



Factors associated with the recurrence of acute pyelonephritis caused by extended-spectrum β -lactamase-producing *Escherichia coli*: the importance of infectious disease consultation

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ABSTRACT

To investigate factors for the recurrence of acute pyelonephritis (APN) caused by extended-spectrum β -lactamase-producing *Escherichia coli* (ESBL-PE), a retrospective cohort study was performed at a tertiary-care hospital from 2014 through 2016. Among 135 patients who had recovered from APN caused by ESBL-PE, the 1-year cumulative recurrence rates of APN caused by any pathogen or by ESBL-PE specifically were 35.6% and 22.1%, respectively. In a multivariate analysis, infectious disease (ID) consultation was associated with decreased recurrence (95% confidence interval [CI] = 0.24–0.96, $P = 0.038$ for recurrence caused by any pathogen; and 95% CI = 0.15–0.84, $P = 0.019$ for recurrence caused by ESBL-PE). History of APN within 1 year was a risk factor for recurrent APN caused by any pathogen ($P = 0.011$). Microbiological cure was a preventive factor for recurrent APN caused by ESBL-PE ($P = 0.024$). In conclusion, our data show that ID consultation protects against APN recurrence caused by ESBL-PE.

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1. Introduction

Infections caused by extended-spectrum β -lactamase-producing *Escherichia coli* (ESBL-PE) have been increasing worldwide, and the urinary tract is one of the most common infection sites (Kang et al., 2010; Pitout and Laupland, 2008). A high Charlson comorbidity score, a history of admission, and previous antibiotic use are known risk factors for acute pyelonephritis (APN) caused by ESBL pathogens (Calbo et al., 2006; Kim et al., 2013). ESBL-PE is also related to long hospitalization stays and recurrent urinary tract infections (UTIs) (Alevizakos et al., 2017; Kim et al., 2013). Despite the difficulty of treating APN caused by ESBL-PE (due to bacterial resistance to various antibiotics), the clinical treatment success rate has been as high as 90–100% for both uncomplicated and complicated APN (Kim et al., 2013, 2018; Naber et al., 2002). Therefore, preventing recurrence might be more important than treatment itself.

There have been very limited data describing the factors associated with APN recurrence caused by ESBL-PE. In 1 study of kidney transplant recipients with UTIs caused by ESBL-pathogens, advanced age and persistent bacteriuria were associated with relapse (Pilmis et al., 2015). Another study suggested that the use of inappropriate antimicrobial agents may lead to recurrent bacteremic UTI caused by ESBL-producing pathogens within 60 days, despite initial clinical treatment success in hospitalized patients (Greenhouse et al., 2017). Nevertheless, the findings of these studies may not be widely applicable because of their limited sample

sizes and follow-up periods. Therefore, we conducted this study to investigate factors associated with the recurrence of APN caused by ESBL-PE.

2. Methods

2.1. Study population and design

This was a retrospective cohort study conducted at Samsung Medical Center, Seoul, South Korea. This is a 1950-bed tertiary care university hospital and referral center combined with the 700-bed Samsung Comprehensive Cancer Center.

We first identified patients with APN caused by ESBL-PE. Among adult patients (aged ≥ 18) who had visited the hospital from January 2014 to December 2016, patients who had been diagnosed with pyelonephritis (N10), cystitis (N59), or other UTIs (N57) by the International Classification of Diseases (ICD)-9 were searched. Only patients who showed clinical treatment success for APN were included in the study. Cases where patients had other febrile urinary infections (such as renal abscess and/or prostatitis), or febrile systemic illness in addition to APN, were excluded. For each study participant, only the index admission was included in this study.

2.2. Definitions, outcomes, and data collection

Patients with APN were defined as those who had pyuria and positive urine culture with ≥ 2 of symptoms and signs suggesting upper UTI. Signs or symptoms suggesting APN were defined as fever (≥ 38.0 °C), chills, flank pain, costovertebral angle tenderness/flank pain, and nausea/vomiting (Fairley et al., 1971). Patients who had a positive urine culture of ESBL-PE $\geq 10^5$ CFU/mL were diagnosed with APN

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caused by ESBL-PE. Patients who had taken antibiotics before visiting the hospital but who still had a positive urine culture of ESBL-PE $\geq 10^3$ CFU/L were also diagnosed with APN caused by ESBL-PE (Sobel et al., 2005). Appropriate antibiotic treatment was defined as the intravenous administration for at least 7 days of antibiotics showing *in vitro* susceptibility, given the limited data describing oral antimicrobial therapy for APN caused by ESBL-PE.

Electronic medical records were reviewed to identify clinical characteristics of patients and their recurrence of APN. The following data about patient characteristics, disease severity, and treatment were collected: onset of UTI (hospital acquired, health care associated (Cardoso et al., 2014), or community acquired), sex, age, high fever (≥ 39.0 °C), hypothermia (≤ 35.0 °C), mental change, Charlson comorbidity index (Charlson et al., 1987), history of APN in the preceding year, bacteremia, complication, definitive treatment with noncarbapenem medication (Park et al., 2014), treatment duration with appropriate antibiotics, infectious disease (ID) consultation, microbiological cure, and transfer to long-term care facility after treatment success. Complicated APN was defined if a case had at least 1 of the following characteristics: non-community-acquired onset, male sex, kidney transplantation, diabetes mellitus, obstructive uropathy by benign disease, urogenital malignancy, indwelling ureteral stent, indwelling Foley catheter or suprapubic catheter, neurogenic bladder, vesicoureteral reflux, or recent urogenital operation (within 3 months). ID consultation was defined as admission to the ID ward or as any consultation in the ID department for treating APN caused by ESBL-PE. Microbiological cure was defined as a negative urine culture for ESBL-PE within 7 days of receiving appropriate antibiotics.

The end point for analysis was APN recurrence within 1 year from antibiotics treatment completion of the index APN episode. The intervals between the index episode antibiotics treatment completion and recurrent APN caused by any pathogen or by ESBL-PE were respectively collected.

2.3. Microbiological tests

All urine samples were taken from one of followings: voided mid-stream urine, clean intermittent catheterization, or a Foley catheter.

Blood samples 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 to 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), following Clinical and Laboratory Standards Institute (CLSI) guidelines for 2017 (CLSI, 2017).

2.4. Statistical analyses

All statistical analyses were performed using SPSS 24.0 for Windows (IBM Corp., 2017). Patients included in the study were observed for 1 year after the end of treatment. Patients were censored at the time of death or at loss to follow-up. The time-to-recurrence and cumulative recurrence rates were analyzed using reverse Kaplan–Meier curves. Associated factors of recurrence were analyzed by the Cox proportional-hazard model. Variables with $P < 0.15$ in the univariate analysis were candidates for the multivariate analysis and were included in the Cox proportional-hazard model. All P values were 2-tailed, and P values < 0.05 were considered to be statistically significant.

3. Results

3.1. Study population and characteristics

From June 2014 to December 2016, a total of 980 patients having ESBL-PE bacteriuria with an ICD-9 code of pyelonephritis (N10), cystitis (N30), or other urinary system infection (N39) were collected. Of these, 62.2% (610/980) were excluded due to a diagnosis of asymptomatic bacteriuria and/or cystitis. Among the 147 adequately treated patients with APN caused by ESBL-PE, 2 cases of clinical failure and 10 cases of follow-up loss after clinical cure were excluded. Ultimately, 135 patients were included in this study (Fig. 1).

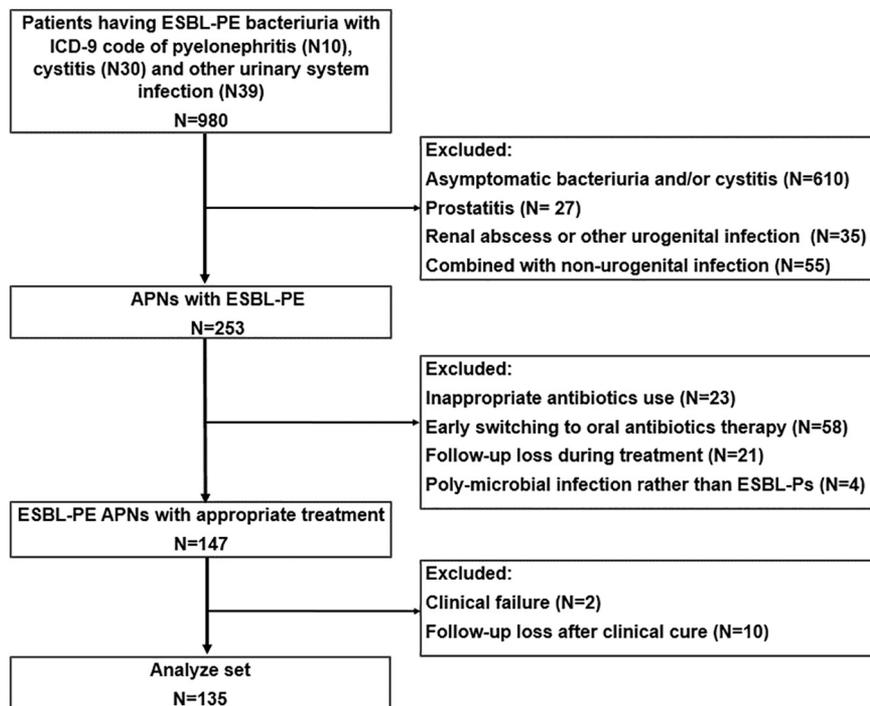


Fig. 1. Study population.

Health care-associated infection was the most common category of onset, and 85.9% (116/136) of APN cases were classified as complicated APN. In total, 83.0% (112/136) of patients consulted with ID doctors. Furthermore, 19.2% (26/136) of patients had hypotension during the treatment period, and 40.7% (45/136) of patients had bacteremia of the same pathogen with urine isolates (Table 1).

3.2. Time to recurrence and other associated factors

There were 41 cases of APN recurrence caused by any pathogen (including cases without an isolated pathogen), and the 1-year cumulative recurrence rate was 35.6%. Among these 41 cases of recurrence, 26 cases were caused by ESBL pathogens, for which the 1-year cumulative recurrence rate was 22.1%. All cases of APN recurrence caused by

Table 1
Factors associated with the recurrence of APN.

	Total (N = 135) No. (%)	By any pathogen		HR ^a	P value	By ESBL-producing pathogen		HR	P value
		With recurrence (n = 41)	Without recurrence (n = 94)			With recurrence (n = 26)	Without recurrence (n = 109)		
Onset									
Hospital acquired	27 (20.0)	9 (33.3)	18 (66.7)	1.10 (0.53–2.31)	0.800	5 (18.5)	22 (81.5)	0.99 (0.37–2.62)	0.979
Health care associated	58 (43.0)	18 (31.0)	40 (69.0)	1.22 (0.66–2.26)	0.532	14 (24.1)	44 (75.9)	1.82 (0.84–3.95)	0.127*
Community acquired	50 (37.0)	14 (28.0)	36 (72.0)	0.76 (0.40–1.45)	0.408	7 (14.0)	43 (86.0)	0.52 (0.22–1.23)	0.137
Patient or pathogen characteristics									
Sex (male)	38 (28.1)	13 (34.2)	25 (65.8)	1.37 (0.71–2.64)	0.354	12 (31.6)	26 (68.4)	2.69 (1.24–5.82)	0.012*
Age ≥ 60	90 (66.7)	28 (31.1)	62 (68.9)	1.08 (0.56–2.08)	0.822	20 (22.2)	70 (77.8)	1.74 (0.70–4.34)	0.233
History of APN within 1 year	32 (23.7)	14 (43.8)	18 (56.2)	2.04 (1.07–3.90)	0.030*	8 (25.0)	24 (75.0)	1.57 (0.69–3.65)	0.278
Complication	116 (85.9)	38 (32.8)	78 (67.2)	2.30 (0.71–7.46)	0.165	26 (22.4)	90 (77.6)	N/A ^b	N/A ^b
Kidney transplantation	22 (16.3)	9 (40.9)	13 (59.1)	1.35 (0.64–2.83)	0.427	3 (13.6)	19 (86.4)	0.56 (0.17–1.87)	0.346
Urogenital malignancy	29 (21.5)	9 (31.0)	20 (69.0)	1.29 (0.62–2.71)	0.498	5 (17.2)	24 (82.8)	1.12 (0.42–2.98)	0.821
Indwelling ureteral stent	6 (4.4)	3 (50.0)	3 (50.0)	2.28 (0.70–7.40)	0.170	2 (33.3)	4 (66.7)	2.54 (0.60–10.77)	0.207
Foley catheter or suprapubic catheter insertion	10 (7.4)	4 (40.0)	6 (60.0)	1.53 (0.55–4.31)	0.417	2 (20.0)	8 (80.0)	1.21 (0.29–5.12)	0.797
Diabetes mellitus	31 (23.0)	8 (25.8)	33 (31.7)	0.77 (0.36–1.67)	0.508	6 (19.4)	25 (80.6)	1.02 (0.41–2.53)	0.972
Recent urogenital surgery	6 (4.4)	3 (50.0)	3 (50.0)	1.88 (0.58–6.10)	0.292	3 (50.0)	3 (50.0)	3.25 (0.97–10.84)	0.055*
Treatment									
Delayed appropriate antibiotics	46 (34.1)	11 (23.9)	35 (76.1)	0.61 (0.31–1.22)	0.165	5 (10.9)	41 (89.1)	0.41 (0.15–1.07)	0.069*
Definitive treatment with noncarbapenems ^c	24 (17.8)	9 (37.5)	15 (62.5)	1.58 (0.75–3.31)	0.227	8 (33.3)	16 (66.7)	2.61 (1.14–6.03)	0.024*
Short-term therapy (≤10 days)	23 (17.0)	8 (34.8)	15 (65.2)	1.10 (0.51–2.38)	0.811	4 (17.4)	19 (82.6)	0.82 (0.28–2.37)	0.708
ID consultation	112 (83.0)	30 (26.8)	82 (73.2)	0.49 (0.24–0.97)	0.040*	18 (16.1)	94 (83.9)	0.40 (0.18–0.93)	0.032*
Microbiological cure	127 (94.1)	37 (29.1)	90 (70.9)	0.44 (0.16–1.24)	0.120*	22 (17.3)	105 (82.7)	0.25 (0.09–0.73)	0.011*
Disease severity									
Fever ≥39 °C or hypothermia ≤35 °C	61 (45.2)	22 (36.1)	39 (63.9)	1.33 (0.72–2.45)	0.369	14 (23.0)	47 (77.0)	1.30 (0.60–2.80)	0.512
Hypotension	26 (19.3)	7 (26.9)	19 (73.1)	0.85 (0.38–1.92)	0.700	5 (19.2)	21 (80.8)	0.99 (0.37–2.64)	0.989
Mental change	9 (6.7)	2 (22.2)	7 (77.8)	0.60 (0.15–2.50)	0.486	2 (22.2)	7 (77.8)	1.04 (0.25–4.452)	0.954
Bacteremia	55 (40.7)	17 (30.9)	38 (69.1)	1.06 (0.57–1.97)	0.855	13 (23.6)	42 (76.4)	1.48 (0.69–3.20)	0.318
CCI ≥ 3	42 (31.1)	11 (26.2)	31 (73.8)	1.06 (0.53–2.12)	0.866	7 (16.7)	35 (83.3)	1.13 (0.47–2.69)	0.790
Transfer to long-term care facility	29 (21.5)	11 (37.9)	18 (62.1)	1.80 (0.90–3.51)	0.097*	8 (27.6)	21 (72.4)	2.25 (0.97–5.22)	0.058*

HR =, hazard ratio; N/A = nonanalyzable; CCI = Charlson comorbidity index.

* Variables analyzed in a multivariate analysis.

^a Hazard ratio in univariate cox regression model.

^b There was no recurrence in patients with uncomplicated APN.

^c Twenty-two patients and 2 patients received piperacillin-tazobactam and fluoroquinolones, respectively.

ESBL-PEs occurred in patients with complicated APN. Among these 26 cases, 25 showed an identical species of pathogen to the index episode. The other 1 case was APN recurrence by ESBL pathogen without recorded information of species. The median time to recurrence caused by any pathogen (or recurrence without an isolated pathogen) was 64.0 days (interquartile range [IQR]: 14.5–155.5 days). The median time to recurrence caused by an ESBL-producing pathogen was 56.5 days (IQR: 13.75–153.25 days) (Fig. 2A and B).

Factors associated with APN recurrence caused by any pathogen and ESBL pathogens are described in Table 1. In a multivariate analysis of APN recurrence caused by any pathogen, ID consultation was associated with a lower recurrence rate (adjusted HR [aHR] = 0.48, 95% confidence interval [CI] = 0.24–0.96, $P = 0.038$). History of APN within 1 year was associated with a higher recurrence rate (aHR = 2.36, 95% CI = 1.21–4.60, $P = 0.011$). In a multivariate analysis of APN recurrence caused by ESBL pathogen, ID consultation (aHR = 0.35, 95% CI = 0.15–0.84, $P = 0.019$) was associated with a lower recurrence rate, as in APN recurrence caused by any pathogen. In addition, microbiological cure (aHR = 0.28, 95% CI = 0.09–0.85, $P = 0.024$) was associated with

Table 2
Factors associated with the recurrence of APN in multivariate analysis.

	By any pathogen		By ESBL-producing pathogen	
ID consultation	0.48 (0.24–0.96)	0.038	0.35 (0.15–0.84)	0.019
Microbiological cure			0.28 (0.09–0.85)	0.024
History of APN within 1 year	2.36 (1.21–4.60)	0.011		

decreased recurrence (Table 2). Male sex and definitive treatment with noncarbapenem were not independently associated with APN recurrence caused by ESBL-PE in multivariate analysis.

Because ID consultation itself might be a confounding factor, we did further analyses to identify which factors were different between ID consultation cases and non-ID consultation cases. Only definitive treatment with noncarbapenems was different (with statistical significance) between the 2 groups (14.3% in the ID consultation group versus 34.8% in the non-ID consultation group, $P = 0.041$). Microbiological cure was more frequently observed in the ID consultation cases but without statistical significance (95.5% in the ID consultation group versus 87.0% in the non-ID consultation group, $P = 0.270$).

4. Discussion

This study showed that ID consultation lowers the recurrence of APN caused by ESBL-PE and any bacteria as well. As in prior reports, the clinical treatment success rate was high in this study (98.5%). However, the 1-year cumulative recurrence rate was 35.6%. This is 3 to 4 times higher than the rate of sporadic APN recurrence for the general population in South Korea calculated from nationwide health insurance claims data including all causative pathogens (Ki et al., 2004). These data demonstrate that ESBL-PE itself is associated with APN recurrence compared to APN in general population. For this reason, we can emphasize the importance of both treatment for ESBL-PE APN and prevention of recurrence.

In this study, not all recurrent APN cases were caused by ESBL-PE. Similarly, the factors associated with APN recurrence were different between cases caused by any pathogen and cases caused specifically by ESBL-PE. History of APN within 1 year is known to be an independent risk factor of recurrent UTI, regardless of the pathogen (Raz et al., 2000). It was also an independent risk factor of APN recurrence caused by any pathogen in our study. However, history of APN was not associated with recurrence caused by ESBL-PE. Microbiological cure, which was not associated with recurrence caused by any pathogen, was an independent preventive factor for APN recurrence caused by ESBL-PE. Regarding treatment, a delay in the use of appropriate antibiotics and definitive treatment with noncarbapenems were not related to recurrence. In a French study of febrile UTIs due to ESBL-producing pathogens in children, the delayed use of appropriate antibiotics was not related to a patient’s clinical outcome (Madhi et al., 2018). Similarly, in another report, the clinical outcomes of patients with community-onset bacteremia caused by ESBL-producing *E. coli* or *K. pneumonia* were similarly not associated with a delay in the appropriate therapy (Joo et al., 2017). Considering these results, the administration of broad-spectrum antibiotics (including carbapenems) in order to increase the effectiveness of empiric antibiotics should be reevaluated.

There have been studies suggesting that ID consultation improves clinical outcomes in cases of complicated infection, such as infection related to solid organ transplantation or *Staphylococcus aureus* bacteremia (SAB) (Bai et al., 2015; Hamandi et al., 2014). In a study that evaluated the impact of ID consultation on SAB, ID consultation was associated with improved quality management. This included repeated blood cultures, echocardiography, and the use of appropriate empirical

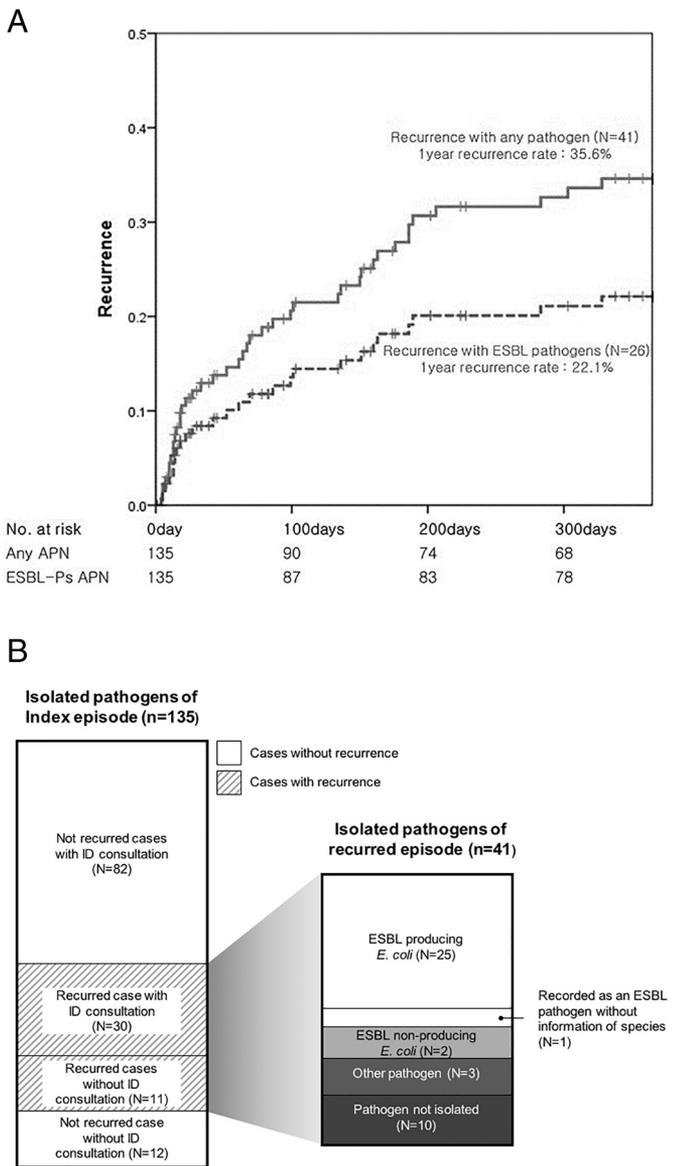


Fig. 2. Recurrence of APN caused by ESBL-PE for 1 year after the index episode. (A) Cumulative rate of recurrence. (B) Comparison of pathogens between index episodes and recurrence episodes.

antimicrobial therapy (Bai et al., 2015). In our study, ID consultation also improved a patient's outcome in terms of APN recurrence caused by ESBL-PE. Even though a microbiological cure was more frequently observed in patients treated with ID consultation, ID consultation and microbiological cure were independently associated with lower recurrence. Definitive treatment with noncarbapenems was less common in the ID consultation group, but it was not an independently associated factor based on the multivariate analysis. Among the 108 patients who received definitive treatment with carbapenems, 103 patients were treated with group 1 carbapenems (e.g., ertapenem). Therefore, these findings do not support the use of carbapenems, especially group 2 carbapenems, to prevent the recurrence of APN caused by ESBL-PE.

There were some limitations to our study. First, because this study was a retrospective study, some patients were excluded because of incomplete data without follow-up. However, 93.1% (135/145) of patients receiving appropriate antimicrobial therapy with clinical treatment success visited our hospital again and left follow-up data for APN recurrence because a significant portion of patients had comorbidity. Second, the subject of this study was ESBL-producing *E. coli*. *E. coli* is the most common causative pathogen of UTIs (Pitout and Laupland, 2008). Nevertheless, there is a possibility that other ESBL-producing uropathogens display different characteristics. To our knowledge, there is a lack of evidence regarding the APN treatment efficacy or recurrence risk according to the causative species. Further studies are needed.

Despite these limitations, this is the first study to analyze factors associated with the recurrence of APN caused by ESBL-PE. In our study, one third of patients experienced APN recurrence within 1 year, but not all recurrence was caused by ESBL-PE. History of APN within 1 year was a risk factor for recurrence caused by any pathogen. Failure of microbiological eradication was a risk factor for recurrence caused by ESBL-PE. ID consultation was a preventive factor in both groups. APN caused by ESBL-PE is not hard to treat, but it is difficult to prevent its recurrence. Because ID consultation decreases APN recurrence, hospitals should encourage physicians to refer patients with APN for ID consultation. Further studies are warranted to externally validate these results and to evaluate which elements of ID consultation are associated with the decreased recurrence of APN.

Conflict of Interest

None.

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