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Prolonged fever is not a reason to change antibiotics among patients with uncomplicated community-acquired acute pyelonephritis

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Abstract

The study aimed to determine the pattern of fever resolution among febrile patients undergoing treatment for acute pyelonephritis (APN) and prove that switching therapy based solely on persistent fever beyond 72 hours of antibiotics treatment may be unwarranted.

For the purpose of this study, non-responders were defined as those patients who had a persistent fever over 72 hours after the initiation of antibiotic therapy. Responders were defined as those patients who became afebrile in less than 72 hours after the initiation of antibiotic therapy. Clinical cure was defined as the complete resolution of all symptoms during antibiotic therapy without recurrence during the follow-up period.

A total of 843 female patients with uncomplicated community-acquired APN met all inclusion criteria. The non-responder group comprised of 248 patients (29%), and the remaining patients constituted the responder group. The median initial C-reactive protein level was higher (15.6 mg/dl vs 12.6 md/dl, $P < .001$) and bacteremia was more frequent (31% vs 40%, $P = .001$) in the non-responder group. *Escherichia coli* (*E. coli*) was the most common pathogen in both groups; there was no significant difference between the groups in the etiology of APN. Antimicrobial resistance and extended spectrum β-lactamase producing strains had an increasing trend in the non-responder group but there was no significant difference between the groups.

This study shows that it is difficult to identify patients at risk of uncomplicated community-acquired APN by antibiotic-resistant pathogens based exclusively on persistent fever. Patients with a prolonged fever for more than 72 hours show similar antibiotic susceptibility patterns and are not associated with adverse treatment outcomes. Therefore, switching of current antibiotics to broad-spectrum antibiotics should be reserved in this patient population until antibiotic susceptibility test results are available.

Abbreviations: APCT = abdomino-pelvic computed tomography, APN = acute pyelonephritis, CA = community-acquired, ESBL = extended-spectrum β-lactamse.

Keywords: fever, pyelonephritis, treatment

1. Introduction

Acute pyelonephritis (APN) is a very common community-acquired (CA) infection in women. The clinical presentation of APN is variable but the presence of fever in patients with APN is used both for diagnosis and to follow up treatment response, and resolution of fever during treatment is one of the clinical markers of adequate treatment.[1,2]

In clinical practice, the risk of complications should be assessed and alertness for underlying urologic abnormalities is part of the approach to the individual patient.[3,4] It has been the common clinical practice to perform radiologic imaging or consider switching the current antibiotic course among patients who remain febrile despite receiving a 3-days of active antimicrobial treatment.[4–7] However, the scientific basis of these recommendations predominantly relies on expert opinion and small, observational, single-center studies limited to young female patients.[6,8] The expected duration of fever among patients with pyelonephritis has not been well-defined and has not been the primary focus of the literature. Moreover, the delayed resolution of fever had neither a correlation with an antibiotic-resistant organism nor the presence of an unknown genitourinary tract abnormality in previous studies.[9–11]

The objective of this study was to determine the pattern of fever resolution among febrile patients undergoing treatment for APN. By describing the clinical outcome of these patients, we hope to prove that additional diagnostic studies or switching therapy may be unwarranted based solely on persistent fever beyond 72 hours of antibiotic treatment.

2. Materials and methods

2.1. Study design and patients

We conducted a retrospective cohort study among female patients who were diagnosed with uncomplicated CA-APN.

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The data were collected at Gachon University Gil Medical Center, a tertiary care hospital with more than 1,400 beds and located in Incheon, South Korea between January 2008 and December 2016. This study was performed by reviewing the medical records and analyzing the antimicrobial susceptibility data of the clinical microbiology laboratory of our hospital. The study protocol was approved by the institutional review board of Gachon University Gil Medical Center.

2.2. Definitions

Community acquired (CA) infection was defined as a positive urine culture obtained at the time of hospital admission or, 48 hours after hospitalization or a visit to an outpatient clinic. CA infections were classified as healthcare-associated if any of the following healthcare-associated risk factors were present:

1. hospitalization for > 48 hours or residence in a nursing home or long-term care facility during preceding 90 days;
2. receipt of intravenous therapy or specialized home care or invasive procedures during the preceding 30 days; and
3. receipt of hemodialysis during the preceding 30 days.[12]

APN was defined as fever with a temperature of ≥ 38.0 °C with

1. at least 1 of the symptoms of urgency, frequency, dysuria, suprapubic tenderness, or flank pain, and
2. a positive dipstick test result for leukocyte esterase or nitrate or more than 5 to 9 white blood cells observed on a high power microscopy field.[13]

Exclusion criteria were a history for urolithiasis or hydronephrosis, known urinary bladder dysfunction, chronic kidney disease, pregnancy, receipt of hemodialysis or peritoneal dialysis, a history of kidney transplantation, or polycystic kidney disease. Patients with concurrent infectious disease or patients with drug fever were also excluded. For the purpose of this study, non-responders were defined as those patients who had a persistent fever over 72 hours after antibiotic therapy. Responders were defined as those patients who became afebrile in less than 72 hours after antibiotic therapy. Clinical cure was defined as complete resolution of all symptoms during antibiotic therapy without recurrence during the follow-up period.[13] Worsened or persistent symptoms during antibiotic therapy and recurrence of symptoms after initial clinical cure during follow-up were designated as clinical failure.

2.3. Microbiologic data

Urine and blood cultures were processed at the time of admission. Etiologic agents were determined when organisms at $\geq 10^5$ colony forming unit/ml were identified in urine cultures and/or urinary pathogens were isolated from blood cultures. Antibiotic susceptibility pattern to antimicrobial agents were determined using a semi-automated system (VITEK II; bioMe'rieux, Hazelwood, MO, USA). Extended-spectrum β-lactamse (ESBL) producing isolates were defined as Enterobacteriaceae proved to be present by an ESBL test in either the semi-automated system or a double disk diffusion test.

2.4. Statistical methods

Categorical variables were compared using the chi-square test or Fisher exact test, as appropriate and continuous variables were compared using the Mann–Whitney *U* test. Univariate and multivariate logistic regression analyses were performed using the backward selection method. A *P*-value of <.05 was considered statistically significant. Statistical analyses were performed using SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 1215 female adult patients with CA-APN were identified. 372 patients were excluded because they had a history of structural or functional urologic abnormality (n = 133), missing data for the determination of the duration of fever (n = 123), pregnancy (n = 10), chronic kidney disease (n = 36), and fever due to another (n = 70). Finally, 843 patients met all inclusion criteria, and 248 patients (29%) constituted the non-responder group, and the remaining constituted the responder group.

The overall clinical characteristics of the 2 groups are shown in Table 1. Of the clinical features, the median initial C-reactive protein level was higher in the non-responder group (15.6 mg/dl vs 14.0 md/dl, $P < .001$). *E. coli* was the most common pathogen in both groups and there was no significant difference in the etiology of APN. Bacteremia was more frequent in the non-responder group (40% vs 28%, $P < .001$). In total, 531(63%) enhanced abdomino-pelvic computed tomography (APCT) scans was performed; 67% were performed ≤ 24 hours after admission, and 91% were performed ≤ 72 hours after admission. There was no significant difference in the number of enhanced APCT scans in both groups, and renal abscess formation was more frequent in the non-responder group than in the responder group (12% vs 5%, $P = .001$). There was no significant difference in the initially administered antibiotics and all the patients with a renal abscess in both groups were treated with antibiotics alone (Table 2).

The antibiotic susceptibility patterns of *E. coli* in the non-responder group and responder group are shown in Table 3. The antimicrobial-resistant and ESBL-producing strains were not significantly different between the groups. Among the 179 patients who had a persistent fever over 72 hours, antibiotics were switched to adequate antibiotics in 25 patients (14%) as soon as the pathogen identification and antimicrobial susceptibility profile had known. The median times to antibiotic change were 5 days (IQR 3.5–7.5).

Risk factors for prolonged fever over 72 hours in patients with CA-APN caused by *E. coli* were analyzed. The results of the univariate and multivariate analyses are shown in Table 4. C-reactive protein level (odds ratio, 1.05; 95% confidence interval, 1.03–1.09) and renal abscess formation (odds ratio, 2.70; 95% confidence interval, 1.14–6.45) were significantly associated with prolonged fever in patients with CA-APN caused by *E. coli*.

4. Discussion

This study showed that it is difficult to identify patients likely to have uncomplicated CA- APN caused by antibiotic resistant pathogens based solely on persistent fever. The antibiotic susceptibility patterns of *E. coli* and the rate of appropriate antibiotic use were not significantly different between the non-responder and responder groups. Persistent clinical symptoms after 48 to 72 hours of antibiotic treatment for uncomplicated acute urinary tract infection are usually reasons to change the ongoing antibiotic therapy to broad-spectrum antibiotics therapy

Table 1

Demographics and baseline characteristics of patients with community acquired APN.

	Total (N = 843)	Non Responder (N = 248)	Responder (N = 595)	*P* value
Age, median years (IQR)	53 (36–69)	53 (35–68)	52 (36–70)	.72
Comorbidities				
Malignancy	36 (4)	10 (4)	26 (4)	.49
COPD	3 (0.3)	1 (0.4)	2 (0.3)	.64
DM	215 (25)	66 (27)	149 (25)	.67
CNS condition	46 (6)	7 (3)	39 (7)	.03
Liver cirrhosis	7 (0.8)	4 (2)	3 (1)	.11
Bed-ridden status	17 (2)	3 (1)	14 (2)	.42
Menopause	430 (51)	130 (52)	300 (51)	.65
Previous UTI	178 (21)	45 (18)	133 (22)	.20
CCI ≥ 1	290 (34)	87 (35)	203 (34)	.81
HCAI	15 (2)	3 (1)	12 (4)	.26
APN characteristics				
Recurrent UTI	62 (7)	14 (6)	48 (8)	.25
CVA tenderness	591 (70)	173 (70)	418 (70)	.93
Duration of fever, median days (IQR)	3 (2–4)	4 (4–5)	2 (1–3)	.00
CRP, median (IQR)	14.0 (7.1–18.8)	15.6 (9.4–21.4)	12.6 (6.2–17.7)	.00
Acute kidney injury	111 (23)	47 (19)	64 (11)	.002
Bacteremia	262 (31)	98 (40)	164 (28)	.001
Etiology of APN				
Culture negativity	192 (23)	47 (19)	145 (24)	.11
E. coli	561 (67)	179 (72)	382 (64)	.03
K. pneumoniae	41 (5)	11 (4)	30 (5)	.86
Proteus spp.	7 (0.8)	2 (0.8)	5 (0.8)	.96
Enterobacter spp.	6 (0.8)	1 (0.4)	5 (0.8)	.49
Pseudomonas aeruginosa	2 (0.2)	1 (0.4)	1 (0.2)	.52
S. aureus	3 (0.4)	2 (1)	1 (0.2)	.16
Enterococcal spp.	21 (3)	9 (4)	12 (2)	.22
Streptococcal spp.	6 (0.7)	1 (0.4)	5 (0.8)	.49

Note. The data represent the no. (%) of patients, unless otherwise specified.

APCT = abdomino-pelvic computed tomography, CCI = Charlson comorbidity index, CI = confidence interval, CNS = cerebrovascular, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein (mg/dl), CVA = costovertebral angle, DM = diabetes mellitus, HCAI = health care associated infection, IQR = interquartile range, OR = odd ratio, UTI = urinary tract infection.

and fever is the most often cited clinical indicator.[14,15] Theoretically, prolonged fever during treatment could be a marker of infections with a higher likelihood of resistant pathogens, but evidence for this phenomenon is lacking.[16,17] Our study showed that a delay of >72 hours to appropriate antibiotic therapy and APN due to antibiotic-resistant species were not different in both the non-responder and responder groups.

The delayed administration of appropriate antibiotic therapy is often believed to lead to adverse outcomes.[17] However, given that most previous studies focused on bloodstream infections from diverse sources and included heterogeneous populations

Table 2

Clinical outcomes of community acquired APN.

	Non responder (N = 248)	Responder (N = 595)	OR (95% CI)	*P* value
Clinical relevant radiologic findings				
Underwent contrast APCT	167 (67)	364 (61)	1.31 (0.96–1.79)	.10
New structural abnormality	17 (7)	34 (6)	1.18 (0.65–2.16)	.64
Renal abscess formation	28 (12)	26 (5)	2.72 (1.56–4.76)	.001
Initial antibiotics regimens				
ESCs	64 (25)	187 (31)	0.75 (0.54–1.10)	.17
FQs	176 (71)	367 (62)	1.52 (1.10–2.09)	.01
Carbapenems	11 (4)	35 (6)	0.73 (0.37–1.49)	.51
Others	8 (3)	22 (4)	0.87 (0.38–1.97)	.84
Appropriate antibiotics usage within 72 hour	165 (67)	378 (64)	1.14 (0.84–1.56)	.43
Duration of antibiotics, median days (IQR)	15 (14–18)	14 (13–16)		.00
Duration of proper antibiotics, median days (IQR)	14 (8–16)	13 (0–15)		.003
Hospital day, median days (IQR)	7 (5–7)	5 (4–8)		.00
Clinical cure	200 (81)	464 (78)	1.22 (0.84–1.77)	.35

Note. The data represent the no. (%) of patients, unless otherwise specified.

CI = confidence interval, ESCs = extended spectrum cephalosporins, FQs = fluoroquinolones, IQR = interquartile range, ORvodd ratio.

Table 3

Antimicrobial susceptibilities of *E. coli* isolates in patients with community acquired APN.

Antimicrobial agent	Number (%) of isolates non-susceptible to antimicrobial agents in group			
	Non responder (n = 179)	Responder (n = 382)	OR (95% CI)	*P* value
ESCs	26 (15)	51 (13)	1.10 (0.66–1.84)	.70
FQs	41 (23)	76 (20)	1.20 (0.79–1.84)	.44
Ampicillin	110 (62)	234 (61)	1.01 (0.70–1.45)	1.00
Aztreonam	23 (13)	45 (12)	1.10 (0.65–1.89)	.78
TMP-SMX	57 (32)	120 (31)	1.02 (0.70–1.50)	.92
AGs	38 (21)	86 (23)	0.92 (0.60–1.43)	.83
ESBL	24 (13)	42 (11)	1.25 (0.73–2.14)	.40
No resistance	58 (32)	126 (33)	0.97 (0.67–1.42)	.92

Note. The data represent the no.(%) of isolates non-susceptible to antimicrobial agents in group.
AGsvaminoglycosides, APN = acute pyelonephritis, ESBL = extended spectrum β-lactamase, ESCs = extended spectrum cephalosporins, FQs = fluoroquinolones, OR = odd ratio, TMP-SMX = trimethoprim-sulfamethoxazole.

Table 4

Risk factors for prolonged fever in patients with community acquired APN caused by *E. coli*.

Risk Factors	Crude OR (95% CI)	Adjusted OR (95% CI)	*P* value
Previous UTI	0.77 (0.53–1.12)	1.17 (0.66–2.07)	.59
Recurrent UTI	0.68 (0.37–1.26)	0.59 (0.22–1.57)	.29
C-reactive protein (mg/dl)	1.06 (1.03–1.08)	1.06 (1.04–1.09)	.00
Bacteremia	1.72 (1.26–2.35)	1.29 (0.87–1.91)	.20
Acute kidney injury	1.94 (1.29–2.92)	0.92 (0.52–1.63)	.78
ESBL	1.25 (0.73–2.14)	1.19 (0.56–2.54)	.66
New structural abnormality	1.18 (0.65–2.16)	0.89 (0.38–2.10)	.80
Renal abscess formation	2.72 (1.56–4.76)	2.38 (1.04–5.47)	.04
Adequate therapy within 72 hours	1.14 (0.84–1.56)	0.73 (0.38–1.42)	.35

APN = acute pyelonephritis, CCI = Charlson comorbidity index, CI = confidence interval, DM = diabetes mellitus, ESBL = extended spectrum β-lactamase, OR = odds ratio.

encompassing patients with both CA and healthcare-associated infections in their analyses, the impact of antibiotic resistance on treatment outcomes might have been overemphasized.[17] Moreover, ESBL-producing *E. coli* strains have been reported to harbor multiple resistance genes, possibly causing a fitness cost leading to a decrease in virulence potential,[18–20] and ESBL production by itself is not associated with adverse treatment outcomes, regardless of a delay in appropriate antibiotic therapy.[16,17]

Although the clinical implications of prolonged fever were less serious in this patient population, prolonged fever might have caused a considerable economic burden because of longer hospitalizations in the non-responder group. In this study, the long period of hospitalization appeared to be due to lack of defervescence without careful consideration of the clinical response to therapy. Since carbapenems are considered as the treatment of choice for infections with ESBL-producing organisms, switching treatment decisions would favor carbapenems. This finding implies that the therapeutic strategy for patients with APN presenting with prolonged fever is uncertain and that physicians are still reluctant to adopt empirical antibiotic strategies to manage APN in the community.

This study demonstrated that the factors associated with prolonged fever in patients with CA-APN caused by *E. coli* were concurrently high CRP level and renal abscess formation. In the result of previous studies, it was demonstrated that a high CRP level, and longer time to defervescence could be used as predictors of bacteremic urinary tract infection.[21,22] Our study showed that patients in the non-responder group were more likely to have bacteremia.

Patients with renal abscesses have often been ill for 2 or more weeks and the diagnosis should be strongly considered in any patient with a febrile illness who does not respond to therapy for APN in the literature.[2,23] Similar to those studies, we found that the rate of renal abscess formation among patients in the non-responder group was as high as 12% and a significant risk factors was associated with prolonged fever over 72 hours in APN in the multivariate analysis. Worsening or no improvement by 72 hours arouses concern for renal abscess may warrant radiologic imaging. However, we did not find an association between fever duration and elevated risk of newly diagnosed urinary tract abnormality. The predictive value of fever duration has been questioned in previous studies that showed similar fever patterns as in our study.[9,11]

This study has some limitations. Due to the single-center retrospective design, there may have been bias during data collection, and the generalizability of our findings might be limited. Patients recruited in this trial are most likely to be representative of women with CA-APN, which is supported by the low occurrence of complicated and recurrent infections. A selection bias towards a more severe disease that did not allow treatment at home might be assumed because the patients arrived at the emergency departments of the hospitals. Despite these limitations, our study clarifies the characteristics of CA-APN patients presenting with prolonged fever and will help guide therapeutic strategies for this infection.

In conclusion, this study shows that it is difficult to identify patients likely to have uncomplicated CA-APN by antibiotic-resistant pathogens based solely on persistent fever. Patients with prolonged fever over 72 hours show similar antibiotic

susceptibility patterns and are not associated with adverse treatment outcomes. Therefore, switching of current antibiotics to broad-spectrum antibiotics should be reserved in this patient population until antibiotic susceptibility test results are available.

Author contributions

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