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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).

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However, a previous report showed that β-lactam/β-lactamase inhibitors (BLBLI), including tazobactam/piperacillin (TAZ/PIPC), 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 bacteriuria 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, ceftazidime, 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.

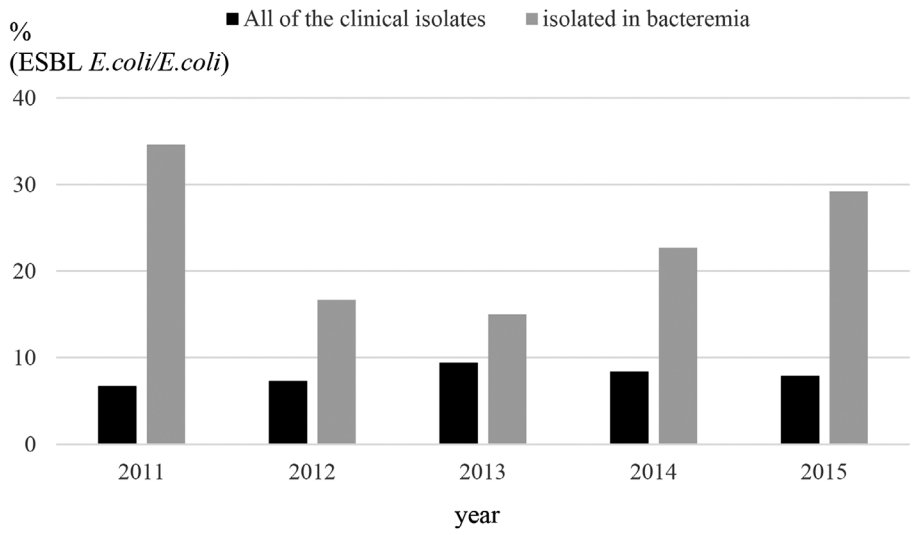

Figure 1. **Isolation frequency of ESBL-producing and non-ESBL-producing *E. coli* at Osaka City University from 2011 to 2015. *E. coli*: *Escherichia coli*, ESBL: extended-spectrum beta-lactamase**

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. Urinary tract infection was the presumed source of ESBL *E. coli* bacteremia in 14 patients (45.2%) and non-ESBL *E. coli* bacteremia in 47 patients (48.0%).

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[a]	3 (9.7%)	9 (9.2%)

[a]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-

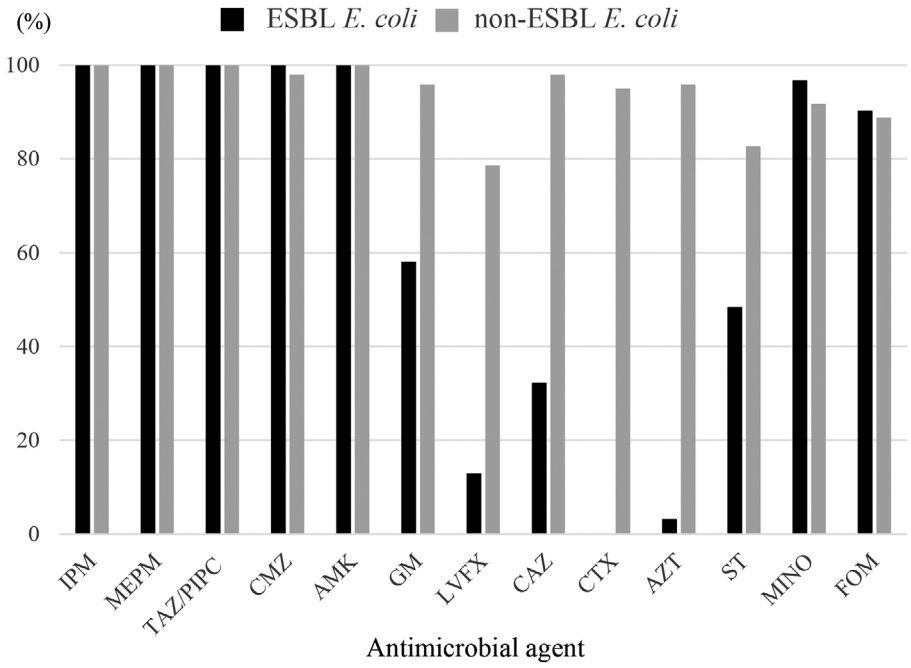

Figure 2. **Various antimicrobial susceptibility rate data against ESBL-producing and non-ESBL-producing *E. coli*. AMK: amikacin, AZT: aztreonam, CAZ: ceftazidime, CMZ: cefmetazole, CTX: cefotaxime, *E. coli*: *Escherichia coli*, ESBL: extended-spectrum beta-lactamase, FOM: fosfomycin, GEM: gentamicin, IPM: imipenem, LVFX: levofloxacin, MEPM: 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		Definitive therapy	
	ESBL *E. coli* (n=31)	non-ESBL *E. coli* (n=98)	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, Souverein 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*, EBSL: extended-spectrum beta-lactamase, MRSA: methicillin-resistant *Staphylococcus aureus*, ND: not detected, OR: odds ratio

nolones, aminoglycoside, and SMX/TMP.

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

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[a]
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[b]	0 (0%)	0 (0%)	1.00

[a]Fisher analysis.

[b]Both *E. coli* infection-related and otherwise.

CRP: C-reactive protein, *E. coli*: *Escherichia coli*, ESBL: extended-spectrum beta-lactamase, SOFA: sequential organ failure assessment

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-

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 cephamycins including CMZ (37) are suitable alternatives to carbapenems 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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References

1. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum β-lactamase production in *Enterobacteriaceae* bacteraemia: a systematic review and meta-analysis. J Antimicrob Chemother **60**: 913-920, 2007.
2. Paterson DL. Resistance in gram-negative bacteria: *Enterobacteriaceae*. Am J Med **119** (6 Suppl 1): S20-S28, 2006.
3. Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing *Enterobacteriaceae*: an emerging public-health concern. Lancet Infect Dis **8**: 159-166, 2008.
4. Peterson LR. Antibiotic policy and prescribing strategies for therapy of extended-spectrum beta-lactamase-producing *Enterobacteriaceae*: the role of piperacillin-tazobactam. Clin Microbiol Infect **14** (Suppl 1): 181-184, 2008.
5. Marchaim D, Gottesman T, Schwartz O, et al. National multicenter study of predictors and outcomes of bacteremia upon hospital admission caused by *Enterobacteriaceae* producing extended-spectrum beta-lactamases. Antimicrob Agents Chemother **54**: 5099-5104, 2010.
6. Rodríguez-Baño J, Navarro MD, Romero L, et al. Risk-factors for emerging bloodstream infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. Clin Microbiol Infect **14**: 180-183, 2008.
7. Freeman JT, McBride SJ, Nisbet MS, et al. Bloodstream infection with extended-spectrum beta-lactamase-producing *Enterobacteriaceae* at a tertiary care hospital in New Zealand: risk factors and outcomes. Int J Infect Dis **16**: e371-e374, 2012.
8. Qureshi ZA, Paterson DL, Peleq AY, et al. Clinical characteristics of bacteraemia caused by extended-spectrum β-lactamase-producing *Enterobacteriaceae* in the era of CTX-M-type and KPC-type β-lactamases. Clin Microbiol Infect **18**: 887-893, 2012.
9. Matsumura Y, Yamamoto M, Matsushima A, et al. Cefotaxime for the detection of extended-spectrum β-lactamase or plasmid-mediated AmpC β-lactamase and clinical characteristics of cefotaxime-non-susceptible *Escherichia coli* and *Klebsiella pneumoniae* bacteremia. Eur J Clin Microbiol Infect Dis **31**: 1931-1939, 2012.
10. Yamada K, Yanagihara K, Hara Y, et al. Clinical features of bacteremia caused by methicillin-resistant *Staphylococcus aureus* in a tertiary hospital. Tohoku J Exp Med **224**: 61-67, 2011.
11. Hooton TM. Clinical practice. Uncomplicated urinary tract infection. N Engl J Med **366**: 1028-1037, 2012.
12. Hammond NA, Nikolaidis P, Miller FH. Infectious and inflammatory diseases of the kidney. Radiol Clin North Am **50**: 259-270, 2012.
13. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis **49**: 1-45, 2009.
14. Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA **286**: 1754-1758, 2001.
15. Paterson DL, Ko WC, Von Gottberg, et al. International prospective study of *Klebsiella pneumoniae* bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial infections. Ann Intern Med **140**: 26-32, 2004.
16. Kaneko M, Okamura Y. Usefulness of measurement of presepsin, a new biomarker for sepsis. J Anal Bio-Sci **37**: 311-320, 2014.

17. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; 19th informational supplement. M100-S19. Clinical and Laboratory Standards Institute, Wayne, PA, 2009.
18. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; 21th informational supplement. M100-S21. Clinical and Laboratory Standards Institute, Wayne, PA, 2011.
19. Lee NY, Lee CC, Huang WH, Tsui KC, Hsueh PR, Ko WC. Cefepime therapy for monomicrobial bacteremia caused by cefepime-susceptible extended-spectrum beta-lactamase-producing *Enterobacteriaceae*: MIC matters. Clin Infect Dis **56**: 488-495, 2013.
20. Nakagawa S, Hisada H, Nomura N, et al. Antimicrobial activity of several drugs against extended-spectrum beta-lactamase positive *Enterobacteriaceae* isolates in Gifu and Aichi prefecture. Jpn J Antibiot **66**: 251-264, 2013.
21. Robicsek A, Jacoby GA, Hooper DC. The worldwide emergence of plasmid-mediated quinolone resistance. Lancet Infect Dis **6**: 629-640, 2006.
22. Strahilevitz J, Jacoby GA, Hooper DC, et al. Plasmid-mediated quinolone resistance: a multifaceted threat. Clin Microbiol Rev **22**: 664-689, 2009.
23. Mammeri H, Van De Loo M, Poirel L, et al. Emergence of plasmid-mediated quinolone resistance in *Escherichia coli* in Europe. Antimicrob Agents Chemother **49**: 71-76, 2005.
24. Souverein D, Boers SA, Veenendaal D, et al. Polyclonal spread and outbreaks with ESBL positive gentamicin resistant *Klebsiella* spp. in the region Kennemerland, The Netherlands. PLoS One **9**: e101212, 2014.
25. Chen L, Chavda KD, Fraimow HS, et al. Complete nucleotide sequences of blaKPC-4- and blaKPC-5-harboring IncN and IncX plasmids from *Klebsiella pneumoniae* strains isolated in New Jersey. Antimicrob Agents Chemother **57**: 269-276, 2013.
26. Ho PL, Lo WU, Yeung MK, et al. Complete sequencing of pNDM-HK encoding NDM-1 carbapenemase from a multidrug-resistant *Escherichia coli* strain isolated in Hong Kong. PLoS One **6**: e17989, 2011.
27. Livermore DM, Mushtaq S, Warner M, et al. Comparative *in vitro* activity of sulfametrole/trimethoprim and sulfamethoxazole/trimethoprim and other agents against multiresistant Gram-negative bacteria. J Antimicrob Chemother **69**: 1050-1056, 2014.
28. Rodríguez-Baño J, Navarro MD, Romero L, et al. Epidemiology and clinical features of infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* in nonhospitalized patients. J Clin Microbiol **42**: 1089-1094, 2004.
29. Rodríguez-Baño J, Picón E, Gijón P, et al. Community-onset bacteremia due to extended-spectrum beta-lactamase-producing *Escherichia coli*: risk factors and prognosis. Clin Infect Dis **50**: 40-48, 2010.
30. McCormack J, Grayson L. The Use of Antibiotics. 6th ed. Grayson L, Ed. Hodder Arnold/ASM Press, Washington DC, 2010: 1288.
31. Sarma JB, Marshall B, Cleeve V, Tate D, Oswald T, Woolfrey S. Effects of fluoroquinolone restriction (from 2007 to 2012) on resistance in *Enterobacteriaceae*: interrupted time-series analysis. J Hosp Infect **91**: 68-73, 2015.
32. Berg RD. Bacterial translocation from the gastrointestinal tracts of mice receiving immunosuppressive chemotherapeutic agents. Curr Microbiol **8**: 285-292, 1983.
33. Lucet JC, Régnier B. Enterobacteria producing extended spectrum beta-lactamases. Pathol Biol (Paris) **46**: 235-243, 1998.
34. Ramphal R, Ambrose PG. Extended-spectrum beta-lactamases and clinical outcomes: current data. Clin Infect Dis **42** (Suppl 4): S164-S172, 2006.
35. Tamma PD, Han JH, Rock C, et al. Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum β-lactamase bacteremia. Clin Infect Dis **60**: 1319-1325, 2015.
36. Rodríguez-Baño J, Navarro MD, Retamar P, et al. β-Lactam/β-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum β-lactamase-producing *Escherichia coli*: a post hoc analysis of prospective cohorts. Clin Infect Dis **54**: 167-174, 2012.
37. Matsumura Y, Yamamoto M, Nagao M, et al. Multicenter retrospective study of cefmetazole and flomoxef for treatment of extended-spectrum-β-lactamase-producing *Escherichia coli* bacteremia. Antimicrob Agents Chemother **59**: 5107-5113, 2015.