38.8 (38.3–39.4)	< 0.001[a]
Costovertebral angle tenderness	319 (72.0)	591 (85.5)	< 0.0001[b]
Flank pain	213 (48.1)	500 (72.4)	< 0.001[b]
Lower urinary tract infection symptoms	267 (60.3)	459 (66.4)	0.035[b]
Nausea or vomiting	143 (32.3)	262 (37.9)	0.053[b]
Pitt bacteraemia score			
≥ 1	155 (35.0)	315 (45.6)	< 0.001[b]
2–4	27 (6.1)	56 (8.1)	0.205[b]
Comorbid condition			
Diabetes mellitus	181 (40.9)	179 (25.9)	< 0.001[b]
Cerebrovascular disorders	46 (10.4)	19 (2.7)	< 0.001[b]
Congestive heart failure	26 (5.9)	12 (1.7)	< 0.001[b]
Chronic kidney diseases	17 (3.8)	10 (1.9)	0.061[b]
Chronic liver diseases	22 (5.0)	20 (2.9)	0.071[b]
Chronic lung disorders	18 (4.1)	11 (1.6)	0.010[b]
Connective tissue disorders	13 (2.9)	13 (1.9)	0.248[b]
Malignancy	21 (4.7)	13 (1.9)	0.006[b]
Underactive bladder[c]	33 (7.4)	13 (1.9)	< 0.001[b]
Non-obstructive renal stone	17 (3.8)	39 (5.6)	0.171[b]
Vesicoureteral reflux	5 (1.1)	15 (2.2)	0.193[b]
Laboratory finding			
Bacteremia	173 (39.1)	192 (27.8)	< 0.001[b]
C-reactive protein, mg/dL	12.0 (7.0–18.5)	10.3 (5.9–16.4)	0.005[a]
C-reactive protein ≥ 15 mg/dL	160 (36.1)	198/679[c] (29.2)	0.015[b]
Extended spectrum β-lactamase (+) uropathogen	40 (9.0)	38 (5.5)	0.022[b]
Hematuria	290 (65.5)	446 (64.5)	0.752[b]
White blood cell counts/mm^3	11,750 (9,040–14,700)	11,260 (9,050–14,190)	0.103[a]
White blood cells ≥ 15,000/mm^3 of blood	106 (23.9)	131 (19.0)	0.045[b]
Past history			
Antibiotic use within 1 year	53/408[d] (13.0)	145/665[d] (21.8)	< 0.001[b]
Previous urinary tract infection history	49/409[d] (12.0)	167/670[d] (24.9)	< 0.001[b]
Prior history of hospitalization within 1 year	69/409[d] (16.9)	106/670[d] (15.8)	0.650[b]

Values are presented as median (interquartile range) or number (%).
APN, acute pyelonephritis.
[a]Mann-Whitney *U* test.
[b]Pearson chi-square test or Fisher exact test.
[c]Underactive bladder not requiring catheterization or urological interventional procedures.
[d]Denominators were the number of patients whose data were available in each group.

http://dx.doi.org/10.3904/kjim.2015.30.3.372

Table 2. Antimicrobial susceptibility of enterobacteriaceae isolated from elderly or non-elderly women with community-onset non-obstructive acute pyelonephritis

Antibiotics	Elderly group (n = 443)			Non-elderly group (n = 691)			*p* value[a]
	Total	Susceptible	Susceptibility, %	Total	Susceptible	Susceptibility, %	
Amikacin	443	439	99.1	691	690	99.9	0.080
Ampicillin	406	144	35.5	625	246	39.4	0.208
Amox/cla	264	202	76.5	462	350	75.8	0.818
Cefazolin[b]	367	250	68.1	615	466	75.8	0.009
Cefuroxime	232	213	91.8	393	372	94.7	0.160
Cefoxitin	230	208	90.4	468	458	97.9	< 0.001
Cefotaxime	443	405	91.4	690	655	94.9	0.019
Ceftazidime	424	399	94.1	645	628	97.4	0.007
Cefepime	376	349	92.8	461	444	96.3	0.024
FQ	443	357	80.6	691	589	85.2	0.113
Gentamicin	443	351	79.2	691	563	81.5	0.351
Imipenem	443	439	99.1	690	690	100	0.023
Piperacillin	266	121	45.5	359	161	44.8	0.873
SXT	443	303	68.4	691	470	68.0	0.893
Tobramycin	263	202	76.8	415	341	82.2	0.088
TZP	442	425	96.2	688	664	96.5	0.754
ESBL	443	40[c]	9.0[d]	691	38[c]	5.5[d]	0.022

Amox/cla, amoxicillin/clavulanate; FQ, fluoroquinolone (ciprofloxacin or levofloxacin); SXT, trimethoprim/sulfamethoxazole; TZP, piperacillin/tazobactam; ESBL, extended-spectrum β-lactamase.
[a]Pearson chi-square test or Fisher exact test.
[b]Cefazolin, cefazolin or cephradine (first cephalosporin).
[c]The number of ESBL-producing Enterobacteriaceae.
[d]The percentage of ESBL-producing Enterobacteriaceae.

versus 95.8% (662/691) at 120 hours after the initial antimicrobial agents were started in the elderly versus non-elderly groups, respectively, and these differences were not significantly different between the two groups (Table 3). The median hours to defervescence were 52 (IQR, 36 to 70) and 50 (IQR, 36 to 68) in the elderly and non-elderly groups, respectively ($p = 0.397$).

The clinical cure rates observed at 4 to 14 days after the EOT were 98.3% (338/344) and 97.4% (519/533) in the elderly and non-elderly groups, respectively ($p = 0.393$). Microbiological outcomes were available for 553 out of 1,134 women at the 4- to 14-day follow-up after the EOT. Microbiological cure rates at 4 to 14 days after the EOT were 89.8% (221/246) versus 90.6% (278/307) in the elderly versus non-elderly groups, respectively ($p = 0.778$).

Out of 1,134 women, 78 had APN due to ESBL-positive Enterobacteriaceae and 1,056 had APN due to ESBL-negative Enterobacteriaceae. The time to defervescence was not significantly different in the ESBL-positive versus ESBL-negative groups at 49.2 hours versus 49.3 hours ($p = 0.990$), respectively. Additionally, no significant differences were observed in urinary tract symptoms, comorbid conditions, frequency of previous UTI history, proportion of hematuria, and bacteremia between the ESBL-positive and ESBL-negative Enterobacteriaceae groups. However, the frequency of antibiotic use and hospitalization within 1 year prior to the hospital visit in the ESBL-positive group were significantly higher than those observed in the ESBL-negative group ($p < 0.001$ and $p < 0.001$). In contrast, the early clinical success rates at 72 hours in the ESBL-positive group were significantly lower than those in the ESBL-negative group (83.4% [881/1,056] vs. 74.4% [58/78], $p = 0.041$). In addition, the clinical and microbiological cure rates 4 to 14 days after

Table 3. Comparison of clinical outcomes of elderly or non-elderly women with community-onset non-obstructive acute pyelonephritis

Variable	Elderly group (n = 443)	Non-elderly group (n = 691)	*p* value
Initial intravenous antibiotics			
Cefuroxime	237 (53.5)	289 (41.8)	
Gentamicin	103 (23.3)	270 (39.1)	
Cefotaxime	103 (23.3)	132 (19.1)	
Use of discordant intravenous antibiotics	78 (17.6)	101 (14.6)	0.178[b]
Duration of initial intravenous antibiotics, day	7 (5–7)	6 (5–7)	< 0.001[a]
No. of cases with alternative intravenous antibiotics	32 (7.2)	53 (7.7)	0.781[b]
Switch to oral antibiotics			
Ciprofloxacin	208 (47.0)	330 (47.8)	
First-generation cephalosporin	55 (12.4)	122 (17.7)	
Second-generation cephalosporin	50 (11.3)	59 (8.5)	
Third-generation cephalosporin	32 (7.2)	24 (3.5)	
Amoxicillin	56 (12.6)	93 (13.5)	
Amoxicillin/clavulanate	8 (1.8)	11 (1.6)	
Trimethoprim-sulfamethoxazole	19 (4.3)	30 (4.3)	
Others or none	15 (3.4)	22 (3.1)	
Duration of oral antimicrobial therapy, day	7 (7–8)	7 (7–9)	< 0.001[a]
The rate of defervescence, hr			
Within 24	53 (12.0)	69 (10.0)	0.294[b]
Within 48	199 (44.9)	323 (46.7)	0.548[b]
Within 72	363 (81.9)	576 (83.4)	0.537[b]
Within 96	405 (91.4)	638 (92.3)	0.583[b]
Within 120	424 (95.7)	662 (95.8)	0.940[b]
Time to defervescence, hr	52 (36–70)	50 (36–68)	0.397[a]
Duration of hospital stay, day	9 (8–13)	8 (7–10)	< 0.001[a]
Hospital duration ≥ 10 days	228 (51.5)	181 (26.2)	< 0.001[b]
Clinical cure at 4–14 days after EOT	338/344[c] (98.3)	519/533[c] (97.4)	0.393[b]
Microbiological cure at 4–14 days after EOT	221/246[c] (89.8)	278/307[c] (90.6)	0.778[b]
Overall mortality	0	0	

Values are presented as number (%) or median (interquartile range).
EOT, the end of therapy.
[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.

the EOT in the ESBL-positive group were significantly lower than those in the ESBL-negative group (92.5% [62/67] vs. 98.1% [795/810], $p = 0.005$; and 77.8% [42/54] vs. 91.6% [457/499], $p = 0.001$).

Clinical significance and risk factors of early clinical failure in women with APN

We classified the women with APN into two groups: the early clinical success group (939 patients, 82.8%) and the early failure group (195 patients, 17.2%) according to the presence of defervescence after 72 hours of antimicro-

http://dx.doi.org/10.3904/kjim.2015.30.3.372

Table 4. Factors related to early clinical failure in elderly and non-elderly women with community-onset acute pyelonephritis caused by Enterobacteriaceae in a final model of multiple logistic regression, 2004 to 2013

Characteristic	Early clinical failure (n = 195)	Univariate		Multivariate	
		OR (95% CI)	*p* value[a]	OR (95% CI)	*p* value[b]
Elderly	80 (41.0)	1.104 (0.806–1.511)	0.537	-	
Clinical feature					
CVAT	157 (80.5)	1.020 (0.692–1.506)	0.918	-	
Flank pain	124 (63.6)	1.037 (0.754–1.431)	0.820	-	
Nausea/vomiting	83 (42.6)	1.420 (1.037–1.946)	0.028	1.261 (0.900–1.769)	0.178
Pitt score ≥ 1	99 (50.8)	1.580 (1.159–2.151)	0.004	1.486 (1.058–2.083)	0.022
Lower UTI Sx	122 (62.6)	0.927 (0.673–1.276)	0.641	-	
Comorbid condition					
Diabetes mellitus	58 (29.7)	0.893 (0.638–1.250)	0.509	-	
Cerebrovascular disorders	11 (5.6)	0.979 (0.503–1.908)	0.952	-	
Chronic liver disease	10 (5.1)	1.531 (0.740–3.175)	0.247	-	
Autoimmune disorders	5 (2.6)	1.151 (0.428–3.086)	0.781	-	
Malignancy	9 (4.6)	1.770 (0.812–3.846)	0.146	-	
Non-obstructive renal stone	11 (5.8)	1.188 (0.603–2.342)	0.619	-	
Vesicoureteral reflux	1 (0.5)	0.250 (0.033–1.876)	0.229	-	
Underactive bladder[c]	13 (6.7)	1.961 (1.012–3.802)	0.042	2.193 (1.060–4.545)	0.034
Laboratory finding					
Bacteremia	95 (48.7)	2.353 (1.718–3.226)	< 0.001	1.841 (1.314–2.581)	< 0.001
Hematuria	144 (73.8)	1.656 (1.171–2.336)	0.004	1.288 (0.885–1.873)	0.186
CRP ≥ 15 mg/dL	101 (52.6)	2.907 (2.114–4.000)	< 0.001	2.309 (1.631–3.268)	< 0.001
ESBL	20 (10.3)	1.736 (1.018–2.959)	0.041	1.259 (0.638–2.488)	0.506
WBC ≥ 15,000/mm^3	71 (36.4)	2.667 (1.905–3.731)	< 0.001	2.045 (1.414–2.959)	< 0.001
Past history					
Antibiotic use within 1 year	26/181[c] (14.4)	0.702 (0.449–1.098)	0.120	-	
Previous UTI history	31/187[c] (16.6)	0.759 (0.500–1.154)	0.196	-	
Hospitalization within 1 year	24/185[c] (13.0)	0.733 (0.462–1.166)	0.188	-	
Discordant antimicrobial therapy	52 (26.7)	2.326 (1.608–3.356)	< 0.001	2.841 (1.764–4.587)	< 0.001

Values are presented as number (%). Final model: bacteremia, CRP ≥ 15 mg/dL in the blood, discordant antimicrobial therapy, ESBL, hematuria, nausea, or vomiting, Pitt score ≥ 1, underactive bladder, WBC counts (/mm^3 in the blood) ≥ 15,000.
OR, odds ratio; CI, confidence interval; CVAT, costovertebral angle tenderness; UTI Sx, urinary tract infection symptoms; CRP, C-reactive protein; ESBL, extended-spectrum β-lactamase; WBC, white blood cell.
[a]Univariate analysis by the chi-square test or Fisher exact test.
[b]Multivariate analysis using logistic regression.
[c]Denominators were the number of patients whose data were available in each group.

bial therapy. These two groups demonstrated no major differences in age, proportion of premenopause, urinary tract symptoms, frequency of previous UTI infection, frequency of antibiotic use, and hospitalization within 1 year prior to the hospital visit. However, the proportion of bacteremia, hematuria, and ESBL-producing Enterobacteriaceae in the early clinical success group were markedly lower. The initial leukocyte count, percentage of segmented neutrophils, and proportion of patients with a leukocyte count ≥ 15,000/mm^3 in the blood were

Table 5. Factors related to a longer hospitalization (≥ 10 days) in 443 elderly women with community-onset non-obstructive acute pyelonephritis caused by Enterobacteriaceae in a final model of multiple logistic regression, 2004 to 2013

Characteristic	Duration of hospital stay ≥10 days (n = 228)	Univariate		Multivariate	
		OR (95% CI)	*p* value[a]	OR (95% CI)	*p* value[b]
Clinical feature					
CVAT	166 (72.8)	1.085 (0.716–1.643)	0.700	-	
Flank pain	122 (53.5)	1.568 (1.077–2.283)	0.019	1.647 (1.121–2.427)	0.011
Nausea/vomiting	75 (32.9)	1.060 (0.711–1.579)	0.776	-	
Pitt score ≥1	87 (38.2)	1.334 (0.901–1.975)	0.150	-	
Lower UTI Sx	140 (61.4)	1.102 (0.753–1.613)	0.616	-	
Comorbid condition					
Diabetes mellitus	95 (41.7)	1.071 (0.733–1.565)	0.721	-	
Cerebrovascular disorders	22 (9.6)	0.850 (0.461–1.566)	0.602	-	
Congestive heart failure	16 (7.0)	1.547 (0.686–3.489)	0.290	-	
Chronic liver disease	14 (6.1)	1.693 (0.696–4.120)	0.241	-	
Chronic renal disease	11 (4.8)	1.766 (0.641–4.861)	0.265	-	
Autoimmune disorders	10 (4.4)	3.242 (0.880–11.942)	0.089	2.902 (0.770–10.941)	0.116
Malignancy	10 (4.4)	0.851 (0.354–2.046)	0.718	-	
Non-obstructive renal stone	8 (3.5)	0.832 (0.315–2.198)	0.711	-	
Vesicoureteral reflux	2 (0.9)	0.625 (0.103–3.779)	0.677	-	
Underactive bladder	14 (6.1)	0.675 (0.329–1.382)	0.280	-	
Laboratory finding					
Bacteremia	107 (46.9)	1.996 (1.352–2.947)	< 0.001	2.028 (1.361–3.021)	0.001
Hematuria	150 (65.8)	1.030 (0.658–1.533)	0.882	-	
CRP ≥ 15 mg/dL	93 (40.8)	1.522 (1.029–2.250)	0.035	1.367 (0.913–2.048)	0.129
ESBL	22 (9.6)	1.169 (0.618–2.380)	0.639	-	
WBC ≥ 15,000/mm^3	61 (26.8)	1.380 (0.882–2.225)	0.151	-	
Past history					
Antibiotic use within 1 year	29/210[c] (13.8)	1.162 (0.651–2.074)	0.612	-	
Previous UTI history	24/210[c] (11.4)	0.893 (0.491–1.622)	0.710	-	
Hospitalization within 1 year	35/211[c] (16.6)	0.959 (0.572–1.610)	0.875	-	
Discordant antimicrobial therapy	42 (18.4)	0.909 (0.607–1.362)	0.643	-	

Values are presented as number (%). Final model: autoimmune disorders, bacteremia, CRP ≥ 15 mg/dL of blood, Flank pain.
OR, odds ratio; CI, confidence interval; CVAT, costovertebral angle tenderness; UTI Sx, urinary tract infection symptoms; CRP, C-reactive protein; ESBL, extended-spectrum β-lactamase; WBC, white blood cell.
[a]Univariate analysis by the chi-square test or Fisher exact test.
[b]Multivariate analysis using logistic regression.
[c]Denominators were the number of patients whose data were available in each group.

also significantly lower in the early clinical success group. Finally, a multivariate analysis using logistic regression determined that a Pitt score ≥ 1 (p = 0.022), underactive bladder (p = 0.034), bacteremia (p < 0.001), a CRP level ≥ 15 mg/dL (p < 0.001), white blood cell counts ≥ 15,000/mm^3 in the blood (p < 0.001), and discordant antimicrobial therapy (p < 0.001) were closely associated with early clinical failure (Table 4).

The clinical cure rates observed at 4 to 14 days after the EOT were not significantly different between the

http://dx.doi.org/10.3904/kjim.2015.30.3.372

early clinical success and early clinical failure groups. However, the microbiological cure rate in the former was significantly higher ($p < 0.001$). The median times to defervescence were 45 hours (IQR, 32 to 60) and 91 hours (IQR, 83 to 103.8; $p < 0.001$), and the median length of the hospital stay was 8 days (IQR, 7 to 10) and 10 days (IQR, 8 to 11.8; $p < 0.001$) in the early clinical success and early clinical failure groups, respectively.

Factors related to a longer hospitalization in the elderly and non-elderly women with APN

The median number of hospital stays in the elderly and non-elderly groups were 9 (IQR, 8 to 13) and 8 (IQR, 7 to 10), respectively ($p < 0.001$) (Table 3).

The proportion of patients requiring hospitalization for 10 days or more was significantly higher in the elderly group compared to the non-elderly group (51.5% vs. 26.2%, $p < 0.001$). Multiple logistic regression analysis using the potential risk factors identified by univariate analysis determined that flank pain and bacteremia were significant predictors of an increased hospitalization period ($p = 0.011$ and $p = 0.001$) (Table 5).

DISCUSSION

Advanced age is one of the complicating factors of APN. In the current study, we compared the initial clinical signs and symptoms, clinical courses, and treatment outcomes of elderly and non-elderly women with community-onset APN. The elderly group, in comparison to the non-elderly group, demonstrated fewer upper UTI symptoms/signs, such as flank pain and costovertebral angle tenderness, fewer lower UTI symptoms, and a lower frequency of nausea or vomiting. In contrast, the proportion of bacteremia, ESBL-producing Enterobacteriaceae, patients with a CRP level ≥ 15 mg/dL, and patients with a leukocyte count ≥ 15,000/mm^3 in the blood were higher in the elderly group. While the median hours to defervescence were not significantly different, the length of hospitalization was notable. The proportion of patients hospitalized for 10 days or longer was significantly higher in the elderly group, even though clinical and microbiological cure rates were not significantly different.

This study determined that the proportion of bacteremic patients was higher in the elderly, and the frequency of upper UTI symptoms/signs, such as flank pain and costovertebral angle tenderness, were significantly lower in the elderly group. Additionally, the proportion of patients with ESBL-producing Enterobacteriaceae was higher in the elderly than in the non-elderly group. However, the proportion of patients who were treated with antibiotics within the past year, or the proportion of patients with a previous history of UTI, was lower in the elderly than in the non-elderly group. Independent risk factors contributing to APN, by ESBL-producing pathogens, were underlying comorbid conditions, antibiotic usage within the previous year, and urinary catheterization within the previous month in Korea [16]. A history of previous UTI's was determined not to be an independent risk factor of APN caused by ESBL-producing pathogens, and the occurrence of urinary catheterization within the previous month was not investigated in patients enrolled in the current study. Therefore, it is presumed that underlying comorbid conditions were a greater risk factor contributing to the development of APN caused by antibiotic-resistant pathogens than the history of antibiotic usage within the previous year.

The proportion of individuals aged 65 and over was less than 1% of the global population in 1900; however, the proportion of elderly people is expected to increase to 20% by 2050 [17,18]. Therefore, physicians should consider that aging of the immune system and underlying comorbid conditions can influence the clinical course or prognosis of APN in an elderly population [17]. Clinical research studies investigating UTIs in the elderly over the past two decades have studied catheter-associated UTI, complicated UTI, nosocomial UTI, asymptomatic bacteriuria, and antimicrobial therapy in lower UTIs. However, only a few studies have compared the clinical characteristics of APN in an elderly population, as compared to those of the non-elderly individuals with APN. These comparative studies can play a critical role in the early diagnosis and prompt treatment of the unusual presentation of APN in the elderly.

Our clinical data demonstrated that the frequency of both upper and lower urinary tract symptoms/signs were significantly lower in the elderly group compared to the non-elderly group. Therefore, the elderly may exhibit an atypical presentation of clinical symptoms/signs.

While diabetes mellitus has been shown to be an independent predictor of longer hospitalizations in a previous study [19], diabetes mellitus was not an independent risk factor contributing to longer hospitalization (≥ 10 days) in the elderly in this study. In contrast, the current study determined that flank pain and bacteremia were independent predictors of longer hospitalization among elderly patients. Analysis of 173 bacteremia cases in the current study revealed no deaths; however, a high mortality rate (33%) was observed in patients 75 years of age or older in a previous study that analyzed 191 episodes of urosepsis [20]. These contrasting results may be due to differences in age distribution, the prevalence of underlying disorders, and the exclusion of obstructive, complicated APN.

In the current study, the clinical cure rate, microbiological cure rate, and mortality rate were not significantly different between the elderly and non-elderly groups. However, we determined that the hospitalization period was much longer for the elderly group, as compared to the non-elderly group.

This study has several limitations. First, the history of prior hospitalization, antibiotic usage, and UTI may have been underestimated, since this is a retrospective study. However, we were able to demonstrate significant differences in the baseline demographics, clinical characteristics, outcomes, and laboratory findings between the elderly and non-elderly groups by performing a retrospective analysis of electronic medical records. Secondly, severe cases of APN may have been excluded from the analysis, because we did not include patients with obstructive APN who required urological interventions. Thirdly, fluoroquinolone was not administered as an initial intravenous antibiotic, although it was recommended for the treatment of hospitalized women with APN in most guidelines [21,22]. In this study, fluoroquinolone was not initially administered due to the relatively high rates of fluoroquinolone-resistant *E. coli* present in Korea, and was preserved for more important uses than the treatment of UTIs [3,23].

In conclusion, elderly women with APN exhibit higher serum CRP levels, an increased frequency of bacteremia, a higher proportion of ESBL-producing uropathogens, and require a longer hospitalization than non-elderly women, even though the typical signs and symptoms of urinary infections may not be observed in the elderly patients during the initial presentation.

KEY MESSAGE

1. Elderly women with community-onset acute pyelonephritis have a higher level of serum C-reactive protein, a higher frequency of bacteremia, a higher proportion of extended-spectrum β-lactamase-producing uropathogens, and require longer hospitalization than non-elderly women.
2. Elderly women with acute pyelonephritis may not exhibit typical urinary infection signs and symptoms during the initial presentation.

Conflict of interest

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

Acknowledgments

The authors would like to acknowledge the financial support of the St. Vincent's Hospital, Research Institute of Medical Science (SVHR-2014-08).

REFERENCES

1. Esposito AL, Gleckman RA, Cram S, Crowley M, McCabe F, Drapkin MS. Community-acquired bacteremia in the elderly: analysis of one hundred consecutive episodes. J Am Geriatr Soc 1980;28:315-319.
2. Gleckman R, Blagg N, Hibert D, et al. Acute pyelonephritis in the elderly. South Med J 1982;75:551-554.
3. Lim SK, Park IW, Lee WG, Kim HK, Choi YH. Change of antimicrobial susceptibility among Escherichia coli strains isolated from female patients with community-onset acute pyelonephritis. Yonsei Med J 2012;53:164-171.
4. Grover ML, Bracamonte JD, Kanodia AK, Edwards FD, Weaver AL. Urinary tract infection in women over the age of 65: is age alone a marker of complication? J Am Board Fam Med 2009;22:266-271.
5. Jackson SL, Boyko EJ, Scholes D, Abraham L, Gupta K, Fihn SD. Predictors of urinary tract infection after menopause: a prospective study. Am J Med 2004;117:903-911.
6. Nicolle LE. A practical guide to antimicrobial manage-

http://dx.doi.org/10.3904/kjim.2015.30.3.372

ment of complicated urinary tract infection. Drugs Aging 2001;18:243-254.
7. High KP, Bradley SF, Gravenstein S, et al. Clinical practice guideline for the evaluation of fever and infection in older adult residents of long-term care facilities: 2008 update by the Infectious Diseases Sociey of America. J Am Geriatr Soc 2009;57:375-394.
8. Gavazzi G, Delerce E, Cambau E, et al. Diagnostic criteria for urinary tract infection in hospitalized elderly patients over 75 years of age: a multicenter cross-sectional study. Med Mal Infect 2013;43:189-194.
9. Wi YM, Kim SW, Chang HH, et al. Predictors of uropathogens other than Escherichia coli in patients with community-onset acute pyelonephritis. Int J Clin Pract 2014;68:749-755.
10. Wie SH, Kim HW, Chang UI. Use of gentamicin for women with community-acquired uncomplicated acute pyelonephritis caused by gentamicin-susceptible or -resistant Escherichia coli: 10-year experience. Microb Drug Resist 2013;19:316-322.
11. Hermanides HS, Hulscher ME, Schouten JA, Prins JM, Geerlings SE. Development of quality indicators for the antibiotic treatment of complicated urinary tract infections: a first step to measure and improve care. Clin Infect Dis 2008;46:703-711.
12. Naber KG, Savov O, Salmen HC. Piperacillin 2 g/tazobactam 0.5 g is as effective as imipenem 0.5 g/cilastatin 0.5 g for the treatment of acute uncomplicated pyelonephritis and complicated urinary tract infections. Int J Antimicrob Agents 2002;19:95-103.
13. Vazquez JA, Gonzalez Patzan LD, Stricklin D, et al. Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study. Curr Med Res Opin 2012;28:1921-1931.
14. Park DW, Peck KR, Chung MH, et al. Comparison of ertapenem and ceftriaxone therapy for acute pyelonephritis and other complicated urinary tract infections in Korean adults: a randomized, double-blind, multicenter trial. J Korean Med Sci 2012;27:476-483.
15. Clinical and Laboratory Standard Institute. Performance Standards for Antimicrobial Susceptibility Testing: 15th Informational Supplement. Vol. 25. Wayne: Clinical and Laboratory Standard Institute, 2005.
16. Kim B, Kim J, Seo MR, et al. Clinical characteristics of community-acquired acute pyelonephritis caused by ESBL-producing pathogens in South Korea. Infection 2013;41:603-612.
17. Crossley KB, Peterson PK. Infections in the elderly. Clin Infect Dis 1996;22:209-215.
18. Matsumoto T. Urinary tract infections in the elderly. Curr Urol Rep 2001;2:330-333.
19. Kim Y, Wie SH, Chang UI, et al. Comparison of the clinical characteristics of diabetic and non-diabetic women with community-acquired acute pyelonephritis: a multicenter study. J Infect 2014;69:244-251.
20. Tal S, Guller V, Levi S, et al. Profile and prognosis of febrile elderly patients with bacteremic urinary tract infection. J Infect 2005;50:296-305.
21. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-e120.
22. The Korean Society of Infectious Diseases; The Korean Society for Chemotherapy; Korean Association of Urogenital Tract Infection and Inflammation; The Korean Society of Clinical Microbiology. Clinical guideline for the diagnosis and treatment of urinary tract infections: asymptomatic bacteriuria, uncomplicated & complicated urinary tract infections, bacterial prostatitis. Infect Chemother 2011;43:1-25.
23. Seo MR, Kim SJ, Kim Y, et al. Susceptibility of Escherichia coli from community-acquired urinary tract infection to fosfomycin, nitrofurantoin, and temocillin in Korea. J Korean Med Sci 2014;29:1178-1181.