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ORIGINAL ARTICLE

Inappropriate empirical antibiotic therapy does not adversely affect the clinical outcomes of patients with acute pyelonephritis caused by extended-spectrum β-lactamase-producing Enterobacteriales

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Abstract

Extended-spectrum β-lactamase-producing Enterobacteriales (ESBL-PE) are often associated with inappropriate empirical therapy (IAT). The aim of this study was to investigate whether IAT of acute pyelonephritis (APN) caused by ESBL-PE is related to adverse outcomes. A retrospective cohort study was performed at a tertiary-care hospital from 2014 through 2016. Patients who had APN caused by ESBL-PE and were definitely treated with appropriate antibiotics for at least 7 days were enrolled. IAT was defined as when inappropriate empirical antibiotics were given 48 h or longer after initial diagnosis of APN. Primary endpoint was treatment failure defined as clinical and/or microbiologic failure. Secondary endpoints were length of hospital stay and recurrence of APN. Propensity score matching was used to adjust heterogeneity of each group. Among 175 eligible cases, 59 patients received IAT and 116 patients received appropriate empirical antimicrobial therapy (AT). Treatment failure was observed in five (8.4%) patients and nine (7.8%) patients in each group, respectively. After matching, the treatment failure rate was similar between both groups (adjusted odd ratio [aOR] 1.05; 95% confidence index [CI] 0.26–4.15). The length of hospital stay (median 11 days in the IAT group versus 11 days in the AT group; $P = 0.717$) and absence of recurrence within 2 months (90.3% in IAT and 86.7% in AT; $P = 0.642$) were also similar. IAT did not adversely affect the clinical outcome. In this regard, clinicians should be more cautious about indiscriminate prescription of broad-spectrum antibiotics such as carbapenem empirically for treatment of APN possibly caused by ESBL-PE.

Keywords Acute pyelonephritis · Extended-spectrum β-lactamase · Empirical antimicrobial therapy · Enterobacteriales

Introduction

The emergence of extended-spectrum β-lactamase-producing Enterobacteriales (ESBL-PE) is a common and challenging problem in both community- and hospital-acquired infections [1, 2]. The urinary tract is one of the most common sites of infection caused by ESBL-PE, which is related to inappropriate administration of empirical antibiotics [3, 4]. Although clinical outcome of septic shock largely depends on early appropriate antimicrobial therapy [5], various infections with different prognoses can present as bacteremia with septic shock. There is controversy over whether a delay in appropriate antimicrobial therapy adversely affects prognosis of bacteremia caused by ESBL-PE [6–13].

Although physicians often fail to select appropriate antibiotics to treat acute pyelonephritis (APN) caused by ESBL-PE, the treatment failure rate has been reported as less than 10% [14, 15]. In addition to high rate of treatment success, a delay in appropriate antibiotics was not related to adverse outcome in pediatric patients with febrile urinary tract infection caused by ESBL-PE in one study [13]. In this regard, we conducted this study to evaluate whether a delay in appropriate antimicrobial therapy of APN caused by ESBL-PE is related to adverse outcomes in adult patients.

Materials and methods

Study population and design

This retrospective cohort study was conducted at Samsung Medical Center, a 1950-bed tertiary-care referral hospital in

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Seoul, South Korea. This study includes the patient cohort of our previous study [16].

Medical records for adult patients (aged ≥18 years) who were diagnosed with acute pyelonephritis (N10), cystitis (N30), or other urinary tract infections (N39) based on the International Classification of Diseases (ICD)-9 were collected and urine cultures were reviewed to enroll patients with APN. Only index admission was included for each study participant. We excluded patients with febrile urinary tract infections other than APN (such as renal abscess and/or prostatitis) or APN patients combined with non-urogenital infection.

Definitions, outcomes, and data collection

Only appropriately treated patients with ≥ 2 of APN signs and symptoms with concomitant positive urine cultures of ESBL-PE were enrolled. APN signs and symptoms were defined as fever (≥ 38.0 °C), chills, flank pain, costovertebral angle tenderness, and nausea/vomiting [17]. Concomitant positive urine culture was defined as a positive urine culture of ESBL-PE ≥ 10^4 CFU/mL, or a positive urine culture of ESBL-PE ≥ 10^3 CFU/L when the patient took antibiotics prior to urine culture. Cases of co-infection with non-ESBL pathogen (except for non-multidrug-resistant Enterobacteriales) were discarded. Appropriately treated patients were defined as those who were definitely treated with intravenous antibiotics showing in vitro susceptibility for at least 7 days regardless of appropriateness of empirical treatment.

Electronic medical records of all enrolled patients were reviewed for identifying clinical characteristics and treatment outcomes. Patients who received inappropriate empirical antimicrobial therapy for 48 h or more after initial diagnosis of APN were classified as the inappropriate empirical therapy (IAT) group, and patients who received appropriate antibiotics within 48 h were classified as the appropriate empirical therapy (AT) group. Antibiotic appropriateness was decided by an in vitro antibiotics susceptibility test. Intermediate susceptibility was considered as resistant. In the case of APN with multiple pathogens, only antibiotics that are susceptible to all isolates are regarded as susceptible agents.

To compare baseline characteristics of each group, the following data were collected: acquisition site (hospital-acquired, health care-associated [18], or community-acquired), sex, age, disease severity [high fever (≥ 39.0 °C) or hypothermia (≤ 35.0 °C), hypotension (systolic blood pressure ≤ 90 mmHg or need for inotropic or vasopressor)], mental change, Charlson comorbidity index (CCI) [19], history of APN in the preceding year, bacteremia, definitive treatment with non-carbapenem antibiotics, treatment duration with appropriate antibiotics, infectious disease (ID) consultation, and transfer to long-term care facility (LTCF) after clinical treatment success. Patients with the following characteristics were considered as complicated APN: hospital-acquired APN, male sex, kidney transplantation, diabetes mellitus, obstructive uropathy by benign disease, urogenital malignancy, ureteral stent, indwelling Foley and/or suprapubic catheter, neurogenic bladder, vesicoureteral reflux, or recent urogenital operation (within 3 months).

In the study, the primary outcome was treatment failure defined as clinical and/or microbiologic failure. Clinical treatment success was defined as either patients' signs and symptoms resolved within 7 days or patients' signs and symptoms did not recur while ongoing antimicrobial treatment. Microbiological success was defined as negative urine culture within 7 days. Secondary endpoint was length of hospital stay, adverse events during treatment: enterocolitis infection including *Clostridium difficile* (≥ Grade 2), Eosinophilia (≥ Grade 1) and/or skin eruption (≥ Grade 1), increased alanine aminotransferase (≥ Grade 1), decreased platelet count (≥ Grade 1), decreased neutrophil count (≥ Grade 1) or gastrointestinal intolerance requiring drug cessation (≥ Grade 2) [20], and recurrence of APN by ESBL-PE within 2 months to 1 year.

Microbiological tests

All urine samples were taken from self-voided mid-stream urine, from a Nelaton or Foley catheter. Blood samples for cultures were taken from peripheral veins and/or a central line. A Bactec-9240 system (Becton Dickinson, Sparks, MD) or a BacT/Alert 3D system (bioMérieux Inc., Marcy l'Etoile, France) was used for blood cultures. A Vitek II automated system (bioMérieux Inc.) and Microscan (Siemens Healthcare Inc.) were used to identify microbes and test their antimicrobial agent sensitivity with a standard identification card, using the modified broth microdilution method. The susceptibility of a uropathogen to an antibiotic was determined by measuring the minimum inhibitory concentration (MIC) as described by the Clinical and Laboratory Standards Institute (CLSI) [21].

Statistical analyses

All statistical analyses were performed using R software version 3.4.3 (The R Foundation, 2017). To compare patient characteristics between the IAT and AT groups, a Student's *t* test or Mann-Whitney test was used to compare continuous variables and the Chi-square test or Fisher's exact test was used to compare categorical variables.

A matched propensity score (PS) modeling of 1:3 was used to reduce the risk of bias for the exposure. PS was calculated based on the logistic regression method including the following variates: community-acquired, treatment with non-carbapenem, and presence of bacteremia. If patients in the IAT group could not be matched with three patients in the AT, they

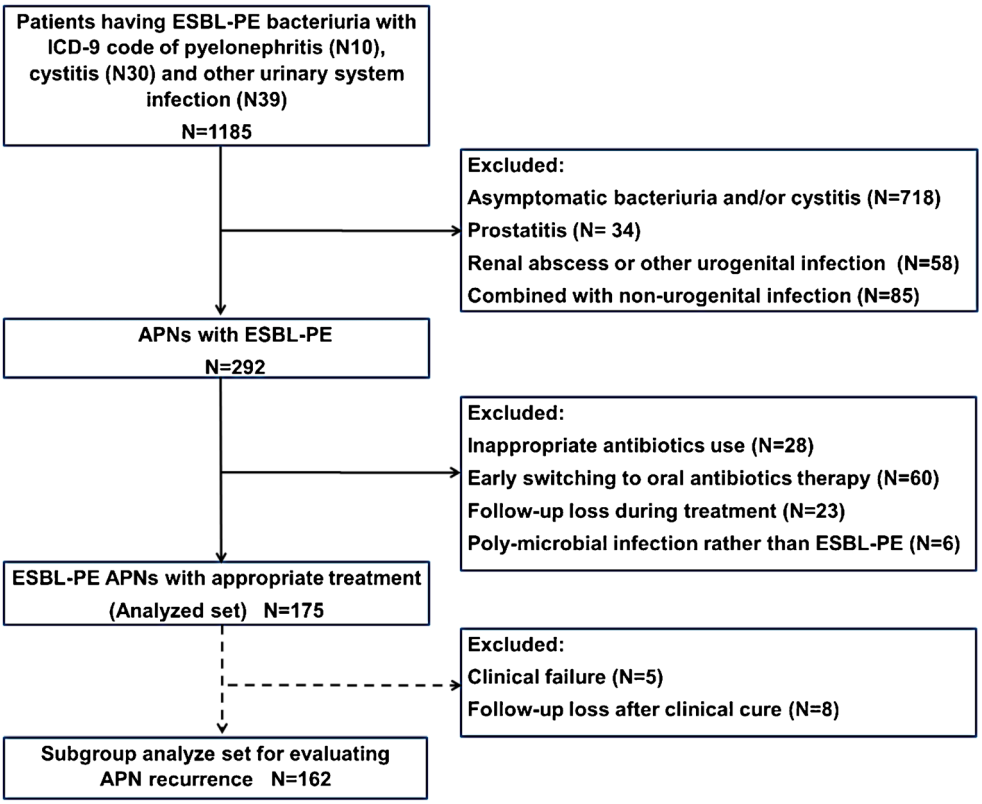

Fig. 1 Study population. ESBL-PE, Extended-spectrum β-lactamase-producing Enterobacteriales; ICD, International Classification of Diseases; APN, acute pyelonephritis

were then matched with one or two patients in the AT group. Non-matched cases were discarded. Because not all pairs were matched equally, weighted-matching analysis was implemented. The conditional logistic regression method was used to adjust primary and secondary outcome. Additionally, we did subgroup analysis to compare recurrence of APN within 2 months and 1 year in each group. In this subgroup analysis, only patients with clinical treatment success and having follow-up data after APN treatment were included. PS was calculated based on logistic regression method including the following variates: community-acquired, treatment with non-carbapenem, presence of bacteremia, and transfer to long-term care facility. After matching, the Cox proportional hazard regression model was used to compare recurrence. All *P* values were two-tailed, and *P* values < 0.05 were considered statistically significant. In addition, we did a power analysis for two-sample non-inferiority test with fixed sample size and the number of events in our study [22].

Results

Study population and initial empirical treatment regimen

During the study period, a total of 1185 patients with ESBL-PE bacteriuria with an ICD-9 code of pyelonephritis (N10), cystitis (N30), or other urinary system infection (N39) were screened. Of these, 718 (60.6%) patients had only asymptomatic bacteriuria or cystitis. Among 292 patients with APN caused by ESBL-PE without other combined urinary tract or systemic infections, 175 patients who were definitely appropriately treated and who had follow-up data were finally enrolled. In subgroup analysis for APN recurrence within 1 year, five patients who failed clinical cure and eight patients who had no follow-up data after clinical cure were excluded, thus 162 patients were included (Fig. 1).

Table 1 summarizes patient characteristics included in this study. Health care–associated infection (77/175, 44%) was the most common acquisition site. Fifty-nine patients (33.7%) received inappropriate empirical antibiotics. Eighty two percent of patients received ID consultation. Median treatment duration of appropriate antibiotics was 13 days. Because some patients received outpatient parenteral antimicrobial therapy, median length of hospital stay was shorter than total duration of intravenous antibiotics therapy. *Escherichia coli* was the most frequently isolated pathogen (144/175, 82.3%), followed by *Klebsiella pneumoniae* (29/175, 16.6%).

Overall, 8% (14/175) of patients were classified as treatment failure. APN recurrence caused by any pathogen or by ESBL-PE within 1 year was 35.2% and 26.3%, respectively. Twenty percent of patients had adverse events during treatment, and CDAD was the most common complication during APN treatment.

Table 1 Demographic characteristics of study population

	Total number, $N = 175$ (%)
Acquisition site	
Hospital-acquired	44 (25.1)
Health care–associated	77 (44.0)
Community-acquired	54 (30.9)
Patient characteristics	
Sex (male)	53 (30.3)
Age, years	63.20 ± 15.15
History of APN within 1 year	45 (25.7)
Complicated APN	155 (88.6)
Kidney transplantation	25 (14.3)
Urogenital malignancy	41 (23.4)
Ureteral stent	14 (8.0)
Foley catheter or cystostomy	17 (9.7)
Diabetes mellitus	43 (24.6)
Recent urogenital surgery within 3 months	8 (4.6)
Disease severity	
Fever > 39 °C or hypothermia < 35 °C	72 (44.4)
Hypotension	31 (19.1)
Mental change	10 (6.2)
Bacteremia	65 (40.1)
Charlson comorbidity index ≥ 3	50 (39.9)
Pathogens	
Escherichia coli	144
Klebsiella pneumoniae	29
Proteus mirabilis	2
Treatment	
Time to appropriate antibiotics, median days (range)	0 (0–2)
Inappropriate empirical antibiotics	59 (33.7)
Definitive treatment with non-carbapenem	30 (17.1)
Treatment duration with appropriate antibiotics (days)	12 (10–14)
Short-term therapy (< 10 days)	26 (16.0)
Infectious disease consultation	133 (82.1)

Data represent the number (%) of patients, unless otherwise specified; *APN* Acute pyelonephritis

In the AT group, piperacillin/tazobactam (56/116, 48.3%) was the most commonly prescribed initial empirical antibiotic within 48 h, followed by ertapenem (32/116, 27.5%) and meropenem (19/116, 16.4%). In the IAT group, most patients received ceftriaxone (26/59, 44.1%) and ciprofloxacin (25/59, 42.3%) as initial empirical antibiotics (Supplementary Table 1).

Non-matched data showed that there were significantly more cases of community-acquired APN in the IAT group and more cases of bacteremia in the AT group. Treatment duration with appropriate antibiotics was shorter in the IAT compared with the AT group (median 10 days versus 13 days, $P = 0.008$). In non-matched data of subgroup analysis for APN recurrence, the patient characteristics were very similar to the original population. Transfer to LTCF was relatively common in the AT group, without statistical significance (Table 2).

Primary and secondary outcomes

No statistically significant differences were observed among variables except for treatment duration with appropriate antibiotics after matching the two groups. Treatment duration was still shorter in the IAT group compared with the AT group (median 10 days versus 13 days, $P = 0.026$).

The adjusted risk of treatment failure in the IAT and AT groups was similar (OR 1.05, 95% CI 0.26–4.15, $P = 0.947$). Because of the limited sample size and the number of events, the expected power was only 31.5% and 74.6% to ensure significant non-inferiority with margin of 5% and 10%, respectively. With sample size and events in our study, the significant non-inferiority with minimum margin of 10.8% can be detected with the 80% power. Adjusted clinical cure and microbiological cure showed no statistically significant differences. The risk of adverse events during treatment showed no significant difference (OR 0.38, 95% CI 0.11–1.30, $P = 0.379$). Even though time to appropriate antibiotics was 2 median days later in the IAT group compared with the AT group, duration of hospital stay was similar in both groups (median 11 days in both groups, $P = 0.717$) (Table 3).

In subgroup analysis for APN recurrence, matched data showed no significant difference of variables in both groups, except for treatment duration with appropriate antibiotics as showed in the original population (Supplementary Table 2). After adjustment, the risk of APN recurrence within 2 months caused by ESBL-PE or by any pathogen in the IAT group was not significantly different than that of the AT group (HR 0.75, 95% CI 0.22–2.56, $P = 0.642$, Fig. 2a; HR 0.52, 95% CI 0.17–1.59, $P = 0.249$, Fig. 2b, respectively). The risk of APN recurrence within 1 year caused by ESBL-PE or by any pathogen in the IAT group was also similar to that of the AT group (HR 0.92, 95% CI 0.43–2.00, $P = 0.947$; HR 0.71, 95% CI 0.36–1.43, $P = 0.345$, not shown in figure).

Discussion

This study showed that inappropriate empirical antimicrobial therapy was not related to adverse short-term and long-term outcomes in treatment of APN caused by ESBL-PE in terms of treatment failure and recurrence. In addition, duration of hospital stay was very similar in both the IAT and the AT group.

ESBL-PE bacteremia was associated with delayed effective antimicrobial therapy and higher mortality than ESBL non-producing Enterobacteriales bacteremia [2, 23]. For improving appropriateness of empirical therapy in patients with

Table 2 Comparison between non-matched data and matched data of characteristics for appropriate and inappropriate empirical treatment groups

Variables	Non-matched				Propensity score matched			
	IAT (59)	AT (116)	*P* value	SMD	IAT (47)	AT (104)	*P* value	SMD
Acquisition site								
Hospital-acquired	11 (18.6)	33 (28.4)	0.219	0.233	11.0 (23.4)	21.8 (21.6)	0.798	0.042
Health care–associated	18 (30.5)	59 (50.9)	0.016	0.424	18.0 (38.3)	38.0 (37.6)	0.918	0.015
Community-acquired	30 (50.8)	24 (20.7)	< 0.001	0.663	18.0 (38.3)	41.2 (40.8)	0.095	0.051
Patient characteristics								
Sex (male)	13 (22.0)	40 (34.5)	0.128	0.279	13.0 (27.7)	25.4 (25.2)	0.745	0.056
Age (mean ± SD)	61.83 ± 14.89	63.90 ± 15.30	0.395	0.137	62.21 ± 15.30	62.88 ± 15.84	0.816	0.043
History of APN within 1 year	13 (22.0)	32 (27.6)	0.541	0.129	9.0 (19.1)	27.9 (27.7)	0.260	0.202
Complicated APN	50 (84.7)	105 (90.5)	0.377	0.176	41.0 (87.2)	90.6 (89.7)	0.682	0.078
Kidney transplantation	12 (20.3)	13 (11.2)	0.16	0.253	8.0 (17.0)	16.1 (16.0)	0.893	0.029
Urogenital malignancy	11 (18.6)	30 (25.9)	0.381	0.174	10.01 (21.3)	24.0 (23.8)	0.744	0.059
Ureteral stent	3 (5.1)	11 (9.5)	0.472	0.17	3.0 (6.4)	7.2 (7.1)	0.870	0.028
Foley catheter or cystostomy	6 (10.2)	11 (9.5)	> 0.999	0.023	6.0 (12.8)	9.7 (9.6)	0.552	0.101
Diabetes mellitus	16 (27.1)	27 (23.3)	0.71	0.089	11.0 (23.4)	20.8 (20.6)	0.721	0.069
Recent urogenital surgery within 3 months	2 (3.4)	6 (5.2)	0.88	0.088	2.0 (4.3)	5.0 (5.0)	0.862	0.034
Disease severity								
Fever > 39 °C or hypothermia < 35 °C	27 (45.8)	49 (42.2)	0.777	0.071	22.0 (46.8)	41.5 (41.1)	0.557	0.014
Hypotension	7 (11.9)	26 (22.4)	0.138	0.283	7.0 (14.9)	21.1 (20.9)	0.429	0.158
Altered mental status	1 (1.7)	10 (8.6)	0.146	0.317	1.0 (2.1)	7.9 (7.8)	0.207	0.263
Bacteremia	17 (28.8)	54 (46.6)	0.036	0.372	17.0 (36.2)	39.8 (39.4)	0.469	0.066
Charlson comorbidity index (median, IQR)	2 (1–3)	2 (1–3)	0.331	0.161	2 (1–3)	2 (1–3)	0.704	0.069
Treatment								
Time to appropriate antibiotics (median, IQR)	2 (2–4)	0 (0–0)	< 0.001	3.435	3 (2–4)	0 (0–0)	< 0.001	3.24
Definitive treatment with non-carbapenem	5 (8.5)	25 (21.6)	0.05	0.372	5.0 (10.6)	12.5 (12.4)	0.693	0.056
Treatment duration with appropriate antibiotics (median, IQR)	10 (9.5–14)	13 (10–14)	0.008	0.425	10 (9–14)	13 (10–14)	0.026	0.455
Short-term therapy (< 10 days)	15 (25.4)	13 (11.2)	0.027	0.374	12.0 (25.5)	11.5 (11.3)	0.021	0.372
Infectious disease consultation	49 (83.1)	95 (81.9)	1.000	0.03	39.0 (83.0)	84.5 (83.7)	0.914	0.019

Data represent the number (%) of patients, unless otherwise specified; *APN* acute pyelonephritis, *IQR* interquartile range

ESBL-PE bacteremia, models for predicting ESBL-PE, which were composed of several clinical factors, were developed [4, 24]. However, whether IAT is associated with adverse outcomes for patients with ESBL infection has been debated in several studies.

Kang et al. have reported a couple of analyses of mortality factors in patients with ESBL bacteremia. Presentation with septic shock and inappropriate definitive therapy were adverse prognostic factors in ESBL-PE bacteremia; however, IAT was never suggested as an adverse prognostic factor [6, 10]. On the other hand, Tumbarello et al. and De Rosa et al. reported that IAT was related to mortality in patients with ESBL-PE bacteremia [7–9]. Meanwhile, another recent study suggested that IAT is not related to outcome of patients with ESBL-PE [11, 12].

The reasons for this inconsistency might be related to heterogeneous focuses of infections causing bacteremia. The proportion of urinary tract infections in patients with ESBL-PE bacteremia was variable (9.4%–42%) in these studies. The overall mortality rates tended to be higher in studies showing that IAT was associated with higher mortality than those in other studies presenting unrelatedness of IAT with mortality (17.2%–38.2% versus 5.2%–25.6%) [6–12]. These suggest that the impact of IAT on mortality might depend on higher mortality rates in patients with ESBL-PE bacteremia. This hypothesis is consistent with other bacteremia studies showing different impact of the appropriateness of empirical antibiotics for patients with bacteremia caused by any pathogen in emergency departments (ED). In that study, only an elderly patient group with higher mortality showed that inappropriateness of empirical antibiotics was related to higher mortality. The effect of IAT in UTI needs to be evaluated separately because the mortality rate is usually low in UTI [25].

Table 3 Comparison of clinical outcomes between appropriate and inappropriate empirical treatment groups

	Non-matched					Adjusted (PS weight)				
	Event		OR	95% CI	*P* value	Event		OR	95% CI	*P* value
	AT (116)	IAT (59)				AT (101)	IAT (47)			
Primary outcome										
Treatment failure	9 (7.8)	5 (8.5)	1.10	0.35–3.47	0.870	8.2 (8.2)	4.0 (8.5)	1.05	0.26–4.15	0.947
Secondary outcome										
Clinical cure	112 (96.6)	58 (98.3)	2.07	0.22–19.20	0.522	98.1 (97.2)	46.0 (97.9)	1.34	0.14–13.06	0.799
Microbiological cure	109 (94.0)	54 (91.5)	0.69	0.21–2.30	0.550	94.2 (93.3)	43.0 (91.5)	0.78	0.18–3.31	0.732
Adverse events during treatment	18 (15.5)[a]	3 (5.1)[b]	0.29	0.08-1.04	0.058	15.4 (15.2)	3.0 (6.4)	0.38	0.11–1.30	0.379
Length of hospital stay (Median, IQR) (days)	11.5 (10–14)	10 (7–14)			0.124	11 (10–14)	11 (7–14)			0.717

Data represent the number (%) of patients, unless otherwise specified; *APN* acute pyelonephritis, *IQR* interquartile range

[a] 7 cases of CDAD, 7 cases of eosinophilia and/or skin rash, 2 cases of increased alanine aminotransferase, 1 case of decreased neutrophil count, and 1 case of decreased platelet count

[b] 2 cases of CDAD and 1 case of decreased neutrophil count

In prior studies, empirical ciprofloxacin treatment for APN caused by ciprofloxacin-resistant *E. coli* was related to delayed microbiological cure; however, there was no meaningful difference in prognosis after completion of treatment [26]. Similar data was shown in empirical cefuroxime treatment for APN caused by cefuroxime-resistant *E. coli* [27]. In a French prospective study of children with febrile UTI caused by ESBL-PE, 95% of patients were apyretic within 5 days regardless of appropriateness of empirical antimicrobial therapy. Length of hospital stay was not different between IAT and AT groups [13]. In our study of adult patients with APN caused by ESBL-PE, treatment failure rate and length of hospital stay were similar in both groups. The recurrence rate, which represents long-term prognosis, was also similar in both groups, although the IAT group received definitive therapy for a shorter duration compared to the AT group.

Taken together, the results of these serial studies suggest that IAT for UTI does not affect prognosis regardless of drug resistance of the causal pathogen. However, the patients who received IAT in those studies were treated with appropriate antibiotics thereafter; thus, appropriate definitive therapy should be emphasized. Inappropriate definitive therapy was reported as a mortality factor of patients with ESBL-PE bacteremia [6] and as a risk factor for recurrence of UTI caused by ESBL-PE [28].

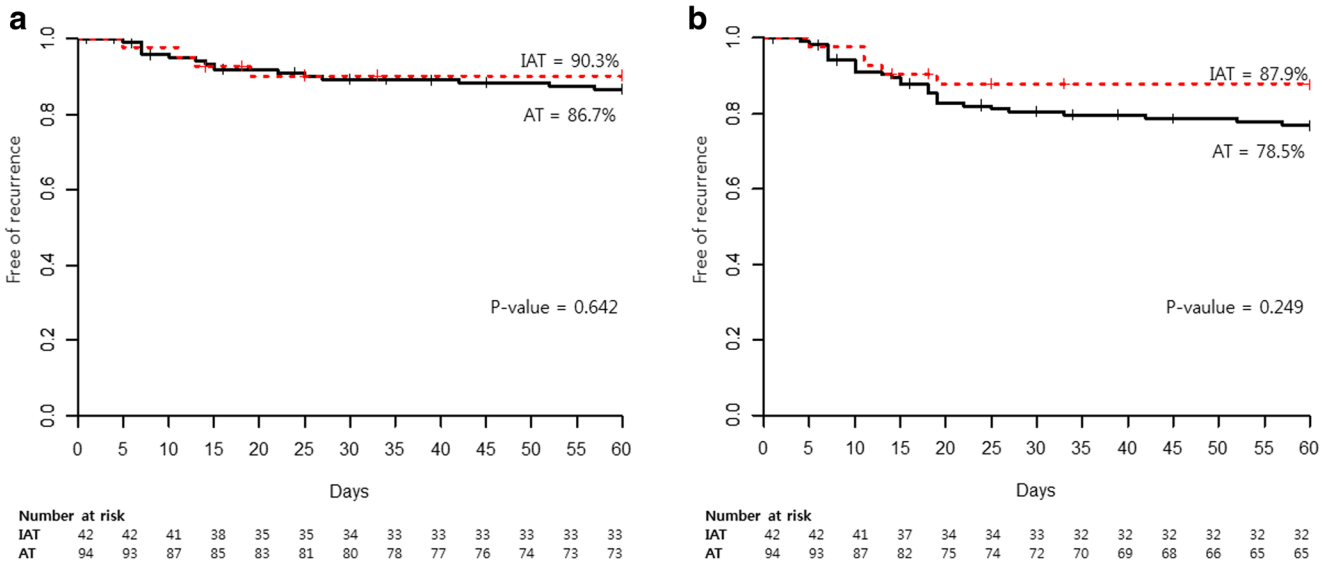

Fig. 2 Kaplan-Meier curve showing probability of free of recurrence in appropriate empirical treatment group (AT) and inappropriate empirical treatment (IAT) group. **a** Recurrence of acute pyelonephritis caused by ESBL-PE (HR 0.75, 95% CI 0.21–2.56). **b** Recurrence of acute pyelonephritis caused by any pathogen (HR 0.52, 95% CI 0.17–1.59)

In 2011, the Infectious Diseases Society of America published guidelines for antimicrobial treatment of acute uncomplicated cystitis and pyelonephritis in women [29]. These guidelines emphasize not just treatment efficacy but also collateral damage and drug resistance which can be increased by injudicious antimicrobial use. Traditionally, carbapenem has been the drug of choice for infections caused by ESBL-PE [30]. However, considering the increase of carbapenem resistance in Enterobacteriales and collateral damage in the human microbiome, carbapenem-saving strategies should be emphasized. Based on our study results, carbapenem use can be avoided as an empirical antibiotic in treatment of UTI even in the setting of infections probably caused by ESBL-PE. In addition, "definitive treatment with non-carbapenem" was not a risk factor for treatment failure in additional analysis in our study population. Clinical models predicting ESBL bacteremia should not be used to justify carbapenem use when treating APN as empirical therapy.

This study has several limitations. First, due to strict inclusion criteria of this study, 40% of patients who had had APN with ESBL-PE were excluded. This could contribute to selection bias. Second, because this is a retrospective study, characteristics of the IAT and AT groups were different before matching. Although we conducted analyses with matched data to reduce bias, differences could remain. Third, the relatively small number of included patients did not give this study enough power to demonstrate non-inferiority as described above. Despite low power of the study, inappropriate empirical treatment was consistently not a risk factor for urinary tract infection in prior studies. Our study could be a pilot study to evaluate clinical impact of antimicrobial inappropriateness in APN caused by ESBL producing Enterobacteriales.

In conclusion, a delay in appropriate antimicrobial therapy for more than 48 h did not affect the clinical outcomes, including treatment efficacy and 1-year APN recurrence, without prolonged hospitalization. Although clinicians should evaluate the possibility of APN caused by ESBL-PE, it does not justify indiscriminate use of broad-spectrum antibiotics such as carbapenems. Alternative antimicrobial agents with narrow spectrums could be empirically administered to non-critically ill patients with APN, even in the setting probably caused by ESBL-PE.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical statement The study was approved by the local ethical research committee (IRB number: 2018–05-089).

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