〈Original Article〉

Extended-spectrum beta-lactamase-producing *Escherichia coli* isolates from patients with urinary tract infections in an acute care hospital: Epidemiology and antibiogram[1]

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Objective: To investigate the epidemiology and antibiogram of the extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (ESBL-EC) isolated from urine samples collected from an acute-care hospital in Japan.

Methods: A descriptive epidemiological study was conducted to compare isolates of ESBL-EC (n＝129) and non-ESBL-EC (n＝279) between April 1, 2019 and March 30, 2020. Data were collected from the microbiology laboratory and medical charts. Multivariate logistic regression analysis was used to assess patients' background, infection risk factors, and ESBL-EC and non-ESBL-EC antibiograms.

Results: *E. coli* was the most common bacteria (30.0%) isolated from urine samples, while urine was the most common (61.0%) source of this bacteria. Among 408 isolates of *E. coli* strains from urine, 129 (31.6%) ESBL-EC and 279 (68.4%) non-ESBL-EC were detected. The background investigation of patients from whom ESBL-EC was isolated revealed worsened performance status and use of antibiotics in the past two months as risk factors. Antibiogram of ESBL-EC showed high resistance to levofloxacin and third-generation cephalosporins, such as ceftazidime and cefotaxime, with high susceptibility to cefmetazole, minocycline, and fosfomycin.

Conclusions: ESBL-EC is one of the most important multidrug-resistant bacteria, along with methicillin-resistant *Staphylococcus aureus*, causing serious

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[1]Abbreviations: ESBL, extended-spectrum beta-lactamase; ESBL-EC, extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli*; UTIs, urinary tract infections; AMR, antimicrobial resistant; MDRP, multidrug-resistant *Pseudomonas aeruginosa*; CRE, carbapenem-resistant *Enterobacteriaceae*; LVFX, levofloxacin; CPFX, ciprofloxacin; MINO, minocycline; ST, trimethoprim/sulfamethoxazole; FOM, fosfomycin; ABPC, ampicillin; CMZ, cefmetazole; CTM, cefotiam; CAZ, ceftazidime; CFPM, cefepime; MEPM, meropenem

complications in hospital settings, with antibiotic administration being a risk factor. Meropenem, cefmetazole, minocycline, or fosfomycin should be used as first-line treatment for urinary tract infections caused by ESBL-EC.

Key words: Extended-spectrum beta-lactamase, *Escherichia coli*, urinary tract infections, cefmetazole, fosfomycin

Introduction

Escherichia coli is one of the major infectious pathogens in hospital-acquired infections, commonly isolated from patients with urinary tract infections (UTIs). In recent years, an increase in extended-spectrum beta-lactamase-producing *E. coli* (ESBL-EC) strains have been observed in clinical settings in Japan[1)], which has caused difficulties in the treatment of infectious diseases. Along with methicillin-resistant *Staphylococcus aureus* (MRSA), ESBL-EC has gradually become the most prevalent antimicrobial resistant (AMR) bacteria in our hospital, although occasionally multidrug-resistant *Pseudomonas aeruginosa* (MDRP), multidrug-resistant *Acinetobacter baumannii*, and carbapenem-resistant *Enterobacteriaceae* (CRE) are also found.

In this study, we aimed to determine the epidemiology and clinical significance of ESBL-EC, including sample distribution, backgrounds of the patients from whom this strain was isolated, risk factors for ESBL-EC infection, and antibiogram. Based on the findings of the study, we aimed to establish the best strategy to treat UTIs caused by ESBL-EC. In addition, we compared the frequency of isolation of ESBL-EC with those of other resistant bacteria to rank the importance of ESBL-EC among resistant bacteria in a hospital environment.

Materials and Methods

Facility

Fukuoka Kinen Hospital is a 239-bed acute-care hospital, located at downtown Fukuoka, the largest city in the southwestern region of Japan. Since 2010, the hospital has operated a microbial laboratory with two dedicated personnel.

Bacteriological Examination

Between 1 April 2019 and 30 March 2020, urine samples were collected from hospital outpatients and inpatients with UTIs to culture and identified *E. coli* in our laboratory. UTI was diagnosed using pyuria, defined as ＞10 white blood cells per high-power field in centrifuged

urine, regardless of symptoms. Microbial identification and antimicrobial susceptibility tests were carried out using VITEK®2 system (bioMérieux, Ink, Craponne, France) and VITEK®2 GN & GP ID card (bioMérieux, Japan, Tokyo). Antibiotic susceptibility of *E. coli* isolates was determined with VITEK® 2 cards (bioMérieux) using the disk diffusion method based on Clinical and Laboratory Standards Institute (CLSI) criteria[2]. The results were expressed as susceptible (S), intermediate (I), or resistant (R). The 11 tested antibiotics were as follows: levofloxacin (LVFX), ciprofloxacin (CPFX), minocycline (MINO), trimethoprim/sulfamethoxazole (ST), fosfomycin (FOM), ampicillin (ABPC), cefmetazole (CMZ), cefotiam (CTM), ceftazidime (CAZ), cefepime (CFPM), and meropenem (MEPM).

ESBL production was screened by measuring the size of inhibition rings using cefotaxime (≤27 mm) and CAZ (≤22 mm). The ESBL confirmation test was performed using cefotaxime-clavulanate and CAZ-clavulanate disks[2]. *S. aureus* isolates resistant to cefoxitin and oxacillin were classified as MRSA according to CLSI guidelines[2] using the disc diffusion method. MDRP was defined as *P. aeruginosa* resistant to fluoroquinolones (minimum inhibitory concentration [MIC] ≥ 4 μg/mL), carbapenems (MIC ≥ 16 μg/mL), and amikacin (MIC ≥ 32 μg/mL), in accordance with the criteria specified by the Ministry of Health, Labour, and Welfare of Japan. AmpC beta-lactamase was detected according to CLSI guidelines[2].

Data collection

Patient data were collected retrospectively, and the parameters investigated were based on previous reports[3–7]. The following data was collected: age, gender, out- or in-patient, worsened performance status, nursing home admission, use of antibiotics in the past two months, indwelling urinary catheter, prior administration, and co-morbidities (diabetes mellitus, cerebrovascular disease, solid tumor, urinary tract abnormality, and immune compromise). Performance status (PS) is a method developed by Eastern Cooperative Oncology Group (ECOG) for evaluating the patient's overall status. PS 3 and 4 (on a scale of 0 to 4) were considered as worsened PS[8]. These factors were statistically analyzed as variables.

The microbial laboratory data system was used to extract the microbiological data of *E. coli* isolates from urine.

We evaluated and compared the patient characteristics and antibiograms of ESBL-EC isolates to those of non-ESBL-EC isolates. Among the 267 patients with *E. coli* detected in their urine, 198 patients with a urine bacterial content of $\geq 10^5$ colony forming units/mL were enrolled in this study.

Statistical analysis

Descriptive statistics were used to represent all variables. The proportion of sensitive or resis-

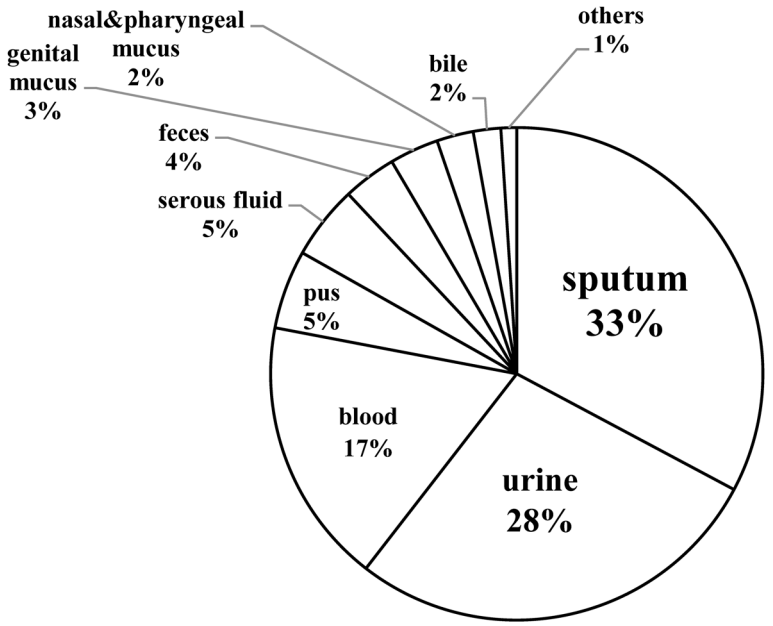
tant isolates was expressed numerically and as a percentage. Statistical analyses were carried out using SPSS software (IBM, Armonk, NY, USA, Version 25). Mann–Whitney U test was used for continuous variables. A chi-square test or Fisher's exact test was used for categorical variables. A p-value of less than 0.05 was considered statistically significant. In the risk factor analysis for ESBL-EC, patient characteristics were analyzed using multivariate logistic regression analysis. Cochran–Armitage test was used to analyze the prevalence trends of MRSA and ESBL-EC.

Ethics committee of the hospital (Project No. 2021007) approved this study.

Results

A total of 4154 clinical samples were cultured in the laboratory between April 2019 and March 2020. The distribution of the samples was as follows: sputum (1362; 32.8%), urine (1151; 27.7%), blood (727; 17.5%), (pus 215; 5.2%), serous fluid (201; 4.8%), feces (146; 3.5%), genital mucus (134; 3.2%), nasopharyngeal mucus (100; 2.4%), bile (75; 1.8%), and others (43; 1.0%) (Fig. 1). A total of 846 bacterial strains were isolated from urine samples including 273 (32.3%) *E. coli*, 125 (14.8%) *Enterococcus* sp., 88 (10.4%) *Staphylococcus* sp., 75 (8.9%) *Klebsiella pneumoniae*, 63 (7.4%) other Gram negative bacilli, 58 (6.9%) *P. aeruginosa*, 47 (5.6%) *Streptococcus* sp., 39 (4.6%) *Citrobacter* sp., 32 (3.8%) *Corynebacterium*, 25 (3.0%) other Gram positive cocci, 18 (2.1%) *Enterobacter*, and 3 (0.4%) other strains (Fig. 2). ESBL production was detected in 82 isolates (30.0%) of *E. coli*, 12 isolates (30.8%) of *Citrobacter* sp., five isolates

Fig. 1. Distribution of samples examined in one year, April 2019 to March 2020 (*N*=4154)



(27.8%) of *Enterobacter* sp., and 13 isolates (17.3%) of *K. pneumoniae*. *E. coli* was isolated from 438 samples, the majority of which were urine (267 isolates; 61.0%) and sputum (81 isolates; 18.5%) (Fig. 3). In addition, among the 1409 isolates of the nine bacterial species, 403 (28.6%) strains exhibited multi-drug resistance (MDR) (Fig. 4). The detected MDR strains as a proportion

Fig. 2. Distribution of bacterial species isolates in urine samples, April 2019 to March 2020 (*N*=846)

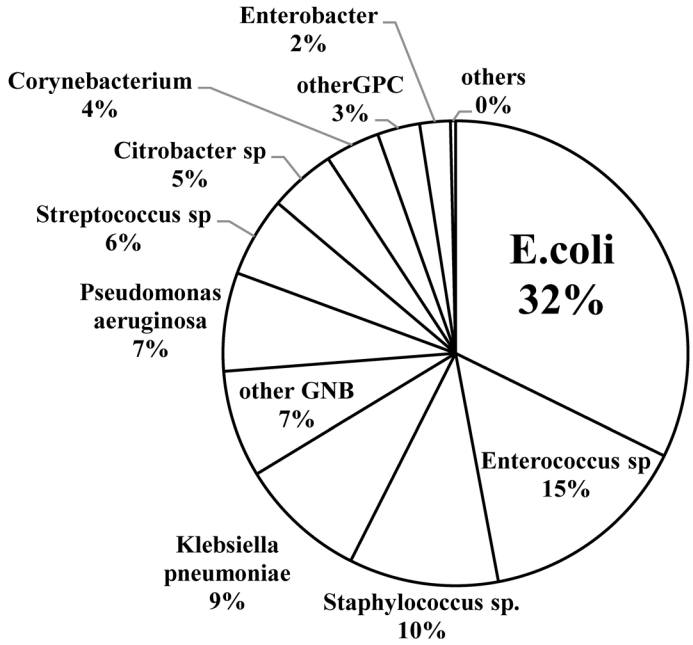


Fig. 3. Distribution of *Escherichia coli* isolates in various samples, April 2019 to March 2020 (*N*=438)

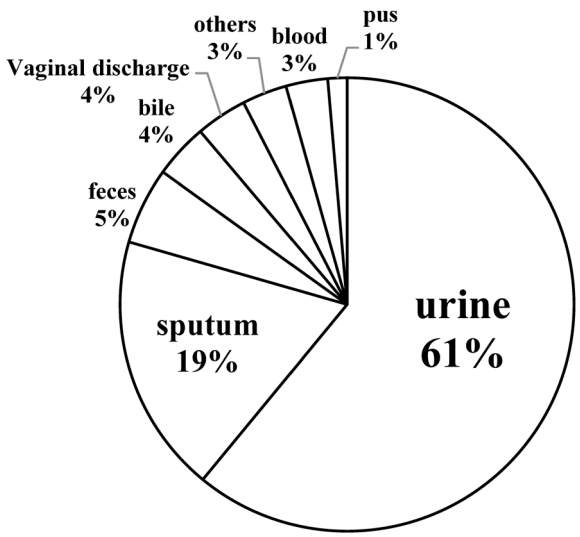
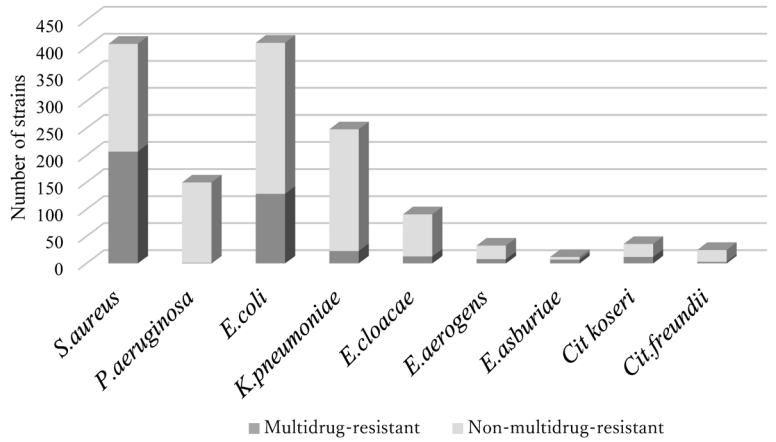


Fig. 4. Distribution of multidrug-resistant bacteria in the hospital, April 2019 to March 2020 (*N*＝1409)



Abbreviations: *S. aureus*, *Staphylococcus aureus*, *P. aeruginosa*, *Pseudomonas aeruginosa*, *E. coli*, *Escherichia coli*, *K. pneumoniae*, *Klebsiella pneumoniae*, *E. cloacae*, *Enterobacter cloacae*, *E. aerogens*, *Enterobacter aerogenes*, *E. asburiae*, *Enterobacter asburiae*, *Cit koseri*, *Citrobacter koseri*, *Cit. freundii*, *Citrobacter freundii*

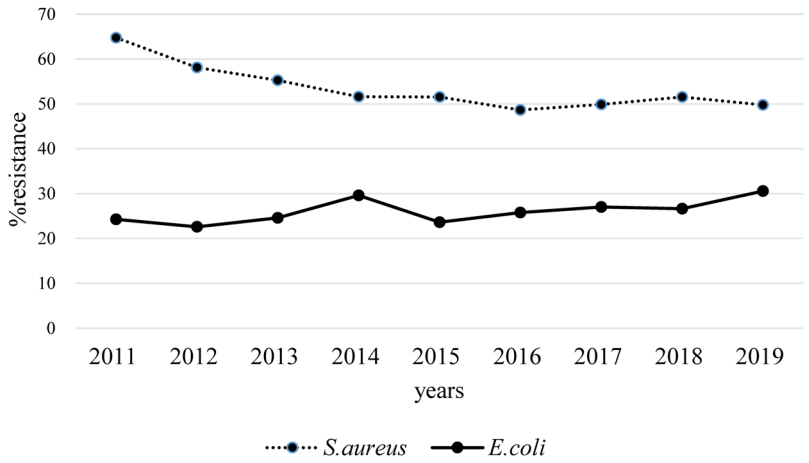
of the total isolates of that species were as follows: ESBL-EC (129/408, 31.6%); MRSA (207/406, 51.0%); ESBL-producing strains of *K. pneumoniae* (23/248, 9.3%); MDRP (1/150, 0.7%); 10 ESBL-producing, two AmpC-producing, and one CRE strains of *Enterobacter cloacae* (13/91, 14.3%); two ESBL-producing strains of *Citrobacter koseri* (12/36, 33.3%); six ESBL-producing and two AmpC-producing strains of *Enterobacter aerogenes* (8/33, 24.2%); three ESBL-producing strains of *Citrobacter freundii* (3/25, 12.0%); two ESBL-producing strains and five AmpC-producing strains of *Enterobacter asburiae* (7/12, 58.3%) (Fig. 4).

Figure 5 depicts the annual change in hospital prevalence of two major MDR bacteria, MRSA, and ESBL-EC. The prevalence of MRSA gradually decreased, while that of ESBL-EC gradually increased from 2011 to 2019.

The mean age, sex, number of outpatients, nursing home admissions, indwelling urinary catheters, prior hospitalization, and co-morbidities did not differ significantly between patients in the ESBL and non-ESBL groups. However, PS was worse in patients in the ESBL group, and the use of antibiotics in the past two months was more frequent in this group (Table 1).

We compared the antimicrobial susceptibility of ESBL-EC to that of non-ESBL-EC. As shown in Table 2, ESBL-EC strains were completely resistant to CTM, CAZ, CTX, CFPM, and ABPC and highly resistant to LVFX and CPFX. Non-ESBL-EC were highly susceptible to CTM, CAZ, CTX, and CFPM, and less susceptible to ABPC, LVFX, and CPFX. However, no differences between ESBL-EC and non-ESBL-EC were identified with regards to susceptibility to MINO, CMZ, FOM, or MEPM.

Fig. 5. Trend of %resistance in *S. aureus* and *E. coli*, 2011–2019



%Resistance of *S. aureus* indicates prevalence of MRSA, and %Resistance of *E. coli* indicates prevalence of ESBL-EC.

Table 1. Comparison of patient characteristics between ESBL-EC and non-ESBL-EC

Risk factor	ESBL-EC (n=63)	non-ESBL-EC (n=135)	OR	CI	p-value
Age	84.6±9.7	80.5±14.7			0.171
Male	19 (30.2)	27 (20.0)	1.722	0.81–3.60	0.148
Outpatient	31 (49.2)	69 (51.1)	0.927	0.49–1.76	0.879
Worsened Performance Status	47 (74.6)	56 (41.5)	4.113	2.05–8.60	<0.001
Nursing home admission	29 (46.0)	44 (32.6)	1.759	0.91–3.40	0.082
Use of antibiotics in the past two months	26 (41.3)	29 (21.5)	2.555	1.27–5.15	0.006
Indwelling urinary catheter	20 (31.7)	41 (30.4)	1.066	0.53–2.12	0.870
Prior hospitalization	25 (39.7)	43 (31.9)	1.405	0.72–2.73	0.335
Co-morbidities					
Diabetes mellitus	22 (34.9)	41 (30.4)	1.229	0.62–2.42	0.518
Cerebrovascular disease	32 (50.8)	69 (51.1)	0.987	0.52–1.88	1.000
Solid tumor	11 (17.5)	29 (21.5)	0.774	0.32–1.75	0.573
Urinary tract abnormality	27 (42.9)	61 (45.2)	0.910	0.47–1.73	0.878
Immune compromise	3 (4.8)	2 (1.5)	3.303	0.37–40.52	0.329

Discussion

This study revealed that ESBC-EC ranks alongside MRSA as one of the most important AMR bacteria at our hospital. Notably, the prevalence of ESBL-EC increased to 31.6% in the hospital, while the prevalence of MRSA gradually declined but remained high at 51.0% (Fig. 5). Other MDR bacteria, such as CRE and MDRP, were detected in fewer instances. Thus, ESBL-EC appears to be the most prevalent drug-resistant bacteria in our facility. Therefore, we were required to establish treatment guidelines and infection control strategies.

Previous reports revealed that prior hospitalization and antibiotic use within the past 60 days were independent risk factors associated with ESBL production[6,7]. ESBL-EC is assumed to be

Table 2. Antimicrobial susceptibility of ESBL-EC and non-ESBL-EC

Antimicrobial agent	Total number*	%Susceptibility**		OR	CI	p-value
		ESBL-EC	non-ESBL-EC			
LVFX	198	12.7 (8/63)	55.3 (72/135)	4.18	1.86–10.67	<0.01
CPFX	198	12.7 (8/63)	55.3 (72/135)	4.18	1.86–10.67	<0.01
MINO	198	87.3 (55/63)	91.9 (124/135)	1.05	0.66–1.67	0.825
ST	67	64.7 (11/17)	78 (39/50)	1.2	0.47–3.20	0.827
FOM	67	88.2 (15/17)	94 (47/50)	0.86	0.35–2.11	0.836
CTM	188	0 (0/58)	91.5 (119/130)	Inf	13.46-Inf	<0.01
CAZ	198	0 (0/58)	91.1 (123/135)	Inf	14.60-Inf	<0.01
CTX	188	0 (0/58)	91.5 (119/130)	Inf	13.46-Inf	<0.01
CFPM	198	0 (0/58)	91.1 (123/135)	Inf	14.60-Inf	<0.01
CMZ	198	87.3 (55/63)	94.1 (127/135)	1.15	0.73–1.81	0.582
MEPM	198	100 (63/63)	100 (135/135)	1.15	0.73–1.81	0.582
ABPC	188	0 (0/58)	60.7 (82/135)	Inf	8.87-Inf	<0.01

*Total number of *E. coli* strains examined for susceptibility. The maximum number of ESBL-EC and non-ESBL-EC were 63 and 135, respectively.

**%Susceptibility means the percentage of susceptible strains (excluding the number of resistant and intermediate strains) divided by the number of total strains of ESBL-EC/ non-ESBL-EC isolated.

isolated older patients, those with worsened overall status, and who have repeatedly undergone treatments using antibiotics in a short period. Similarly, in our study, only two risk factors (worsened PS and antibiotic use in the past two months) showed a significant correlation with ESBL-EC isolation, while prior hospitalization did not. These two factors may serve as predictors of ESBL-EC infection, and the results suggested that ESBL-EC was easily isolated from disabled and immunocompromised patients, who were repeatedly administered antimicrobial agents. Contrary to our expectations, age, nursing home admissions, prior hospitalizations, and co-morbidities were not correlated with ESBL-EC infection.

According to the antibiogram (Table 1), use of CMZ, MINO, FOM, and MEPM are recommended to treat UTIs caused by ESBL-EC because of its superior susceptibility to these agents. Non-ESBL-EC strains were also susceptible to these agents. On the other hand, cephalosporins such as CTM, CAZ, CTX, and CFPM, and quinolones such as LVFX and CPFX were not recommended for ESBC-EC infections because of its low susceptibility to these antibiotics.

Carbapenems, such as MEPM, have been recommended as the "gold standard" for severe UTIs caused by ESBL-producing organisms[9]. However, prior exposure to carbapenems is a significant risk factor for the CRE development; hence, carbapenem administration should be restricted to severe conditions, such as bacteremia[10,11]. Therefore, if ESBL-EC is isolated in culture examination, carbapenems should be de-escalated to CMZ, flomoxef, or FOM[12], in combination with aminoglycosides, such as gentamycin and amikacin[9]. Moreover, bacteremia-related mortality caused by ESBL-producing *E. coli* did not differ between the carbapenem group and *β*-lactam/*β*-lactamase inhibitor combination groups, such as tazobactam/piperacillin (TAZ/PIPC) or CMZ groups[9]. In addition, a retrospective multicenter study using a propensity score-adjusted analysis

showed that empirical treatment with CMZ or flomoxef for ESBL-EC bacteremia was not associated with mortality, and demonstrated comparable clinical success rates compared to carbapenem treatment[10].

MINO, despite being an old tetracycline antibiotic, possesses a broad spectrum of activity against bacteria as well as non-bacterial pathogens such as *Chlamydophila* and *Mycoplasma*. In addition, minocycline demonstrates antibacterial activity not only against AMR Enterobacteriaceae, such as ESBL-EC, but also against CRE[13]. Studies re-evaluating MINO for ESBL-EC treatment are limited. Yamamoto *et al.* reported that MINO in combination with FOM was effective in the treatment of mild cases of UTIs caused by ESBL-EC[14]. On the other hand, FOM has been strongly recommended for ESBL-EC UTI treatment in many studies. In previous reports, more than 90% of ESBL-EC isolates were susceptible to FOM[15–17]. In general, oral FOM administration has been recommended for the treatment of lower UTIs, such as cystitis, in the ambulatory setting[16,17]. Oral FOM is considered non-inferior to intravenous carbapenems in the treatment of lower UTIs, whereas intravenous FOM could be superior to TAZ/PIPC in the treatment of upper UTIs, such as pyelonephritis[18].

Based on these findings, we could propose a possible strategy for the management of UTIs. As *E. coli* remains the major pathogen involved in UTIs, we can initiate treatment with cephamycin antibiotics such as CMZ. In addition, CMZ is effective against both ESBL-EC and non-ESBL-EC. If CMZ is determined to be ineffective, association with other Enterobacteriaceae or anaerobes is expected, or the patient develops a septic state, we may step-up the treatment to broad-spectrum antimicrobial agents, such as carbapenems, including MEPM. If symptoms improve after CMZ administration, we can transition from parenteral to oral treatment (also called “switching”) and use oral forms of MINO or FOM, with the patient being discharged early and continuing ambulatory treatment. For lower UTIs, we may initiate treatment with oral FOM or MINO.

Our study had a few limitations. Genotyping was not conducted because of the lack of capacity and facilities in our laboratory. Although we analyzed the background of the patients from whom ESBL-EC was isolated, we did not discriminate between upper and lower UTIs or evaluate their clinical courses including the efficacy of the antimicrobial agents administered, the use of drainage catheters, or the clinical outcome.

In the future, we intend to investigate the treatment of ESBL-EC, taking into account the UTI type and clinical efficacy of antimicrobial agents.

Conflict of interest

None.

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Authorship statement

Kosuke Jo was the chief investigator and was responsible for the data analysis. Kenji Kono was responsible for the organization and coordination of the trial. All authors contributed to the writing of the final manuscript.

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