CTX-M Group Distribution and Positivity of Extended-Spectrum β-Lactamase (ESBL)-Producing Enterobacteriaceae in Urinary Tract Infections in a Tertiary Metropolitan Hospital in Japan

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Abstract
Urinary tract infection (UTI) is one of the most common clinical diagnoses managed by primary care physicians both in outpatient and inpatient care. The increasing ratio of extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) among UTI-causing pathogens is an epidemiological concern both in Japan and worldwide, leading to a higher empirical usage of broad-spectrum antibiotics. Commercially available genotypic diagnostic technologies for ESBL-E have been incorporated in clinical settings to facilitate earlier de-escalation to narrow-spectrum antibiotics. However, genotypic testing can detect only certain genotypes of the ESBL (CTX-M) group, and there are insufficient data regarding the ratio of other ESBL genotypes (TEM, SHV), especially in severe UTI cases. In this study, we collected consecutive ESBL-E isolates from UTI cases that fulfilled the systemic inflammatory response syndrome (SIRS) criteria from June 2012 to July 2017 in a tertiary metropolitan hospital in Japan and evaluated their genotypic distribution. Among 36 isolates, the number of cases with genotypes CTX-M-1, CTX-M-2, CTX-M-9, SHV, and TEM were 12, 4, 21, 1, and 14, respectively. Notably, all isolates with SHV and/or TEM genotypes concomitantly had one of the CTX-M genotypes, and there were no ESBL-E isolates that harbored only SHV or TEM. Further research is warranted to investigate the utility of commercially available genotypic diagnostic technologies for ESBL-E in the clinical setting.

Key Words
Urinary tract infection (UTI), extended-spectrum β-lactamase producing enterobacteriaceae (ESBL-E), SIRS (systemic inflammatory response syndrome), sepsis, genotype distribution

Introduction
Urinary tract infection (UTI), including severe cases with pyelonephritis and/or bacteremia, is one of the most common diagnoses in primary care outpatient clinics, emergency departments, general wards, and critical care units. An increasing number of multidrug-resistant (MDR) isolates, especially extended spectrum beta-lactamase producing Enterobacteriaceae (ESBL-E) in recent years is a growing global health concern. National and international research indicates that the proportion of ESBL-E among Enterobacteriaceae is 9.4-20% in Japan. Studies evaluating the clinical outcomes of patients with ESBL-E infection have shown a tendency toward higher mortality, longer hospital stay, greater hospital expenses, and reduced rates of clinical and microbiological responses. However, prolonged use

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of unnecessarily broad-spectrum antibiotics such as carbapenems, can lead to further increase in MDR isolates\(^6,7\). However, clinicians need to determine the initial antibiotics empirically before the culture and sensitivity results are available. Until recently, the traditional method for ESBL-E identification was to use cultures and assessment of growth inhibition by antibiogram with different genotypes and the imprecision of several observational studies on ESBL-E genotype distribution in other countries\(^12–14\), CTX-M genotype groups are the predominant genotype group that constitute ESBL-E. However, there are no sufficient preceding reports regarding genotype distribution in clinical isolates from severe cases of adult UTI in Japan to anticipate the current genotype distribution precisely. In Japan, the CTX-M group has been reported to constitute 90% of the ESBL genotype distribution in adults\(^15\). This suggests that rapid PCR methods can detect approximately 90% of ESBL-E with have a false negative ratio of 10%, which could be detrimental if the antibiotic is inappropriately de-escalated, especially in severe cases caused by ESBL-E. Birgy et al. have demonstrated differences in antibiograms with different genotypes and the importance of conducting epidemiological studies to monitor the bacterial evolution\(^13\).

Therefore, data regarding the distribution of ESBL genotypes in clinical isolates, especially in severe UTI cases, are essential in clinical decision making when utilizing PCR-based detection methods for ESBL-E. To this end, we conducted the present study to assess the genotypic distribution of ESBL-E and to evaluate the antimicrobial resistance patterns for each genotype in clinical isolates from severe UTI cases.

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**Material and Methods**

**The study population**

This retrospective observational study was conducted from June 2012 to July 2017 at St. Marianna University School of Medicine, Yokohama City Seibu Hospital, Yokohama, Japan, which is a tertiary metropolitan hospital. The study protocol was approved by the institutional review board of St. Marianna University School of Medicine (Approval Number 2276). Basic information including patient characteristics, destination of care (outpatient vs. inpatient, etc.), underlying conditions, causative pathogens, blood culture collection and positivity, empirical initial antibiotics, definitive antibiotics, and clinical outcomes were obtained. This study was initiated in 2012 when the SIRS criteria were the gold standard for categorizing severe and non-severe cases resulting in simple, objective, and practical categorization in a clinical setting.

Cases showing positive urine cultures (UCx) with \(\geq 10^5\) colony forming units (CFU)/mL were selected. The exclusion criteria included age younger than 18 years old, identical cases within 6 months, cases considered not to have active UTI based on the chart review (“considered not to have active UTI” was determined based on urine WBC < 10/high power field (HPF), chart review revealing the documentation of the clinician’s assessment as urinary colonization and/or assessment of an infection source other than UTI (e.g., pneumonia, cellulitis, and surgical site infection)), cases with a “do not attempt to resuscitate (DNAR)” order or “comfort measures only,” and cases with missing data. ESBL-E bacterial isolates from UTI cases that fulfilled the systemic inflammatory response syndrome (SIRS) criteria were collected\(^16\). Clinical outcomes were assessed as follows. In the management of outpatient cases, the case was considered as ‘improved’ if it fulfilled the following two criteria: 1) the chart did not indicate deterioration, return to the clinic with exacerbation of UTI, or inpatient management secondary to deterioration of the current UTI episode, and 2) there was a record of outpatient follow-up at our facility after recovery from the UTI. The clinical outcome was considered as ‘unknown’ if the case did not show a follow-up visit to our facility. In the management of inpatient cases, the case was considered “improved” if the UTI symptoms, fever, and general condition including vital signs, had ameliorated. The case was considered “unchanged” if these factors did not amel-
iorate as expected with antibiotic use.

**Microbiology and gene content analysis**

ESBL-E was identified based on the CLSI description utilizing discs with cefpodoxime, cefpodoxime-clavulanic acid, ceftazidime, ceftazidime-clavulanic acid, cefotaxime, and cefotaxime-clavulanic acid\(^9\). The culture isolates were inoculated on CHROMagar \(\text{TM} \) ESBL (Kanto Chemical Co., Inc.), which were evaluated for ESBL-E genotype utilizing the Cica Genius\(^\circledR \) ESBL detection kit 2\(^{14}\). The thermal cycler PCR conditions were as described in the instruction manual of the Cica Genius\(^\circledR \) ESBL detection kit 2 \{(94°C 15 s, 63°C 15 s, 72°C 40 s) repeated for 30 cycles\}. The PCR products were then electrophoresed on a TAE buffered 2% agarose gel for approximately 30 min under 100 V. Detection of the electrophoresed DNA bands was performed using 0.5 \(\mu\)g/mL ethidium bromide solution and an ultraviolet illuminator. Sensitivity to each antibiotic was determined at the microbiology laboratory of Yokohama City Seibu Hospital, as described in CLSI\(^8\).

**Statistical analysis**

js-STAR version 9.8.4j was used for the statistical analyses\(^7\). Categorical variables were evaluated using Fisher’s exact test. A p-value < 0.05 was considered statistically significant.

**Results**

In all, 36 isolates were obtained from ESBL-E UTI cases that fulfilled the SIRS criteria. The average age and standard deviation were 74.0 ± 13.4 years. Seventeen patients (47.2%) were male. The majority of cases \((n = 35, 97.2%)\) were inpatients and 5 cases \((13.9%)\) were in the intensive care unit (ICU). One case was managed as an outpatient. Overall, 20 cases were hospital-acquired infections, defined as UTI developed on hospital day 4 or later \((55.6%)\). The cases had a wide variety of underlying medical conditions. The majority \((n = 33, 91.7%)\) of causative pathogens were Escherichia coli \((E. \text{coli})\), whereas were 1 \((2.8%)\) and 2 \((5.6%)\) isolates were Klebsiella pneumoniae \((K. \text{pneumoniae})\) and Proteus mirabilis \((P. \text{mirabilis})\), respectively \((\text{Table 1})\).

The initial antibiotics administered are summarized in **Table 1**. Among the 36 cases, 34 \((94.4%)\) were treated with intravenous (IV) antibiotics. Piperacillin-tazobactam \((n = 8, 22.2%)\), ceftriaxone \((n = 7, 19.4%)\), and meropenem \((n = 7, 19.5%)\) were the three most frequently selected initial antibiotic regimens \((\text{Table 1})\). Twenty-four cases \((66.7%)\) improved with the initial antibiotics and 9 cases \((25.0%)\) improved after changing antibiotics. Three cases \((8.3%)\) died, which all had severe comorbidities \(\)transfusion dependent myelodysplastic syndrome, extreme of age \((105 \text{ years old})\) with femoral neck fracture and acute kidney injury on chronic kidney disease with recent dialysis initiation, respectively\) and UTI was one of the contributing factor but not the sole etiology of their death.

The PCR genotyping results are shown in **Figure 1** as gel electrophoresis images. Reaction mixture 1 \((\text{the left column})\) included the primer combinations to detect CTX-M-1, CTX-M-8, CTX-M-25, and CTX-M-64. Reaction mixture 2 \((\text{the right column})\) included the primer combinations to detect CTX-M-2, CTX-M-9, SHV, TEM, and GES-1.

The genotyping results shown in **Figure 1** are summarized in **Table 2**. The most detected genotypes were CTX-M-9 \((n = 21)\), TEM \((n = 14)\), and CTX-M-1 \((n = 12)\). CTX-M-2 and SHV were detected in 4 and 1 isolates, respectively. CTX-M-8, CTX-M-25, CTX-M-64 \((\text{chimeric type})\), and GES-1 \((\text{ESBL type})\) were measured but were not detected among the 36 isolates included in our study. Among the 36 isolates, 22 harbored only one ESBL genotype, whereas 14 isolates harbored two or three ESBL genotypes. The genotype combinations are summarized in **Table 3**. CTX-M-1/TEM, CTX-M-1/SHV/TEM, CTX-M-1/CTX-M-9, CTX-M-9/TEM, and CTX-M-2/TEM were found in 6, 1, 1, 6, and 1 isolate, respectively. Notably, there were no isolates that harbored only SHV or TEM. Thus, all 36 isolates had one or more of the CTX-M group genotype(s).

**Table 4** describes the antibiotic-resistant isolates of each ESBL-E genotype group. All available combinations were analyzed. The rate of resistance to ampicillin sulbactam was significantly higher in the CTX-M-1 group than in the CTX-M-9 group and in the TEM group compared to the CTX-M-9 group \(p = 0.0267\) for both.

**Discussion**

This observational study investigated the genotype distribution of ESBL-E isolated as causative pathogens in severe UTI cases positive for the SIRS criteria at a tertiary metropolitan medical facility in Japan. A substantial percentage of non-CTX-M genotypes were detected \((15 \text{ PCR bands out of a total of 52 PCR bands})\) in the study; however, all isolates that harbored non-CTX-M genotypes \(\)i.e., SHV and/or
### Table 1. Patient Characteristics and Background in UTI Cases with SIRS Caused by ESBL-E

| Patient characteristics | n=36 |
|-------------------------|------|
|                         | n    | %   |
| Male                    | 17   | 47.2% |
| Age (average ± S.D.)    | 74.0 ± 13.4 |

#### Destination

| Destination          | n    | %   |
|----------------------|------|-----|
| Outpatient           | 1    | 2.8% |
| Inpatient            | 35   | 97.2% |
| Inpatient wards      | 18   | 50.0% |
| HDU                  | 12   | 33.3% |
| ICU                  | 5    | 13.9% |

#### Acquisition of UTI of inpatient cases

| Hospital Day          | n    | %   |
|-----------------------|------|-----|
| 1–3                   | 15   | 41.7% |
| 4 and later           | 20   | 55.6% |

#### Department of admission for inpatient cases

| Department             | n    | %   |
|------------------------|------|-----|
| Medical service        | 24   | 66.7% |
| Surgical service       | 9    | 25.0% |
| Urology service        | 2    | 5.6% |

#### Underlying conditions

| Condition             | n    | %   |
|-----------------------|------|-----|
| Cardiac disease       | 7    | 19.4% |
| Neurological disease  | 6    | 16.7% |
| Pulmonary disease     | 7    | 19.4% |
| Gastrointestinal disease | 2  | 5.6% |
| Moderate-severe renal dysfunction† | 13 | 36.1% |
| Orthopedic disease    | 3    | 8.3% |
| Immune compromise     | 4    | 11.1% |
| Malignancy            | 7    | 19.4% |
| Urological disease    | 2    | 5.6% |

#### Pathogens ≥ 10⁵ CFU/mL

| Pathogen              | n    | %   |
|-----------------------|------|-----|
| *E. coli*             | 33   | 91.7% |
| *K. pneumoniae*       | 1    | 2.8% |
| *P. mirabilis*        | 2    | 5.6% |

#### Blood culture

| Culture               | n    | %   |
|-----------------------|------|-----|
| Obtained              | 33   | 91.7% |
| Positivity‡           | 13/33| 30.2% |

#### Initial antibiotics

| Antibiotics            | n    | %   |
|------------------------|------|-----|
| Oral antibiotics       | 2    | 5.6% |
| Levofloxacin           | 2    | 5.6% |
| IV antibiotics         | 34   | 94.4% |
| Piperacillin-Tazobactam| 8    | 22.2% |
| Ceftriaxone (III-Cephalosporin) | 7 | 19.4% |
| Meropenem              | 7    | 19.4% |
| Cefazolin (I-Cephalosporin) | 3  | 8.3% |
| Cefepime (IV-Cephalosporin) | 3  | 8.3% |
TEM) also harbored one of the CTX-M groups. This indicates that the genotype detection methods used to target the CTX-M group had 0 out of 36 false-negative results and that clinicians could safely incorporate the PCR genotyping results of ESBL-E in clinical decision-making. Currently, rapid genotype diagnosis of ESBL-E utilizing PCR is increasingly becoming the mainstream of early diagnosis for ESBL-E infection. In Japan, there are two commercially available modalities from Verigene® and FilmArray®. Both these systems detect only CTX-M genotype groups. Our results showed that the modality to detect CTX-M genotypes in cases with severe UTI is safe and reliable for antibiotic selection.

In a previous report from the United States, the rate of *E. coli* among pyelonephritis ranged from 70 to 80%[38]. A report from Japan on bacteremic UTI demonstrated that the ratio of ESBL *E. coli* among all ESBL isolates was 81.8% (27/33).[5] The proportion of *E. coli* among ESBL isolates in the present study was 91%, which was higher than that in previous reports. Generally, *E. coli* tended to have a higher ratio (>90%) of CTX-M genotypes[19] whereas *K. pneumoniae* tended to have a higher ratio of concomitant multiple ESBL genotypes,[20], similar to our results.

The ratio of ESBL genotype distribution could differ from place to place. For instance, a lower ratio of CTX-M genotypes, 30% in *K. pneumoniae*, has been reported in Iran[4]. A study from the United States revealed that 91.7% (22/24) of ESBL *E. coli* harbored one or more CTX-M genotypes.[5] Another report from Europe showed that 90.7% (107 /118) harbored one or more CTX-M genes[21]. Higher ratios of CTX-M genotypes were also confirmed in our study.

Previous reports indicate that some genotypes may differ in resistance patterns[19]. The sample size in the present study was not large enough to demonstrate statistical significance in most of the combinations, but the rate of resistance to ampicillin sulbactam was significantly higher in the CTX-M-1 group than in the CTX-M-9 group and in the TEM group compared to the CTX-M-9 group (p = 0.0267 for both). We hope that further investigation will provide more information.

Our study has several strengths and clinical implications. UTI with SIRS is a common clinical observation[1]. In such cases, it is important to continue effective antibiotics. When blood culture results are positive, PCR methods can be used for ESBL-E detection. However, a previous study from Japan reported that among ESBL-E isolates, 91.3% (95/104) were in the CTX-M-1 group and 8.7% (9/104) were non-CTX-M group[3]. This suggests that application of the PCR genotype detection method to detect only the CTX-M group may result in nearly 10% false negative results, which could be detrimental in severe cases of ESBL-E infection. Inappropriate de-escalation of antibiotics based solely on PCR ESBL-E detection methods may pose a risk to critically ill patients. Simultaneously, prolonged use of broad-spectrum antibiotics, especially carbapenems, will
lead to a higher incidence of carbapenem-resistant Enterobacteriaceae (CRE)\textsuperscript{22}. CRE infection is associated with higher mortality\textsuperscript{23}. Therefore, early de-escalation is ideal. In our study, ESBL-E clinical isolates were collected and evaluated. All isolates were found to harbor at least one of the CTX-M genotypes. These data thus provide supportive information to guide judicial antibiotic selection and de-escalation in clinical practice for primary care physicians based on ESBL-E PCR genotype detection methods.

The limitations of our study are as follows. First, microbiological distribution differs from place to place but this study was performed in a single urban tertiary-care hospital. However, we excluded bacterial cultures from identical cases within six months and conducted this study over a period of 5 years. Thus, this study at least represents the standard distribution of ESBL-E genotypes in our region. Second, our study evaluated 36 cases of ESBL-E which is not a large enough number to lead definitive information. Third, our study evaluated genotype groups and does not include further genotypic differentiation using multi locus sequencing typing (MLST), pulsed-field gel electrophoresis (PFGE) or PCR-based ORF typing (POT). Fourth, although our study aimed to evaluate severe UTI case, one case was managed as an
Table 2. Positivity for Each of the ESBL Genotype Groups

| Species          | CTX-M-1 | CTX-M-2 | CTX-M-9 | SHV | TEM | Total |
|------------------|---------|---------|---------|-----|-----|-------|
| E. coli (n = 33) |         |         |         |     |     |       |
| K. pneumoniae (n = 1) |     |         |         |     |     |       |
| P. mirabilis (n = 2) |     |         |         |     |     |       |
| Total            | 12      | 4       | 21      | 1   | 2   | 14    |

CTX-M-8, CTX-M-25, CTX-M-64 (chimeric type), and GES-1 (ESBL type) were not detected among the 36 isolates tested.

Table 3. Number of Isolates Positive for ESBL Genotype Group Combinations

| CTX-M-1 | CTX-M-2 | CTX-M-9 | SHV | TEM | No. of isolates |
|---------|---------|---------|-----|-----|----------------|
| ●       | ●       | ●       | 4   |     |                |
| ●       | ●       | ●       | 6   |     |                |
| ●       | ●       | ●       | 1 (K. pneumoniae; n = 1) |   |                |
| ●       | ●       | ●       | 14  |     |                |
| ●       | ●       | ●       | 6   |     |                |
| ●       | ●       | ●       | 3 (P. mirabilis; n = 2)   |   |                |
| ●       | ●       | ●       | 1   |     |                |

Total 36

All the isolates were E. coli, except for those described as P. mirabilis or K. pneumoniae. Notably, there were no isolates positive only for SHV or TEM.

Conclusion

Clinicians may be able to safely de-escalate antimicrobials in cases with urinary tract infection based on the ESBL-E genotyping modality.

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Table 4. Number of Antibiotic Resistant Isolates in Each ESBL Genotype Group

| Genotype       | CTX-M-1 (n = 12) | CTX-M-2 (n = 4) | CTX-M-9 (n = 21) | SHV (n = 1) | TEM (n = 14) |
|----------------|-----------------|----------------|-----------------|-------------|--------------|
|                | % R or I †       | % R or I †     | % R or I †      | % R or I †  | % R or I †   |
| Cefmetazole    | 0.0 (0/12)       | 0.0 (0/4)      | 0.0 (0/21)      | 0.0 (0/1)   | 0.0 (0/13)   |
| Ceftazidime     | 100.0 (9/9)      | 100.0 (4/4)    | 93.8 (15/16)    | 100.0 (1/1) | 100.0 (9/9)  |
| Cefepime        | 0.0 (0/12)       | 0.0 (0/4)      | 0.0 (0/21)      | 0.0 (0/1)   | 0.0 (0/13)   |
| Flomoxef        | 0.0 (0/12)       | 0.0 (0/2)      | 0.0 (0/21)      | 0.0 (0/1)   | 0.0 (0/14)   |
| Imipenem        | 0.0 (0/9)        | 0.0 (0/4)      | 0.0 (0/16)      | 0.0 (0/1)   | 0.0 (0/9)    |
| Meropenem       | 41.7 (5/12)      | 75.0 (3/4)     | 47.6 (10/21)    | 100.0 (1/1) | 78.6 (11/14) |
| Cefoperazone Sulbactam | 100.0 (9/9)* | 100.0 (4/4) | 56.3 (9/16)* | 100.0 (1/1) | 100.0 (9/9)* |
| Ampicillin Sulbactam | 0.0 (0/12) | 0.0 (0/4) | 9.5 (2/21) | 0.0 (0/1) | 14.3 (2/14) |
| Gentamycin      | 25.0 (3/12)      | 25.0 (1/4)     | 23.8 (5/21)     | 0.0 (0/1)   | 42.9 (6/14)  |
| Minomycin       | 33.3 (4/12)      | 75.0 (3/4)     | 23.8 (5/21)     | 100.0 (1/1) | 28.6 (4/14)  |
| Levofloxacin    | 83.5 (10/12)     | 100.0 (4/4)    | 90.5 (19/21)    | 100.0 (1/1) | 71.4 (10/14) |
| Fosfomycin      | 33.3 (4/12)      | 50.0 (2/4)     | 33.3 (7/21)     | 100.0 (1/1) | 35.7 (5/14)  |
| Trimethoprim    | 58.3 (7/12)      | 25.0 (1/4)     | 42.9 (9/21)     | 100.0 (1/1) | 64.3 (9/14)  |
| Piperacillin Tazobactam | 0.0 (0/9) | 0.0 (0/4) | 12.5 (2/16) | 0.0 (0/1) | 10.0 (1/10) |
| Amoxicillin Clavulanate | 100.0 (2/2) | 50.0 (3/6) | 100.0 (1/1) | 100.0 (1/1) | 100.0 (1/1) |
| Cefoxazone      | 100.0 (1/1)      | 100.0 (1/1)    | 100.0 (1/1)     | 100.0 (1/1) | 100.0 (1/1)  |
| Tobramycin      | 100.0 (1/1)      | 100.0 (1/1)    | 100.0 (1/1)     | 100.0 (1/1) | 100.0 (1/1)  |
| Ciprofloxacin   | 100.0 (1/1)      | 100.0 (1/1)    | 100.0 (1/1)     | 100.0 (1/1) | 100.0 (1/1)  |
| Doripenem       | 0.0 (0/1)        | 0.0 (0/1)      | 0.0 (0/1)       | 0.0 (0/1)   | 0.0 (0/1)    |

There were statistically significant differences between CTX-M-1/CTX-M-9 and CTX-M-9/TEM in ampicillin sulbactam resistance rate (*, p value = 0.0267)

ESBL, extended-spectrum β-lactamase; R, resistant; I, intermediate. †R or I, the denominators are the number of isolates tested for antibiotic sensitivity. The numerators are the number of isolates with resistant or intermediate sensitivity results.

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**Conflicts of interest**

The authors have nothing to disclose.

**References**

1) Belyayeva M, Jeong JM. Acute Pyelonephritis. http://www.ncbi.nlm.nih.gov/books/NBK519537/. Retrieved on Jul 12, 2019.
2) Doi Y, Park YS, Rivera JI, et al. Community-associated extended-spectrum β-lactamase-producing Escherichia coli infection in the United States. Clin Infect Dis 2013; 56: 641–648.
3) Mawatari M, Hayakawa K, Fujiya Y, et al. Bacteraemic urinary tract infections in a tertiary hospital in Japan: the epidemiology of community-acquired infections and the role of non-carbapenem therapy. BMC Res Notes 2017; 10: 336. doi:10.1186/s13104-017-2680-z.
4) CDDEP. Resistance map. https://resistanceresources.cddep.org/AntibioticResistance.php. Retrieved on May 8, 2020.
5) Paterson DL, Ko W-C, Von Gottberg A, et al. Antibiotic therapy for Klebsiella pneumoniae bacteremia: implications of production of extended-spectrum beta-lactamases. Clin Infect Dis 2004; 39: 31–37.
6) McLaughlin M, Advincula MR, Malczynski M, et al. Correlations of antibiotic use and carbapenem resistance in Enterobacteriaceae. Antimicrob Agents Chemother 2013; 57: 5131–5133.

7) Chang H-J, Hsu P-C, Yang C-C, et al. Risk factors and outcomes of carbapenem-nonsusceptible Escherichia coli bacteremia: A matched case–control study. J Microbiol Immunol Infect 2011; 44: 125–130.

8) Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing, 27th ed, Pennsylvania, Wayne, 2017.

9) Demirci M, Ünlü Ö, İstanbullu Tosun A. Detection of O25b-ST131 clone, CTX-M-1 and CTX-M-15 genes via real-time PCR in Escherichia coli strains in patients with UTIs obtained from a university hospital in Istanbul. J Infect Public Health 2019; 12: 640–644.

10) Dallenne C, Da Costa A, Decré D, et al. Development of a set of multiplex PCR assays for the detection of genes encoding important beta-lactamases in Enterobacteriaceae. J Antimicrob Chemother 2010; 65: 490–495.

11) Luminex Japan. VERIGENE® Bloodstream Infection Testing Panels. https://www.luminex corp.com/ja/bloodstream-infection-tests/. Retrieved on May 8, 2020.

12) Tayh G, Al Laham N, Ben Yahia H, et al. Extended-spectrum β-lactamases among Enterobacteriaceae isolated from urinary tract infections in Gaza Strip, Palestine. BioMed Res Int 2019; 2019: 1–11.

13) Birgy A, Madhi F, Jung C, et al. Diversity and trends in population structure of ESBL-producing Enterobacteriaceae in febrile urinary tract infections in children in France from 2014 to 2017. J Antimicrob Chemother 2020; 75: 96–105.

14) Yazdansetad S, Alkhudhairey MK, Najafpour R, et al. Preliminary survey of extended-spectrum β-lactamases (ESBLs) in nosocomial uropathogen Klebsiella pneumoniae in north-central Iran. Heliyon 2019; 5: e02349. doi:10.1016/j.heliyon.2019.e02349.

15) Kishi K. Genotype destruction of ESBL producing E. coli in Shimane Prefecture. Report of the Shimane Prefectural Institute of Public Health and Environmental Science. 2008; 50: 66–69.

16) Kitano Y, Wakatake H, Saito H, et al. Clinical outcomes of urinary tract infection caused by extended spectrum beta-lactamase producing Enterobacteriaceae: a retrospective observational study comparing patients with and without systemic inflammatory response syndrome. Acute Med Surg 2020; 7: e472. doi:10.1002/ams2.472.

17) js-STAR. version 9.8.4j. http://www.kisnet.or.jp/nappa/software/star/freq/2x2.htm#. Retrieved on May 10, 2020.

18) Czaja CA, Scholes D, Hooton TM, et al. Population-based epidemiologic analysis of acute pyelonephritis. Clin Infect Dis 2007; 45: 273–280.

19) Nakane K, Kawaamura K, Goto K, et al. Long-term colonization by bla CTX-M-harboring Escherichia coli in healthy Japanese people engaged in food handling. Appl Environ Microbiol 2016; 82: 1818–1827.

20) Miyoshi S. Epidemiology of extended-spectrum β-lactamase-producing bacteria in Kagawa University Hospital from 2006 to 2013. Igakukensa [In Japanese] 2014; 63: 714–718.

21) Doumith M, Dhanji H, Ellington MJ, et al. Characterization of plasmids encoding extended-spectrum β-lactamases and their addiction systems circulating among Escherichia coli clinical isolates in the UK. J Antimicrob Chemother 2012; 67: 878–885.

22) Marimuthu K, Ng OT, Cherng BPZ, et al. Antecedent carbapenem exposure as a risk factor for non-carbapenemase-producing carbapenem-resistant Enterobacteriaceae and carbapenemase-producing Enterobacteriaceae. Antimicrob Agents Chemother 2019; 63: e00845-19. doi:10.1128/AAC.00845–19.

23) Xu L, Sun X, Ma X. Systematic review and meta-analysis of mortality of patients infected with carbapenem-resistant Klebsiella pneumoniae. Ann Clin Microbiol Antimicrob 2017; 16: 18. doi:10.1186/s12941-017-0191-3.