Clinical Characteristics of Bacteremia Caused by Extended-spectrum Beta-lactamase-producing Escherichia coli at a Tertiary Hospital

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Abstract

Objective In recent years, infection caused by extended-spectrum beta-lactamase (ESBL)-producing organisms has become an important issue. However, comparative studies of the bacteremia caused by ESBL Enterobacteriaceae and non-ESBL Enterobacteriaceae are extremely rare in Japan. This study aimed to assess the risk factors and prognosis of patients with bacteremia due to ESBL Escherichia coli (E. coli).

Methods The medical records of 31 patients with ESBL E. coli bacteremia and 98 patients with non-ESBL E. coli bacteremia who had been admitted to Osaka City University Hospital between January 2011 and June 2015 were retrospectively reviewed. The patient backgrounds, risk factors for infection, and prognosis were evaluated.

Results The male-to-female ratio, mean age, underlying disease, leukocyte count, and C-reactive protein (CRP) level did not differ between the patients in the ESBL E. coli bacteremia and non-ESBL E. coli bacteremia groups. The mean Sequential Organ Failure Assessment (SOFA) score for patients with ESBL and non-ESBL E. coli bacteremia were 3.6 and 3.8, respectively. Further, the mortality did not differ between the two groups (9.7% vs 9.2%). However, the independent predictors associated with ESBL E. coli bacteremia according to a multivariate analysis were the use of immunosuppressive drugs or corticosteroids (p=0.048) and quinolones (p=0.005) prior to isolation. The mortality did not differ between the carbapenem and tazobactam/piperacillin (TAZ/PIPC) or cefmetazole (CMZ) groups for the patients with ESBL E. coli bacteremia.

Conclusion Whenever we encountered patients with a history of immunosuppressive drug, corticosteroid, quinolone administration, it was necessary to perform antibiotic therapy while keeping the risk of ESBL E. coli in mind.

Key words: Escherichia coli, extended-spectrum beta-lactamase, bacteremia, quinolones, immunosuppressive drug

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Introduction

In recent years, extended-spectrum beta-lactamase (ESBL) is well recognized worldwide as a major cause of cephalosporin resistance among Enterobacteriaceae (1), with Escherichia coli (E. coli) in particular being a clinically important pathogen (2). Carbapenems have become widely recognized as the primary choice for the treatment of serious infections caused by ESBL-producing Enterobacteriaceae (3).
However, a previous report showed that β-lactam/β-lactamase inhibitors (BLBLI), including tazobactam/piperacillin (TAZ/PIP), are clinically reliable for the treatment of serious infections caused by ESBL-producing Enterobacteriaceae (4). When treating an Enterobacteriaceae infection, the differential diagnosis to determine whether the infection is caused by ESBL or non-ESBL-producing Enterobacteriaceae is important in actual clinical practice. Although some comparative studies have been reported overseas concerning bacteremia caused by ESBL-producing and non-ESBL-producing Enterobacteriaceae (5-8), little has been reported on this in Japan (9).

The purpose of the present study was to investigate the clinical characteristics of patients with bacteremia due to ESBL-producing E. coli (ESBL E. coli) at a tertiary hospital, including the risk factors and prognosis.

### Materials and Methods

The medical records of 31 patients with ESBL E. coli bacteremia and 98 patients with non-ESBL E. coli bacteremia who had been admitted to Osaka City University Hospital between January 2011 and June 2015 were retrospectively reviewed.

The age, sex, underlying disease, clinical features, patient medication records, and prognosis were evaluated. If E. coli had been isolated on multiple occasions within a five-year period in the same patient, only the first episode of E. coli bacteremia was reviewed. This study was approved by the Ethics Committee of Osaka City University, and the thesis was approved on January 4, 2016 with approval number 3311.

**Definition of bacteremia**

Bacteremia was defined as one or more positive blood cultures from patients with clinical signs of infection, such as fever, shaking chills, and sweats with or without local signs and symptoms (10). The diagnosis of E. coli urinary tract infection (UTI) was defined when the clinical and diagnostic findings included two more of following: 1) E. coli proven from a specimen of urine, 2) clinical manifestations suggestive of UTI, and 3) imaging findings suggestive of pyelonephritis. Symptoms and urinary findings including dysuria, suprapubic pain, hematuria, flank pain, costovertebral angle tenderness, nausea or vomiting, and pyuria or bacteruria are characteristic of UTI (11). Further, the imaging findings including perinephric stranding, renal swelling, thickening of Gerota’s fascia, and a segmental poor enhancement region are characteristic of pyelonephritis (12). The diagnosis of E. coli biliary tract infection was made when the clinical and diagnostic findings included three or more of the following: 1) fever and/or shaking chills or laboratory evidence of an inflammatory response, 2) jaundice or abnormal liver chemistries, 3) biliary dilation or evidence of an etiology observed on imaging, 4) E. coli isolated from a specimen of bile. The diagnosis of an E. coli intravascular device infection was made when the clinical and diagnostic findings included one or more of the following: 1) E. coli growth in at least one percutaneous blood culture and in a culture of the catheter tip, 2) E. coli growth in a blood sample drawn from a catheter hub at least 2 hours before growth of E. coli is detected in a blood sample obtained from a peripheral vein (13).

**Assessment of the laboratory data**

The leukocyte count and C-reactive protein (CRP) levels were recorded within two days of the initial blood culture and yielded a positive result. The severity of illness was evaluated by the Sequential Organ Failure Assessment (SOFA) score (14) and Pitt Bacteremia Score (15). Patients were defined as having severe sepsis when the SOFA score was ≥5 (16).

**Identification of bacteria**

All E. coli isolates were identified by a colony morphologic analysis, gram staining, and Triple Sugar Iron Agar. Isolate identification was confirmed using the MicroScan WalkAway-96 SI (Beckman Coulter, Brea, USA). The minimum inhibitory concentrations (MICs) were also determined using the MicroScan WalkAway-96 SI. The results of the period from January 2011 to June 2013 were interpreted in accordance with the 2009 Clinical and Laboratory Standards Institute (CLSI) breakpoints (17), and the results of the period from July 2013 to June 2015 were interpreted in accordance with the 2011 CLSI breakpoints (18). The production of ESBL was screened by measuring the MICs of cefotaxime, cefazidime, and aztreonam.

Confirmational testing was performed using an Ambler class C & ESBL Identification Set (Kanto Chemical, Tokyo, Japan). All plates were incubated at 35°C for 24 hours.

**Antimicrobial treatment**

The specific design of the initial antimicrobial treatment regimen was the responsibility of the attending physician. Antimicrobial treatment administered within five days after bacteremia onset was defined as empirical therapy and that administered afterward as definitive therapy (19). When clinicians administered the definitive therapy, they checked that the causative isolate was in vitro-susceptible to the prescribed drug according to the susceptibility criteria of CLSI.

**Statistical analysis**

The patient characteristics and outcomes were compared between the ESBL E. coli bacteremia patients and non-ESBL E. coli bacteremia patients. The Fisher’s exact test was used for univariate comparison of categorical data. Variables with a p value <0.20 in the univariate analyses were considered for inclusion in forward stepwise multivariate logistic regressions using SPSS 22.0 (IBM SPSS Statistics) to determine risk factors of this ESBL E. coli infection. A p value <0.05 indicated the presence of a statistically significant difference.
Results

Clinical characteristics and laboratory findings

The isolation frequency of ESBL E. coli and non-ESBL E. coli from 2011 to 2015 are summarized in Fig. 1. The clinical characteristics and laboratory findings of the 31 patients with ESBL E. coli bacteremia and 98 patients with non-ESBL E. coli bacteremia are summarized in Table 1. The 31 patients with ESBL E. coli bacteremia consisted of 12 males and 19 females with a mean age of 62.5 years. In addition, the 98 patients with non-ESBL E. coli bacteremia were composed of 46 males and 52 females with a mean age of 67.6 years. Of the 31 patients with ESBL E. coli bacteremia, 19 (61.3%) had malignancy, 13 (41.9%) had received immunosuppressive drugs or corticosteroids, and 13 (41.9%) were treated with quinolones 60 days prior to isolation. On the other hand, of the 98 patients with non-ESBL E. coli bacteremia, 46 (46.9%) had malignancy, 24 (24.5%) had received immunosuppressive drugs or corticosteroids, and 17 (17.3%) were treated with quinolones 60 days prior to isolation. The patients’ overseas travel history was unclear. The mean SOFA scores for patients with ESBL and non-ESBL E. coli bacteremia were 3.6 and 3.8, respectively.

Antimicrobial susceptibility

Various antimicrobial susceptibility rate data against ESBL and non-ESBL E. coli are shown in Fig. 2. Notably, the susceptibility rates of levofloxacin, gentamicin, and sulfamethoxazole/trimethoprim (SMX/TMP) against ESBL E. coli were significantly lower than those of non-ESBL E. coli (12.9% vs 78.6%, 58.1% vs 96.0%, 48.4% vs 82.7%, p<0.001, respectively).

Treatment

The empirical and definitive therapies against ESBL E. coli bacteremia and non-ESBL E. coli bacteremia are summarized in Table 2. The utilization rates of carbapenems against ESBL or non-ESBL E. coli bacteremia as both an empirical and definitive therapy were significantly higher than for other antimicrobial agents. Eighteen patients (58.1%) received carbapenems or TAZ/PIPC, or cefmetazole (CMZ) as appropriate empirical therapy (20) among those in the ESBL E. coli bacteremia group. Among the patients in the non-ESBL E. coli bacteremia group, the de-escalation rate was 26.7%.

Risk factors associated with ESBL E. coli bacteremia

The findings of a univariate analysis of risk factors associated with ESBL E. coli bacteremia are shown in Table 3. The male-to-female ratio, mean age, underlying disease, leukocyte count (>12,000/μL), CRP level (>10 mg/dL), and SOFA score (>5) did not differ between the patients in the ESBL E. coli bacteremia group and the non-ESBL E. coli bacteremia group. However, the use of quinolones 60 days prior to isolation was more frequent in the patients in the ESBL E. coli bacteremia group (p=0.007). Furthermore, nosocomial infection was more frequently observed (p=0.04). The mortality did not differ between the patients in the two groups. The independent predictors associated with ESBL E. coli bacteremia according to a multivariate analysis were the use of immunosuppressive drugs or corticosteroids (p=0.048) and quinolones (p=0.005) prior to isolation (Table 4).

Carbapenems group vs. tazobactam/piperacillin and cefmetazole group

Of the 31 patients with ESBL E. coli bacteremia, nine (29.0%) received carbapenems, four (12.9%) received TAZ/
**Table 1. Clinical Characteristics and Laboratory Findings of ESBL E. Coli and Non-ESBL E. Coli bacteremia.**

| Variables                           | ESBL E. coli (n=31) | non-ESBL E. coli (n=98) |
|-------------------------------------|---------------------|-------------------------|
| **Sex (male/female)**               | 12/19               | 46/52                   |
| **Mean age (years)**                | 62.5±18.9           | 67.6±13.9               |
| **Underlying disease**              |                     |                         |
| Malignancy                          | 19 (61.3%)          | 46 (46.9%)              |
| Immunosuppressive drug or corticosteroid use | 13 (41.9%)       | 24 (24.5%)              |
| Diabetes mellitus                   | 7 (22.6%)           | 28 (28.6%)              |
| Cardiovascular disease              | 5 (16.1%)           | 16 (16.3%)              |
| Autoimmune disease                  | 1 (3.2%)            | 11 (11.2%)              |
| Respiratory disease                 | 4 (12.9%)           | 6 (6.1%)                |
| Digestive disease                   | 3 (9.7%)            | 11 (11.2%)              |
| Endocrine disease                   | 3 (9.7%)            | 11 (11.2%)              |
| Chronic renal failure               | 3 (9.7%)            | 10 (10.2%)              |
| Central nervous system disease      | 3 (9.7%)            | 7 (7.1%)                |
| **Others**                          | 4 (12.9%)           | 12 (12.2%)              |
| **Leukocyte count (/μL)**           | 9,609.7±6,786.7     | 11,518.4±9,855.0        |
| **CRP (mg/dL)**                     | 10.6±8.2            | 11.2±9.1                |
| **SOFA score**                      | 3.6±2.6             | 3.8±4.0                 |
| **Pitt Bacteremia Score**           | 1.45±1.74           | 1.62±2.41               |
| **Use of antibiotics prior to isolation** | 25 (80.6%)       | 45 (45.9%)              |
| Quinolones                          | 13 (41.9%)          | 17 (17.3%)              |
| Third-generation cephalosporins     | 8 (22.5%)           | 14 (14.3%)              |
| Anti-MRSA agents                    | 8 (22.5%)           | 11 (11.2%)              |
| Carbapenems                         | 6 (19.4%)           | 9 (9.2%)                |
| Fourth-generation cephalosporins    | 6 (19.4%)           | 7 (7.1%)                |
| Second-generation cephalosporins    | 5 (16.1%)           | 6 (6.1%)                |
| None                                | 6 (19.4%)           | 53 (54.1%)              |
| Others                              | 12 (38.7%)          | 19 (19.4%)              |
| **Nosocomial infection**            | 24 (77.4%)          | 55 (56.1%)              |
| **Hospitalization within 90 days**  | 15 (48.4%)          | 39 (39.8%)              |
| **Two or more of the number of hospitalization within 90 days** | 0 (0%)      | 11 (11.2%)              |
| **Urinary catheter**                | 10 (32.3%)          | 15 (15.3%)              |
| **Infection site**                  |                     |                         |
| Urinary tract                       | 14 (45.2%)          | 47 (48%)                |
| Biliary tract                       | 3 (9.7%)            | 14 (14.3%)              |
| Intravascular device                | 2 (6.5%)            | 3 (3.0%)                |
| Others                              | 2 (6.5%)            | 4 (4.1%)                |
| Unknown                             | 10 (32.3%)          | 30 (30.6%)              |
| Polymicrobial infection             | 1 (3.2%)            | 9 (9.2%)                |
| Confirmation of blood culture-negative conversion | 12 (38.7%)       | 31 (31.6%)              |
| **Mortality**                       | 3 (9.7%)            | 9 (9.2%)                |

*Both E. coli infection-related and otherwise

CRP: C-reactive protein, E. coli: Escherichia coli, ESBL: extended-spectrum beta-lactamase, MRSA: methicillin-resistant Staphylococcus aureus, SOFA: sequential organ failure assessment

PIPC, and two (6.5%) received CMZ consistently from the empirical therapy until the end of treatment. The univariate analyses of clinical characteristics and laboratory findings of patients with ESBL E. coli bacteremia treated with TAZ/PIPC, CMZ, or carbapenems are shown in Table 5. The patients’ background and mortality did not differ between the patients in the TAZ/PIPC or CMZ groups and the carbapenems group.

**Discussion**

Our study showed the following results: First, the susceptibility rates of levofloxacin, gentamicin, and SMX/TMP against ESBL E. coli were significantly lower than those against non-ESBL E. coli. Second, the use of quinolones and immunosuppressive drugs or corticosteroids was an independent predictor of ESBL E. coli bacteremia. Third, the mortality did not differ between the patients with ESBL E. coli bacteremia and those with non-ESBL E. coli bactere-
Figure 2. Various antimicrobial susceptibility rate data against ESBL-producing and non-ESBL-producing E. coli. AMK: amikacin, AZT: aztreonam, CAZ: ceftazidime, CMZ: cefmetazole, CTX: cefotaxime, E. coli: Escherichia coli, ESBL: extended-spectrum beta-lactamase, FOM: fosfomycin, GEM: gentamicin, IPM: imipenem, LVFX: levofloxacin, MEP: meropenem, MINO: minocycline, ST: sulfamethoxazole/trimethoprim, TAZ/PIPC: tazobactam/piperacillin.

Table 2. Empirical and Definitive Therapy against ESBL E. Coli and Non-ESBL E. Coli bacteremia.

| Variables                  | Empirical therapy ESBL E. coli (n=31) | non-ESBL E. coli (n=98) | Definitive therapy ESBL E. coli (n=30)$^a$ | non-ESBL E. coli (n=92)$^b$ |
|----------------------------|--------------------------------------|-------------------------|------------------------------------------|---------------------------|
| Carbapenems                | 11 (35.5%)                           | 40 (40.8%)              | 17 (56.7%)                               | 26 (28.2%)                |
| Tazobactam/Piperacillin    | 4 (12.9%)                            | 14 (14.3%)              | 5 (16.7%)                                | 9 (9.8%)                  |
| Fourth-generation cephalosporins | 3 (9.7%)                          | 10 (10.2%)              | 0 (0%)                                   | 5 (5.4%)                  |
| Third-generation cephalosporins | 6 (19.3%)                        | 14 (14.3%)              | 2 (6.7%)                                 | 22 (23.9%)                |
| Cefmetazole                | 3 (9.7%)                            | 6 (6.1%)                | 5 (16.7%)                                | 5 (5.4%)                  |
| Quinolones                 | 0 (0%)                               | 4 (4.1%)                | 0 (0%)                                   | 9 (9.8%)                  |
| Others                     | 3 (9.7%)                            | 5 (5.1%)                | 1 (3.2%)                                 | 10 (11.0%)                |
| None                       | 1 (3.2%)                            | 5 (5.1%)                | 0 (0%)                                   | 6 (6.5%)                  |

Antimicrobial combination against ESBL E. coli bacteremia was not present in all cases.

$^a$One patient died before definitive therapy.

$^b$Four patients died and two patients was transferred to a different hospital before definitive therapy.

E. coli: Escherichia coli, ESBL: extended-spectrum beta-lactamase

mia. Fourth, regardless of the background and severity in patients with ESBL E. coli bacteremia, the mortality did not differ between the patients in the TAZ/PIPC or CMZ group and the carbapenems group.

In the past, the mechanisms of quinolone resistance in the Enterobacteriaceae were reported to be associated with a chromosomal mutation. However, in recent years, the resistant strains with plasmid-mediated quinolone resistance (PMQR) have been frequently reported (21, 22). It has thus become clear that plasmids with PMQR genes frequently hold ESBL genes at the same time (23). In addition, Soverein et al. reported that the genes encoding for the resistance of aminoglycosides are frequently found in the plasmids of ESBL-producing Enterobacteriaceae (24). Furthermore, sulphonamides and antifolate combinations almost certainly demonstrate the fact that ESBL-encoding plasmids often carry sulphonamides 1 (sul1) and sul2 along with various dihydroflavonol 4-reductase genes, which compromise TMP (25, 26). Livermore et al. reported that sul1 and sul2 genes were associated with SMX MICs of >1,024 mg/L compared with 1-128 mg/L for the gene-negative E. coli isolates (27). In addition, organisms with sul1 or sul2 genes together with SMX resistance determinants were resistant to SMX/TMP, with MICs generally of ≥128 mg/L. From the above, many of the ESBL-producing Enterobacteriaceae are thus considered to confer multidrug resistance against qui-
Table 3. Univariate Analysis of Risk Factors Associated with ESBL E. Coli bacteremia.

| Variables                                      | OR (95% CI) | p value \( ^{a} \) |
|------------------------------------------------|-------------|---------------------|
| Female sex                                     | 1.40 (0.57-3.52) | 0.54                |
| Age ≥ 70 years                                  | 0.53 (0.21-1.31) | 0.15                |
| Underlying disease                             |             |                     |
| Malignancy                                      | 1.78 (0.73-4.50) | 0.22                |
| Immunosuppressive drug or corticosteroid use    | 2.21 (0.86-5.62) | 0.07                |
| Diabetes mellitus                              | 0.73 (0.24-2.01) | 0.65                |
| Cardiovascular disease                         | 0.99 (0.26-3.18) | 1.00                |
| Autoimmune disease                             | 0.27 (0.006-1.97) | 0.29                |
| Respiratory disease                            | 2.25 (0.44-10.33) | 0.25                |
| Digestive disease                              | 0.85 (0.14-3.53) | 1.00                |
| Endocrine disease                              | 0.85 (0.14-3.53) | 1.00                |
| Chronic renal failure                          | 0.94 (0.16-4.02) | 1.00                |
| Central nervous system disease                 | 1.39 (0.22-6.60) | 0.70                |
| Others                                         | 1.06 (0.23-3.89) | 1.00                |
| Leukocyte count ≥ 12,000 (/μL)                  | 0.65 (0.24-1.66) | 0.40                |
| CRP ≥ 10 (mg/dL)                                | 1.68 (0.68-4.13) | 0.21                |
| SOFA score ≥ 5                                 | 1.25 (0.46-3.22) | 0.65                |
| Use of antibiotics prior to isolation          |             |                     |
| Quinolones                                     | 3.40 (1.28-9.06) | 0.007               |
| Third-generation cephalosporins                | 2.07 (0.67-6.10) | 0.17                |
| Anti-MRSA agents                               | 2.73 (0.85-8.48) | 0.08                |
| Carbapenems                                    | 2.35 (0.63-8.26) | 0.19                |
| Fourth-generation cephalosporins               | 3.09 (0.78-11.84)| 0.08                |
| Second-generation cephalosporins               | 2.92 (0.65-12.53)| 0.13                |
| Others                                         | 2.60 (0.98-6.85) | 0.05                |
| Nosocomial infection                           | 2.66 (0.99-8.02) | 0.04                |
| Hospitalization within 90 days                 | 1.41 (0.58-3.45) | 0.41                |
| Urinary catheter                               | 2.61 (0.91-7.30) | 0.07                |
| Mortality\( ^{b} \)                            | 1.06 (0.17-4.64) | 1.00                |

\(^{a}\)Fisher analysis.
\(^{b}\)Both E. coli infection-related and otherwise.

CI: confidence interval, CRP: C-reactive protein, E. coli: Escherichia coli, ESBL: extended-spectrum beta-lactamase, MRSA: methicillin-resistant Staphylococcus aureus, OR: odds ratio, SOFA: sequential organ failure assessment.

Table 4. Multivariate Analysis of Risk Factors Associated with ESBL E. Coli bacteremia.

| Risk factor                                  | OR (95% CI) | p value |
|----------------------------------------------|-------------|---------|
| Immunosuppressive drug or corticosteroid use | 2.45 (1.01-5.96) | 0.048 |
| Quinolones                                   | 3.70 (1.49-9.18) | 0.005 |
| Third-generation cephalosporins              | ND          | ND      |
| Anti-MRSA agents                             | ND          | ND      |
| Carbapenems                                  | ND          | ND      |
| Fourth-generation cephalosporins             | ND          | ND      |
| Second-generation cephalosporins             | ND          | ND      |
| Nosocomial infection                         | ND          | ND      |
| Urinary catheter                             | ND          | ND      |

CI: confidence interval, E. coli: Escherichia coli, ESBL: extended-spectrum beta-lactamase, MRSA: methicillin-resistant Staphylococcus aureus, ND: not detected, OR: odds ratio.

Some studies reported the use of quinolones to be an independent predictor of ESBL E. coli bacteremia (6, 7, 28, 29). A previous report showed that quinolones, aminoglycoside, and SMX/TMP...
will wield selection pressure on the intestinal flora that will favor ESBL E. coli proliferation and infection in susceptible patients (30). Further, a previous report showed a decline in the isolation rate of ESBL E. coli due to the reduction of fluoroquinolone usage (31). Therefore, with proper quinolone use, there is a potential to reduce the incidence of ESBL E. coli bacteremia.

Although previous studies indicate that there are various factors associated with ESBL bacteremia, the particular association with immunosuppressive drugs or corticosteroid use that we observed based on a multivariate analysis is an unusual finding. A previous report has shown that in mice, bacterial translocation from the intestinal tract was induced by immune deficiency due to immunosuppressive agents, even without any direct invasion into the intestinal tract (32). Furthermore, another report has shown that ESBL producing bacteria also frequently colonize the lower intestinal system, and therefore are a major source for ESBL distribution (33). These findings suggest that patients receiving immunosuppressive agents are at greater risk for ESBL producing bacteria acquisition and bacteremia. In the present study, although the existence of a relationship between ESBL E. coli bacteremia and use of immunosuppressive agents or steroids was suggested, we believe that more cases should be collected to confirm this relationship.

Some studies reported that the mortality was higher among patients in the ESBL-producing Enterobacteriaceae bacteremia group than in patients in the non-ESBL-producing Enterobacteriaceae bacteremia group (1, 5, 7, 8). One such study in a tertiary hospital showed that 30-day mortality of patients with bacteremia due to ESBL E. coli was significantly higher than for the patients in the non-ESBL E. coli control group (62.5% vs 12.5%, p=0.0091) (7). Moreover a study in Japan reported the SOFA score and 30-day mortality of patients with bacteremia due to Cefotaxime-non-susceptible E. coli or Klebsiella pneumoniae to be higher than that of patients with bacteremia due to cefotaxime-susceptible E. coli or Klebsiella pneumoniae (SOFA score: 5 vs 2, p<0.001, 30-day mortality: 21% vs 5% p<0.001) (9). In contrast, in the present study, the SOFA score and 30-day mortality did not differ between the patients in the ESBL E. coli bacteremia and non-ESBL E. coli bacteremia groups (SOFA score: 3.6 vs 3.8, 30-day mortality: 9.7% vs 9.2%). Further, in our study, the use of carbapenems or TAZ/PIPC, or CMZ as treatment for patients with ESBL E. coli bacteremia were relatively high among empirical and definitive therapy (58.1% and 90%, respectively). Therefore, we speculated that the mortality did not differ be-

Table 5. Clinical Characteristics and Laboratory Findings of ESBL E. Coli bacteremia Treated with Tazobactam/piperacillin or Cefmetazole or Carbapenem Consistently from Empirical Therapy until the End of Treatment.

| Variables                        | Tazobactam/Piperacillin or Cefmetazole Group (n=6) | Carbapenem Group (n=9) | p value* |
|----------------------------------|--------------------------------------------------|------------------------|---------|
| Female gender                    | 3 (50%)                                          | 7 (77.8%)              | 0.33    |
| Age ≥ 70                         | 4 (66.7%)                                        | 1 (11.1%)              | 0.09    |
| Underlying disease               |                                                  |                        |         |
| Malignancy                       | 3 (30%)                                          | 7 (77.8%)              | 0.33    |
| Immunosuppressive drug or corticosteroid use | 2 (33.3%)                                        | 4 (44.4%)              | 1.00    |
| Diabetes mellitus                | 0 (0%)                                           | 2 (22.2%)              | 0.49    |
| Cardiovascular disease           | 0 (0%)                                           | 2 (22.2%)              | 0.49    |
| Autoimmune disease               | 0 (0%)                                           | 1 (11.1%)              | 1.00    |
| Respiratory disease              | 0 (0%)                                           | 1 (11.1%)              | 1.00    |
| Digestive disease                | 1 (16.7%)                                        | 1 (11.1%)              | 1.00    |
| Endocrine disease                | 1 (16.7%)                                        | 0 (0%)                 | 0.40    |
| Chronic renal failure            | 1 (16.7%)                                        | 2 (22.2%)              | 1.00    |
| Central nervous system disease   | 1 (16.7%)                                        | 1 (11.1%)              | 1.00    |
| Leukocyte count ≥ 12,000 (μL)    | 1 (16.7%)                                        | 1 (11.1%)              | 1.00    |
| CRP ≥ 10 (mg/dL)                 | 2 (33.3%)                                        | 4 (44.4%)              | 1.00    |
| SOFA score ≥ 5                   | 4 (66.7%)                                        | 3 (33.3%)              | 0.32    |
| Nosocomial infection             | 5 (83.3%)                                        | 6 (66.7%)              | 0.60    |
| Hospitalization within 90 days   | 3 (50%)                                          | 4 (44.4%)              | 1.00    |
| Urinary catheter                 | 1 (16.7%)                                        | 4 (44.4%)              | 0.58    |
| Source of bacteremia             |                                                  |                        |         |
| Urinary tract                    | 3 (50%)                                          | 3 (33.3%)              | 0.62    |
| Biliary tract                    | 1 (16.7%)                                        | 1 (11.1%)              | 1.00    |
| Mortality*                       | 0 (0%)                                           | 0 (0%)                 | 1.00    |

*aFisher analysis.

*bBoth E. coli infection-related and otherwise.

CRP: C-reactive protein, Enterobacteria coli, ESBL: extended-spectrum beta-lactamase, SOFA: sequential organ failure assessment.
tween the two groups because there was no significant difference in the underlying disease and SOFA scores among the two groups, and the use of appropriate empirical and definitive therapy for ESBL *E. coli* bacteremia was relatively high.

The current standard therapy for infections caused by ESBL-producing pathogens is a carbapenem (3, 34). A previous report at a tertiary hospital showed that the adjusted risk of death was 1.92 times higher for patients receiving TAZ/PIPC compared with carbapenem as empirical therapy (35). In contrast, it has recently been reported that β-lactam/β-lactamase inhibitors (BLBLI) including TAZ/PIPC (36) and cephemycins including CMZ (37) are suitable alternatives to carbapenem for treating patients with bacteremia caused by ESBL *E. coli*. Our study results show that the mortality rates of the patients with ESBL *E. coli* bacteremia treated with TAZ/PIPC or CMZ versus carbapenem were both 0%. These findings may suggest that TAZ/PIPC or CMZ are effective alternatives to carbapenem treatment for patients with ESBL *E. coli* bacteremia.

Our study is associated with several limitations. First, the only bacteria targeted in this study were *E. coli*. We will need to collect and analyze the number of patients with bacteremia caused by ESBL-producing organisms such as *Klebsiella* spp. and *Enterobacter* spp. in addition to *E. coli*. Second, as this study was conducted only with patients at a tertiary hospital, there is unavoidably some selection bias. We will need to collect and analyze the number of patients with bacteremia caused by ESBL-producing organisms in a community hospital setting in addition to a tertiary hospital. Third, we conducted a retrospective study in order to primarily investigate the risk factors of bacteremia caused by ESBL *E. coli*. We will need to carry out a prospective study, such as in the comparative study between carbapenems and other antibiotics against bacteremia caused by ESBL-producing organisms. Fourth, in Table 5, because of the small number of cases, the power of the statistical evaluation decreased. We will need to collect and analyze the number of patients with ESBL *E. coli* bacteremia treated with TAZ/PIPC or CMZ, or carbapenem.

In conclusion, our study showed that mortality did not differ between patients in the ESBL *E. coli* bacteremia and non-ESBL *E. coli* bacteremia groups. TAZ/PIPC or CMZ may therefore be an effective treatment modality for patients with ESBL *E. coli* bacteremia. The use of quinolones and immunosuppressive drugs or corticosteroids was suggested to be an independent predictor of ESBL *E. coli* bacteremia. Whenever we encountered patients with a history of receiving these drugs, it was necessary to perform antibiotic therapy with ESBL *E. coli* in mind. Furthermore, it is crucial to elucidate whether the proper use of quinolones has the potential to reduce the chance of patients developing ESBL *E. coli* bacteremia.

The authors state that they have no Conflict of Interest (COI).

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