Clinical characteristics predicting early clinical failure after 72 h of antibiotic treatment in women with community-onset acute pyelonephritis: a prospective multicentre study

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Abstract

In patients with community-onset acute pyelonephritis (CO-APN), assessing the risk factors for poor clinical response after 72 h of antibiotic treatment (early clinical failure) is important. The objectives of this study were to define those risk factors, and to assess whether early clinical failure influences mortality and treatment outcomes. We prospectively collected the clinical and microbiological data of women with CO-APN in South Korea from March 2010 to February 2012. The numbers of cases in the early clinical success and early clinical failure groups were 840 (79.1%) and 222 (20.9%), respectively. Final clinical failure and mortality were higher in the early clinical failure group than in the early clinical success group (14.9% vs 2.3%, p <0.001; 6.8% vs 0.1%, p 0.001, respectively). In a multiple logistic regression model, the risk factors for early clinical failure among the total 1062 patients were diabetes mellitus (OR 1.5; 95% CI 1.1–2.1), chronic liver diseases (OR 3.3; 95% CI 1.6–6.7), malignancy (OR 2.2; 95% CI 1.1–4.4), Pitt score ≥2 (OR 2.5; 95% CI 1.6–3.8), presence of azotaemia (OR 1.8; 95% CI 1.2–2.7), white blood cell count ≥20 000/mm^3 (OR 2.5; 95% CI 1.6–4.0), serum C-reactive protein level ≥20 mg/dL (OR 1.7; 95% CI 1.2–2.4), and history of antibiotic usage within the previous year (OR 1.5; 95% CI 1.1–2.2). Analysing the subgroup of 743 patients with CO-APN due to Enterobacteriaceae, fluoroquinolone resistance of the uropathogen was another factor associated with early clinical failure (OR 1.7; 95% CI 1.1–2.5). Simple variables of underlying diseases, previous antibiotic usage and initial laboratory test outcomes can be used to decide on the direction of treatment in CO-APN.

Keywords: acute pyelonephritis, early clinical failure, risk factor
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Introduction

Acute pyelonephritis (APN) is an upper urinary tract infection characterized by inflammation of the renal parenchyma and renal pelvis typically due to a bacterial infection ascending from the bladder. It is a common bacterial infection in the community, especially in otherwise healthy women. It has been estimated that women are almost five times as likely as

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men to be hospitalized for APN (11.7/10 000 vs 2.4/10 000) [1,2]. In South Korea, the annual incidence of APN is 35.7 per 10 000 people, with the rate of hospitalization for APN being 9.96 per 10 000 women and 1.18 per 10 000 men [3]. Several factors such as frequency of sexual intercourse in the previous 30 days, diabetes mellitus, urinary incontinence and a family history of urinary tract infections have been shown to increase the risk of APN [4,5].

Although APN is a common disease and is usually treated successfully with antimicrobial agents, it often requires hospitalization, and when accompanied by bacteraemia has a mortality rate of 5–20% [6–8]. In a retrospective study, factors associated with death among men and women with APN included age >65 years, septic shock and bedridden status; immunosuppression was a risk factor for death among men only and recent antibiotic use was a risk factor among women only [9]. Another study analysing uncomplicated APN in women showed that hospitalization at baseline, the presence of a resistant infecting organism, diabetes mellitus and a history of kidney stones were significant risk factors for a poor clinical response [10]. Patients with APN who have a risk of death or of a poor clinical response need hospitalization and close observation.

In clinical practice, if patients with APN do not show a clinical response after 72 h of antibiotic treatment (early clinical failure), radiological imaging of the urinary tract, investigation of other complicating factors or modification of the initial antimicrobial regimen in line with antibiotic susceptibility results are usually required [11]. Objective assessment of the risk factors for a poor clinical response after 72 h of treatment would help physicians to determine at the initial presentation whether hospitalization is needed. Furthermore, the increase of antimicrobial resistance among urinary pathogens in community-onset APN (CO-APN) makes the assessment of antibiotic resistance even more necessary [11]. We anticipate that demographic and clinical factors such as age, menopausal status, diabetes mellitus or other underlying diseases, simple laboratory test results that can be obtained in a short time in most hospitals and risk factors for antimicrobial resistance could be used to predict which APN patients are likely to suffer early clinical failure.

The objectives of our study were to define and characterize the risk factors for early clinical failure in CO-APN patients, and to establish whether early clinical failure has an effect on mortality and final treatment outcomes. To this end, we prospectively collected and analysed the clinical and microbiological data of women with CO-APN who visited 11 hospitals in South Korea from March 2010 to February 2012.

Materials and Methods

Study design

This study was a prospective, observational, multicentre cohort study of women with CO-APN in South Korea performed from 1 March 2010 to 28 February 2012. The study was conducted in 11 South Korean university hospitals with between 582 and ~1250 beds each. The hospitals that participated in this study were located throughout the Korean peninsula (three in Seoul, three in Gyeonggi-do, two in Incheon, two in Daegu and one in Busan), and ten were academic hospitals. The study protocol was approved by the institutional review boards of each participating centre. The institutional review boards waived the requirement for written informed consent from patients. All the data collected for this study were kept confidential.

Patient population

All patients admitted to the participating hospitals for CO-APN from March 2010 to February 2012 were enrolled consecutively in the study. APN was defined as fever ≥37.8°C, and presence of at least three of the followings: (i) pain in the flanks; (ii) costovertebral angle tenderness on examination; (iii) symptoms of lower urinary tract infection (dysuria, urgency, frequency, pain in the suprapubic region); (iv) pyuria (≥5–9 leucocytes/high-power field); and (v) leucocytosis (peripheral white blood cell (WBC) count >11 600/mm^3 or polymorphonuclear cells plus bands >65%) [12,13]. CO-APN was defined as a case presenting to the emergency department or an outpatient clinic from the community with the signs of APN just described. Any patient who was diagnosed with APN >48 h after admission or with a urinary-catheter-related infection was excluded from the study. Patients under 15 years, of male gender, those with other reasons for pyuria and fever and those with insufficient data were also excluded. Cases of CO-APN were enrolled at admission by an infectious diseases specialist.

Data collection and definitions

The clinical characteristics of all the eligible patients were collected prospectively using a web-based medical records system. Variables included demographic features (age, menopause status), clinical features and treatment outcomes. Treatment outcome was assessed in terms of early clinical response after 72 h of treatment, final clinical outcome (clinical cure or failure), microbiological outcome (microbiological eradication or failure), hospitalization days, and febrile days. Early clinical success was defined if the following criteria were met at 72 h after the start of empirical antimicrobial

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therapy: (i) resolution of fever and (ii) improvement of urinary tract symptoms or signs. Those patients who did not meet the criteria of early clinical success were regarded as early clinical failures. Clinical cure was defined as resolution of fever and absence of urinary tract symptoms or signs upon the completion of therapy and/or within 7–14 days of follow up after completion of therapy. Clinical failure was defined as recurrence of urinary tract symptoms and/or signs within 7–14 days of follow up after completion of therapy, or death. Microbiological failure was defined as detection of the same pathogen or different pathogens in urine culture within 7–14 days of follow up after completion of therapy. Patients who did not have follow-up cultures were excluded from the analysis of microbiological outcome.

Risk factor variables included age, history of antibiotic usage within the previous year, history of urinary tract infection, hospital admission history within the previous year, menopause status, diabetes mellitus, underlying co-morbidities and structural or functional abnormalities of the urinary tract [14–17]. The underlying systemic co-morbidities were: cerebrovascular accident, congestive heart failure, malignancy, chronic liver disease, renal disease, dementia, etc. Co-morbidities of the urinary tract were: neurogenic bladder, urolithiasis, history of urinary tract catheterization for 1 month, etc. Pitt score was measured as a risk factor variable: (i) oral temperature: 2 points for a temperature of ≤35°C or ≥40°C, 1 point for a temperature of 35.1–36.0°C or 39.0–39.9°C, and 0 point for a temperature of 36.1–38.9°C; (ii) hypotension: 2 points for an acute hypotensive event with decreases in systolic and diastolic blood pressure of >30 and >20 mmHg, respectively, use of intravenous vasopressor agents, or systolic blood pressure <90 mmHg; (3) receipt of mechanical ventilation: 2 points; (4) cardiac arrest: 4 points; and (5) mental status: alert, 0; disoriented, 1 point; stuporous, 2 points; and comatose, 4 points [18]. Among laboratory tests, azotaemia (serum blood urea nitrogen ≥7.14 mM and/or serum creatinine ≥123.76 μM), C-reactive protein (CRP) and WBC counts in blood were checked as risk factor variables; CRP was stratified into four levels (<5.0, 5.0–9.99, 10.0–19.99 and ≥20.0 mg/dL), and WBC counts into three levels (<10 000, 10 000–19 999 and ≥20 000 per mm^3). In addition, after reporting of the results of urine culture, antimicrobial resistance of uropathogens and initial antibiotic use were collected as risk factor variables. Treatment regimens in hospitals were recorded. Initial antimicrobial therapy was considered concordant if the treatment regimen included one or more antibiotics found to be active against the causative organism by *in vitro* susceptibility testing, and if the dose and route of administration conformed to current medical standards [2].

Microbiological data

Urine and blood culture were processed at the time of admission. Aetiological agents were determined when organisms at $\geq 10^5$ CFU/mL were identified on urine culture, and/or urinary pathogens were isolated from blood culture [19,20]. Species identification and susceptibilities to antimicrobial agents were determined by means of a semi-automated system (VITEK, bioMérieux, Hazelwood, MO, USA; or Microscan, DADE Behring, West Sacramento, CA, USA). Extended-spectrum β-lactamase-producing isolates were defined as Enterobacteriaceae proven to be positive by extended-spectrum β-lactamase test in either the semi-automated system or a double disc diffusion test according to the criteria of the CLSI [21].

Statistical methods

We compared participants' medical and laboratory data using chi-square tests or Fisher's exact tests for categorical variables, and independent *t*-tests or Mann–Whitney tests for continuous variables. A backward stepwise multiple logistic regression analysis was performed to evaluate the effect of independent variables on early clinical failure. A p-value of <0.05 (two-sided) was considered statistically significant. SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Results

Patient population and clinical characteristics

During the study period a total of 1138 women with a diagnosis of CO-APN were screened. Of these, 76 women were excluded because their final clinical outcomes were not available. Finally, 1062 women with a diagnosis of CO-APN were enrolled (Fig. 1). The median age of the 1062 women was 56.0 years (interquartile range, 39.0–71.0 years). Of these patients, 784 (73.8%) gave positive urine and/or blood cultures. *Escherichia coli* was the most common pathogen (708 patients; 90.3%) and non-*E. coli* bacteria were isolated from 76 patients (9.7%). The latter comprised 23 *Klebsiella pneumoniae*, nine *Proteus mirabilis*, six *Enterococcus faecalis*, five *Enterococcus faecium*, four *Pseudomonas aeruginosa*, four *Streptococcus* spp., two *Staphylococcus* spp., two *Providentia* spp. and others. Of the *E. coli* isolates tested, 78.7% were susceptible to fluoroquinolone, 72.2% to trimethoprim-sulfamethoxazole, 90.7% to cefotaxime and 99.7% to imipenem (Table 1).

After 72 h of treatment the patients were classified into either the early clinical success group (840 cases; 79.1%) or the early clinical failure group (222 cases; 20.9%) according to the definitions above. Table 2 shows the demographic, clinical and

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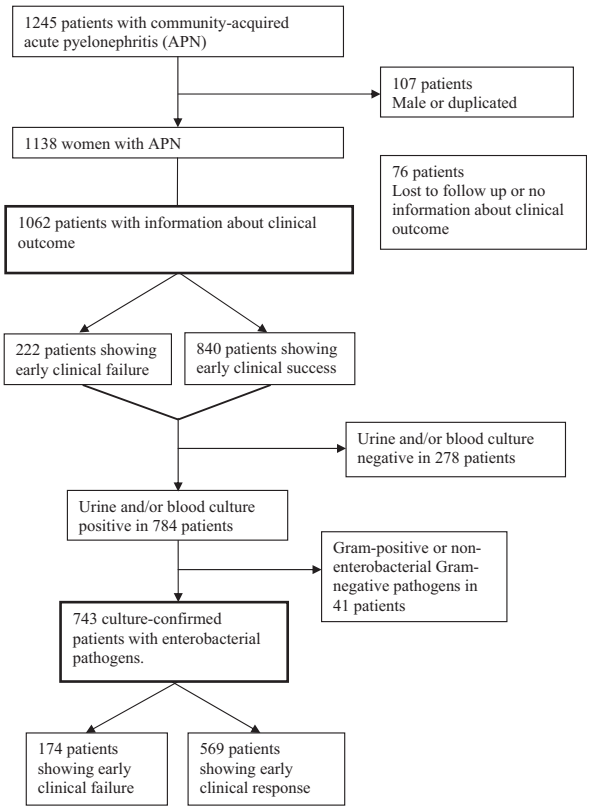

FIG. 1. Consort flow diagram.

laboratory characteristics of the patients according to their early clinical response. The median age of the early clinical failure group was higher than that of the early clinical success group, and more of the former were postmenopausal. The frequencies of diabetes mellitus, cerebrovascular disorders, malignancy and chronic liver diseases were significantly higher in the early clinical failure group than in the early clinical success group. In terms of clinical features, more patients in the early failure group suffered from vomiting and had Pitt scores ≥2. The proportions of patients with blood WBC counts >20 000/mm^3, CRP level >20 mg/dL and azotaemia were also significantly higher in the early clinical failure group than in the early clinical success group

As initial treatment regimens, intravenous antimicrobial agents were used in 1055 cases (99.3%) and oral antimicrobial agents in seven cases (0.7%). More patients in the early clinical failure group received third-generation cephalosporins and fewer of them received second-generation cephalosporins or aminoglycosides (Table 2).

Clinical implications of the early clinical failure in women with CO-APN

Table 2 presents the overall clinical outcomes of the patients in the two groups. Final clinical failure was more common in the early clinical failure group than in the early clinical success group (14.9% vs 2.3%; p <0.001) and deaths were also more frequent: 6.8% (15/220) in the early clinical failure group and 0.1% (1/840) in the early clinical success group. Median times (interquartile range) to defervescence were 5 (4–6) days and 2 (1–2) days (p <0.001), and median hospitalization durations (interquartile range) were 9 (7–14) and 7 (5–9) days in the early clinical failure and early clinical success group, respectively (p <0.001) (Table 2).

Factors related to early clinical failure in women with CO-APN

In order to identify the risk factors associated with early clinical failure, multiple regression analysis was performed

TABLE 1. Antimicrobial susceptibilities of Enterobacteriaceae (*Escherichia coli* and non-*E. coli*) isolated from community-onset acute pyelonephritis patients (*n* = 743), South Korea, 2010–2012

	E. coli (*n* = 708)				Non-*E. coli* (*n* = 35)			
Antibiotics	**Resistant (*n*)**	**Susceptible (*n*)**	**Total (*n*)**	**Susceptibility (%)**	**Resistant (*n*)**	**Susceptible (*n*)**	**Total (*n*)**	**Susceptibility (%)**
Amikacin	18	690	708	97.5	1	28	29	96.6
AMOX/CLA	111	453	564	80.3	11	19	30	63.3
Ampicillin	422	274	696	39.4	32	1	33	3.0
AMP/SUL	78	145	223	65.0	1	2	3	66.7
Cefazolin	89	300	389	77.1	4	6	10	60.0
Cefuroxime	15	196	211	92.9	2	3	5	60.0
Cetotaxime	65	635	700	90.7	4	28	32	87.5
Ceftriaxone	13	189	202	93.6	2	3	5	60.0
Ceftazidime	65	638	703	90.8	5	29	34	85.3
Cefepime	58	641	699	91.7	4	28	32	87.5
FQ	151	557	708	78.7	11	24	35	68.6
Gentamicin	159	545	704	77.4	7	26	33	78.8
Imipenem	2	703	705	99.7	0	34	34	100
Meropenem	4	575	579	99.3	0	23	23	100
Piperacillin	335	234	569	41.1	19	1	20	5.0
SXT	169	440	609	72.2	6	17	23	73.9
Tobramycin	152	525	677	77.5	7	18	25	72.0
TZP	28	633	661	95.8	3	17	20	85.0

AMOX/CLA, amoxicillin/clavulanate; AMP/SUL, ampicillin/sulbactam; FQ, fluoroquinolone (ciprofloxacin or levofloxacin); SXT, trimethoprim-sulfamethoxazole; TZP, piperacillin/tazobactam.

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TABLE 2. Demographic and clinical characteristics of study subjects by early clinical failure, South Korea, 2010–2012

	Early clinical failure (*n* = 222) *n* (%)	Early clinical success (*n* = 840) *n* (%)	p value[a]
Demographic data			
Age (median, 1Q–3Q) (years)	60.5, 43.8–72.0	54.0, 38.0–71.0	0.023[b]
Elderly (≥65 years)	98 (44.1)	310 (36.9)	0.049
Past history			
Admission within 1 year	65/202[c] (32.2)	168/787[c] (21.3)	0.001
Antibiotic use within 1 year	71/168[c] (42.3)	208/717[c] (29.0)	<0.001
Previous urinary tract infection	63/181[c] (34.8)	216/767[c] (28.2)	0.078
Co-morbid conditions			
Diabetes mellitus	84 (37.8)	207 (24.6)	<0.001
Congestive heart failure	14 (6.3)	50 (6.0)	0.844
Cerebrovascular disorders	30 (13.5)	59 (7.0)	0.002
Malignancy	16 (7.2)	28 (3.3)	0.01
Chronic liver diseases	16 (7.2)	20 (2.4)	<0.001
Chronic renal diseases	18 (8.1)	41 (4.9)	0.062
Dementia	10 (4.5)	20 (2.4)	0.089
Menopause	145 (65.3)	451 (53.7)	0.002
Urinary tract conditions			
History of catheterization within 1 month	5 (2.3)	11 (1.3)	0.305
Neurogenic bladder	3 (1.4)	10 (1.2)	0.741
Urolithiasis	6 (2.7)	11 (1.3)	0.141
Clinical features			
Pitt score[d] 1	42 (18.9)	169 (20.1)	0.69
Pitt score 2–4	53 (23.9)	84 (10.0)	<0.001
Lower urinary tract infection symptoms[e]	139 (62.6)	577 (68.7)	0.086
Flank pain	77 (34.7)	308 (36.7)	0.585
Costovertebral angle tenderness	153 (68.9)	577 (68.7)	0.948
Vomiting or nausea	85 (38.3)	217 (25.8)	<0.001
Laboratory features			
Pyuria (≥5~9 leucocytes/high-power field)	206 (92.8)	746 (88.8)	0.083
Haematuria (≥5~9 red blood cells/high-power field)	138 (62.2)	433 (51.5)	0.005
White blood cells ≥20 000/mm^3 of blood	45 (20.3)	58 (6.9)	<0.001
C-reactive protein ≥20 mg/dL	98 (44.1)	223 (26.5)	<0.001
Azotaemia[f]	63 (28.4)	105 (12.5)	<0.001
Initial antibiotics regimens			
Second-generation cephalosporins	10 (4.5)	177 (21.1)	<0.001
Third-generation cephalosporins	118 (53.2)	364 (43.3)	0.009
Fluoroquinolones	53 (23.9)	178 (21.2)	0.389
Aminoglycosides	2 (0.9)	75 (8.9)	<0.001
Other antibiotics	39 (17.6)	46 (5.5)	<0.001
Clinical outcomes			
Final clinical failure	33 (14.9)	19 (2.3)	<0.001
Mortality	15 (6.8)	1 (0.1)	<0.001
Time to fever clearance (days), median (1Q–3Q)	5 (4–6)	2 (1–2)	<0.001[b]
Hospitalization period (days), median (1Q–3Q)	9 (7–14)	7 (5–9)	<0.001[b]
Microbiological failure	11/78[c] (14.1)	43/471[c] (9.1)	0.172

[a]Chi-square test or Fisher's exact test.
[b]Mann–Whitney test.
[c]Denominators were the number of patients whose data were available in each group.
[d]The Pitt bacteraemia score was calculated using the following criteria [18]: (i) oral temperature: 2 points for a temperature of ≤35°C or ≥40°C, 1 point for a temperature of 35.1–36.0°C or 39.0–39.9°C, and 0 point for a temperature of 36.1–38.9°C; (ii) hypotension: 2 points for an acute hypotensive event with decreases in systolic and diastolic blood pressure of >30 and >20 mmHg, respectively, use of intravenous vasopressor agents, or systolic blood pressure <90 mmHg; (iii) receipt of mechanical ventilation: 2 points; (iv) cardiac arrest: 4 points; and (v) mental status: alert, 0 point; disoriented, 1 point; stuporous, 2 points; and comatose, 4 points.
[e]Lower urinary tract infection symptoms contain dysuria, frequency, urgency and nocturia.
[f]Azotaemia was defined as serum blood urea nitrogen ≥7.14 mM and/or serum creatinine ≥123.76 μM.

using the demographic, clinical and historical variables identified by simple analysis. Table 3 shows the final multiple logistic regression models for the total patients with CO-APN (*n* = 1062) and for the subgroup infected by Enterobacteriaceae (*n* = 743).

Factors identified based on the 1062 patients included diabetes mellitus, chronic liver diseases, malignancy, Pitt score ≥2, WBC count ≥20 000/mm^3 of blood, serum CRP level ≥20 mg/dL, azotaemia and history of antibiotic usage within 1 year (Table 3). These factors increased the risk of early clinical failure from 1.5 to 3.3-fold.

To assess the effects of antibiotic resistance and empirical antibiotic treatment, we analysed the factors associated with early clinical failure in the 743 patients with Enterobacteriaceae as urinary pathogens, and the antibiotic susceptibility of these pathogens. This revealed that fluoroquinolone resistance, extended spectrum β-lactamase production by the uropathogens and inadequacy of initial antibiotics were additional variables influencing early clinical failure. We then performed a multiple logistic regression analysis using all of these risk factors (Table 3). This revealed that fluoroquinolone resistance was independently associated with the early clinical failure of women with CO-APN due to Enterobacteriaceae, in addition to the risk factors for early clinical failure already identified in the total cohort of 1062 patients except azotaemia.

Factors related to mortality in women with CO-APN

To compare the factors related to early clinical failure and those related to mortality, we performed a logistic regression

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TABLE 3. Related factors for early clinical failure of patients with community-onset acute pyelonephritis (CO-APN; *n* = 1062) and subgroup of CO-APN due to Enterobacteriaceae (*n* = 743) in final model of multiple logistic regression, 2010–2012

		All patients with CO-APN (*n* = 1062)					Patients with CO-APN due to Enterobacteriaceae (*n* = 743)			
		Simple		Multiple[a]			Simple		Multiple[b]	
Characteristics	Early clinical failure (*n* = 222) *n* (%)	OR (95% CI)	p value	OR (95% CI)	p value	Early clinical failure (*n* = 174) *n* (%)	OR (95% CI)	p value	OR (95% CI)	p value
Age group (years)										
Elderly (>65)	98 (44.1)	1.351 (1.001–1.823)	0.049			83 (47.7)	1.206 (0.858–1.696)	0.281		
Pitt score 1	42 (18.9)	1.149 (0.779–1.694)	0.484			31 (17.8)	0.866 (0.553–1.356)	0.528		
Pitt score 2–4	53 (23.9)	2.916 (1.967–4.323)	<0.001	2.482 (1.621–3.8)	<0.001	40 (23.0)	2.088 (1.336–3.263)	0.001	1.99 (1.22–3.247)	0.006
Laboratory features										
WBC ≥20 000/mm^3 of blood	45 (20.3)	3.428 (2.247–5.228)	<0.001	2.537 (1.599 –4.025)	<0.001	35 (20.1)	3.422 (2.090–5.603)	<0.001	2.634 (1.537–4.513)	<0.001
Azotaemia	63 (28.4)	2.774 (1.942–3.961)	<0.001	1.806 (1.212–2.69)	0.004	49 (28.2)	2.328 (1.553–3.490)	<0.001	1.541 (0.978–2.431)	0.063
C-reactive protein ≥20 mg/dL	98 (44.1)	2.187 (1.610–2.969)	<0.001	1.679 (1.198–2.353)	0.003	80 (46.0)	2.399 (1.687–3.411)	<0.001	1.961 (1.326–2.902)	0.001
Haematuria	138 (62.2)	1.544 (1.140–2.091)	0.005			110 (63.2)	1.416 (0.998–2.008)	0.051		
Underlying medical conditions										
Diabetes mellitus	84 (37.8)	1.861 (1.361–2.546)	<0.001	1.489 (1.057–2.099)	0.023	72 (41.4)	1.743 (1.226–2.479)	0.002	1.508 (1.026–2.217)	0.037
Cerebrovascular disorders	30 (13.5)	2.068 (1.297–3.299)	0.002			26 (14.9)	1.951 (1.169–3.258)	0.011		
Chronic liver diseases	16 (7.2)	3.184 (1.622–6.254)	<0.001	3.323 (1.636–6.746)	0.001	13 (7.5)	3.453 (1.570–7.598)	0.001	3.718 (1.617–8.549)	0.002
Malignancy	16 (7.2)	2.252 (1.196–4.242)	0.01	2.219 (1.12–4.397)	0.022	15 (8.6)	2.731 (1.357–5.497)	0.004	2.805 (1.314–5.988)	0.008
Past history										
Admission within 1 year	65/202[c] (32.2)	1.748 (1.243–2.458)	0.001			48/155[c] (31.0)	1.401 (0.945–2.078)	0.093		
Antibiotic use within 1 year	71/168[c] (42.3)	1.791 (1.267–2.532)	0.001	1.54 (1.062–2.232)	0.023	55/132[c] (41.7)	1.938 (1.298–2.893)	0.001	1.575 (1.017–2.438)	0.042
Antimicrobial susceptibility										
Fluoroquinolone resistance						52 (29.9)	1.779 (1.210–2.615)	0.003	1.667 (1.093–2.541)	0.018
ESBL (+)						22 (12.6)	1.864 (1.077–3.226)	0.024	1.230 (0.656–2.307)	0.518
Discordant antimicrobial therapy						31 (17.8)	2.408 (1.475–3.929)	<0.001		

ESBL, extended-spectrum β-lactamase.
[a]Full model : Pitt score, white blood cells ≥20 000 per mm^3 of blood, azotaemia, C-reactive protein ≥20 mg/dL, haematuria, diabetes mellitus, cerebrovascular disorders, chronic liver diseases, malignancy, history of admission and history of antibiotic usage.
[b]Full model : Pitt score, white blood cells ≥20 000 per mm^3 of blood, azotaemia, C-reactive protein ≥20 mg/dL, diabetes mellitus, cerebrovascular disorders, chronic liver diseases, malignancy, history of antibiotics usage, fluoroquinolone resistance, and ESBL.
[c]Denominators were the number of patients whose data were available in each group.

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TABLE 4. Related factors for mortality of community-onset acute pyelonephritis in final model of multiple logistic regression (*n* = 1062), 2010–2012

Characteristics	Survivors (*n*)	Deaths (*n*)	Rate of mortality (%)	Simple OR (95% CI)	p value	Multiple OR (95% CI)	p value
Total patients	1046	16	1.5				
Age group (years)							
Elderly (≥65)	393	15	3.7	24.924 (3.28–189.41)	0.002	10.649 (1.26–90.05)	0.03
Pitt score 1	211	0	0				
Pitt score 2–4	124	13	9.5	24.847 (6.979–88.457)	<0.001	17.984 (4.35–74.39)	<0.001
Laboratory features							
WBC ≥20 000/mm^3 of blood	97	6	5.8	5.870 (2.088–16.500)	0.001		
Azotaemia	158	10	6.0	9.367 (3.357–26.138)	<0.001	2.947 (0.92–9.445)	0.069
C-reactive protein ≥20 mg/dL	316	5	1.6	1.050 (0.362–3.047)	0.928		
Haematuria	556	15	2.6	13.219 (1.74–100.441)	0.013	11.095 (1.37–89.94)	0.024
Underlying medical conditions							
Diabetes mellitus	285	6	2.1	1.602 (0.577–4.448)	0.366		
Congestive heart failure	60	4	6.3	5.478 (1.715–17.495)	0.004		
Cerebrovascular disorders	84	5	5.6	5.206 (1.767–15.335)	0.003		
Chronic liver diseases	36	0	0		>0.999		
Chronic renal diseases	58	1	1.7	1.136 (0.147–8.747)	0.903		
Malignancy	42	2	4.5	3.415 (0.752–15.511)	0.112		
Dementia	27	3	10.0	8.709 (2.345–32.352)	0.001		
Urinary tract conditions							
Urolithiasis	15	2	11.8	9.819 (2.049–47.047)	0.004	13.171 (1.9–91.55)	0.009
Past history							
Admission within 1 year	225	8	3.4	4.444 (1.526–12.943)	0.006		
Antibiotic use within 1 year	274	5	1.8	1.562 (0.491–4.964)	0.45		

Full model : Elderly, Pitt score, white blood cells ≥20 000 per mm^3 of blood, azotaemia, haematuria, congestive heart failure, cerebrovascular disorders, dementia, urolithiasis and history of admission.

analysis for mortality in all 1062 patients (Table 4). The 16 patients who died as a result of this episode of infection were compared with the 1046 surviving patients. Pitt score ≥2 emerged as a risk factor common to mortality and early clinical failure, and age >65 years, urolithiasis and haematuria were significant risk factors for mortality only. Pitt score ≥2 and haematuria increased the risk of death 18-fold and 11-fold, respectively, and age >65 years and urolithiasis increased the risk of death 11-fold and 13-fold, respectively. Neither underlying chronic liver disease, malignancy and diabetes mellitus nor a history of previous antibiotic usage contributed to mortality.

Discussion

In clinical practice, physicians need to consider complicating factors such as urinary tract abnormalities and underlying diseases when making decisions about treatment of patients with CO-APN [19–21]. Patients who have risk factors for mortality or poor clinical response [9,10,22] must be hospitalized. Patients who are at risk of clinical failure after 72 h of treatment also need hospitalization because decisions to modify treatment or carry out further work up might be required at short notice. Furthermore, this study showed that early clinical failure was associated with failure to improve subsequently, and even with death.

Interestingly, we found that the variables predictive of early clinical failure fell into three categories: the first were underlying diseases such as chronic liver disease, malignancy and diabetes; the second consisted of parameters reflecting the severity of infection such as Pitt score, azotaemia, serum CRP level and WBC counts in the blood, while the third category consisted of history of antibiotic usage within 1 year among the 1062 cases, and fluoroquinolone resistance in the subgroup of patients with enterobacterial infections. It is reasonable to expect that these three categories of variable would influence treatment outcome.

Risk factors for mortality due to CO-APN were age >65 years, septic shock, bedridden status and immunosuppression in one report [9], and age, McCabe score II–III, Pitt score ≥2 and hospital-acquired APN in another report [22]. In this study, age >65 years, Pitt score ≥2, haematuria and urolithiasis were associated with mortality. Interestingly, underlying diseases, such as chronic liver disease, malignancy, diabetes and antibiotic resistance, did not contribute to mortality, whereas age and severity of infection did. Antibiotic resistance was also not associated with mortality in previous reports [9,22].

Community-onset APN is a common infection caused mostly by *E. coli*. Although antibiotic resistance of uropathogens varied according to regions or countries, the epidemiology and clinical characteristics of the disease are globally similar. Comparing the populations of several studies, two studies were similar to ours [9,22] but one was different; the patients' average age was younger and co-morbidities were fewer [10]. In that report, need for hospitalization, antibiotic-resistant infecting organisms, diabetes mellitus and renal stones were risk factors for final

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clinical failure [10]. Despite the difference in populations, that study and ours shared several factors such as diabetes, renal stones and antibiotic-resistant infecting organisms either as predisposing factors for final clinical failure, early clinical failure or mortality. Furthermore, we provided the initial medical presentations of CO-APN patients requiring hospitalization. Empirical antibiotic usage and antibiotic susceptibility can also influence treatment results. Because the guidelines for antibiotic usage in CO-APN in South Korea are similar to those in other countries and our risk factors for poor clinical response at 72 h were composed of the findings at the initial presentation, we consider that the results of our study are applicable in other regions.

In the light of all these findings, we would like to recommend that CO-APN patients with the following medical presentation should be observed closely: (i) patients with age ≥65 and co-morbidities of chronic liver disease, diabetes, malignancy and renal stones; (ii) patients with a Pitt score ≥2, azotaemia, haematuria, WBC count ≥20 000/mm^3 and CRP level ≥20 mg/dL; (iii) patients with a history of antibiotic usage within the previous year.

The significance of this study is that it is a prospectively performed multicentre study of a large number of cases aiming to identify simple clinical factors predicting an early clinical response in patients with CO-APN to help physicians decide on the need for patient admission. However, this study also has several potential limitations. First, it was not possible to assess microbial factors or host genetic factors that might influence individual susceptibility to urinary tract infections and clinical course. Second, as this was a prospective, observational study without any interventions in terms of diagnostic approach and therapeutic regimen, the procedures used to diagnose structural and functional abnormalities of the urinary tract were not performed in all patients. Third, the frequencies of co-morbidities and antibiotic usage may be underestimated because the information was obtained from hospital medical records and questionnaires completed by patients and their families.

In conclusion, careful review of underlying medical conditions and antibiotic usage history, a thorough physical examination and initial laboratory test would help physicians to identify patients requiring close observation and to make appropriate decisions at initial presentation in patients with CO-APN.

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Transparency Declaration

The authors declare no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Demographic and clinical characteristics of subgroup patients of community-onset acute pyelonephritis due to Enterobacteriaceae (n = 743) by early clinical failure, South Korea, 2010–2012.

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