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Research Article

Research: Clinical Characteristics of Bacteremia Caused by Extended-Spectrum β - Lactamase-Producing *Escherichia coli* and Outcome in Relation to Empiric Therapy

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ABSTRACT

We investigated the clinical characteristics of 30 inpatients with ESBL-producing *Escherichia col i*bacteremia (ESBL group) and 85 inpatients with non-ESBL-producing *E. coli* bacteremia (non-ESBL group) and evaluated the relationship between empiric therapy and prognosis. In the ESBL group, urinary tract infection was most frequently. Most patients were hospitalized, had a history of admission to geriatric health care facilities, or intravenous antimicrobial drug injection. The rate of patients to whom susceptible antimicrobial drugs were administered as empiric therapy was significantly lower in the ESBL group than non-ESBL group (50 vs. 100%, p=0.0001). The total antimicrobial drug administration period in the ESBL group with ineffective empiric therapy was significantly longer than non-ESBL group (14.1 ± 3.1 vs. 9.9 ± 3.7 days, p=0.03). The mortality rate in the ESBL group with ineffective empiric therapy was significantly higher than ESBL group with effective empiric therapy and non-ESBL group (26.7% vs. 0%, 8.2%, p<0.05). In conclusion, when treating patients with bacteremia of *E. coli* due to urinary tract infection, with a history of admission to geriatric health care facilities, admission to hospitals, or intravenous antimicrobial drug injection, empiric therapy under the assumption of ESBL-producing *E. coli* may be shortened the total antimicrobial drug administration period and reducing mortality.

Keywords: Extended-spectrum β -lactamases; *Escherichia coli*; Bacteremia; Empiric therapy

INTRODUCTION

Extended-spectrum β -lactamases (ESBLs) refer to those of which the spectra to decompose penicillin to third-generation cephalosporins and monobactams are extended through β -lactamase-producing gene mutations. As ESBL-producing genes are coded on transmission-type plasmids held by bacteria, transmission to different types of Enterobacteriaceae is possible [1].

Recently, the incidence of hospital/community-acquired infection with ESBL-producing bacteria has increased [2]. Many strains are also resistant to other classes of antimicrobial drugs such as fluoroquinolones [3]. In particular, one study reported that the selection of antimicrobial drugs markedly influenced the outcome in patients with bacteremia [4]. Although some comparative studies have been reported concerning bacteremia caused by ESBL-producing and non-ESBL producing *Escherichia coli* (*E. coli*) in Japan [3,5], the relationship between antibiotic treatment and prognosis is controversial.

In this study, we clarified the clinical characteristics of bacteremia caused by ESBL-producing *E. coli* at our hospital and evaluated the relationship between empiric therapy and prognosis.

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MATERIALS AND METHODS

Materials

Of 2,681 adult patients from whom blood samples were submitted to the bacterial laboratory in Teikyo University Mizonokuchi hospital (permitted number of hospital beds: 400) between January 2016 and December 2018, 754 had positive cultures. Of these, the subjects consisted of 30 patients from whom ESBL-producing *E. coli* was isolated (ESBL group) and 85 from who non-ESBL-producing *E. coli* was isolated (non-ESBL group). Prior to this study, its protocol was approved by the ethics review board of Teikyouniversity (board No. 18-174, date of approval: January 7, 2019). This study was conducted according to the guidelines of our university.

Methods

Blood culture: For blood culture, two sets of BD BACTEC^{TM} 23F (for aerobic bacteria) and 22F bottles (for anaerobic bacteria) (Becton Dickinson and Co., Franklin Lakes, NJ, USA) were placed in a BD BACTEC^{TM} 23F Smart Container GT. After blood collection, the bottles for blood culture were promptly attached to a BD BACTEC^{TM} FX system, and cultured at 35°C for 5 days. The type of bacteria was identified using a MicroScan WalkAway 96 plus system (Siemens) and Neg combo 6.12J panel (Beckman Coulter Inc., Brea, CA, USA).

Definition of extended-spectrum β-lactamase: ESBL-producing bacteria were suspected when the Minimum Inhibitory Concentration (MIC) of Ceftazidime (CAZ), Cefotaxime (CTX), Aztreonam (AZT), or Ceftriaxone (CTRX) was ≥ 2 g/mL using the microliquid dilution method, or when the MIC of Cefpodoxime (CPDX) was ≥ 8 g/mL. As a confirmatory test, the disc method was used, and *E. coli* was evaluated as ESBL-producing when the inhibitory circle of a Clavulanic Acid (CVA)-containing disc increased by ≥ 5 mm in comparison with discs containing CAZ or CTX alone.

Collected data

We investigated the clinical background, such as the age, sex, concomitant diseases, infected foci, complications, outcome, admission to geriatric health care facilities within the past 6 months, previous admission to hospitals, and previous intravenous antimicrobial drug injection, drug susceptibility, antimicrobial drugs used for empiric therapy, and total antimicrobial drug administration period on electronic charts, and compared the results between the ESBL and non-ESBL groups.

Statistical analysis

For statistical analysis, GraphPadPrism version 7.0 software for Macintosh (graph pad software, San Diego, USA) was used. To compare the results between the two groups, Fisher's exact test and the unpaired t-test were used. To compare the results among the three groups, one-way ANOVA with the post-hoc Tukey multiple comparison tests was used. A p-value of 0.05 was regarded as significant. The age and total antimicrobial drug administration period were expressed as the mean Standard Deviation (SD).

RESULT

Clinical background

The clinical background in the ESBL and non-ESBL groups is shown in Table 1. The mean age of the 30 patients in the former was 83.3 ± 8.0 years and that of the 85 patients in the latter was 78.1 ± 9.7 years, demonstrating no difference. There was also no difference in the male-to-female ratio. Concerning concomitant diseases, 5 patients in the ESBL group, and 10 in the non-ESBL group had malignant tumors. An immunosuppressive drug had been administered to 1 patient in the former. Four patients in the former and 8 in the latter had diabetes mellitus. There were no other differences between the two groups.

Table 1: Clinical background in the ESBL and non-ESBL group.

	ESBL group (n=30)	Non-ESBL group (n=85)
Age (years: range)	83.3 ± 8.0 (58-99)	78.1 ± 9.7 (23-95)
Sex (male/female)	10/20	24/61
Malignant tumors/immunosuppressive drugs/diabetes mellitus	5/1/4	10/0/8
Infected foci, Urinary tract	26 (86.7%)	58 (68.2%)
Intraperitoneal cavity	3 (10.0%)	19 (22.4%)
Others	1 (3.3%)	8 (9.4%)
Isolation within 48 hours after admission	15 (50.0%)	69 (81.2%)
Shock	6 (20.0%)	13 (15.3%)
DIC	2 (6.7%)	8 (9.4%)

30 day mortality	4 (13.3%)	7 (8.2%)
History of admission to geriatric health care facilities	13 (43.3%)	19 (22.4%)
History of admission to hospitals	25 (83.3%)	40 (47.1%)
History of intravenous antimicrobial drug injection	22 (73.3%)	29 (34.1%)

In the two groups, the most frequently infected focus was the urinary tract, followed by the intraperitoneal cavity. Twenty-six patients (86.7%) in the ESBL group and 58 (68.2%) in the non-ESBL group developed urinary tract infection; its incidence was significantly higher in the former (p=0.04). Hydronephrosis was noted in 12 patients (14.1%) in the latter, whereas no patient in the former developed this disease, demonstrating a significant difference (p=0.02).

E. coli was isolated from blood samples within 48 hours after admission from 15 patients (50%) in the ESBL group and 69 (81.2%) in the non-ESBL group, being significantly different (p=0.001). Regarding complications, there were no differences in the incidences of septic shock or disseminated intravascular coagulation between the two groups. As for the outcome, there was no difference in 30-day mortality.

In the ESBL group, 13 (43.3%), 25 (83.3%), and 22 (73.3%) patients had a history of admission to geriatric health care facilities, admission to hospitals, and intravenous antimicrobial drug injection within the past 6 months, respectively. In the non-ESBL group, 19 (22.4%), 40 (47.1%), and 29 (34.1%) patients had such histories, respectively; the percentages were significantly higher in the former (p=0.02, p=0.0004, and p=0.0002, respectively). In the ESBL group, 13 of 15 patients from whom *E. coli* was isolated from blood samples within 48 hours after admission had a history of admission to long-term care health facilities, admission to hospitals, or intravenous antimicrobial drug injection. 2 patients of previous ESBL-producing *E. coli*carriage were recognized in the ESBL group.

Drug susceptibility

We compared the antibiograms of 5 antimicrobial drugs that had been frequentlyused for patients with bacterial infection at our hospital, excluding 3rd-generation cephalosporins, which are ineffective against ESBL-producing *E. coli* (Figure 1). Six patients (20%) in the ESBL group and 76 (89.4%) in the non-ESBL group responded to levofloxacin (LVFX) (p=0.0001). Eight patients (26.7%) in the former and 63 (74.1%) in the latter responded to Ampicillin/Sulbactam (ABPC/SBT) (p=0.0001). In the two groups, ≥ 90% of the patients responded to Piperacillin/Tazobactam (PIPC/TAZ), and all patients (100%) responded to Cefmetazole (CMZ) and Meropenem (MEPM).

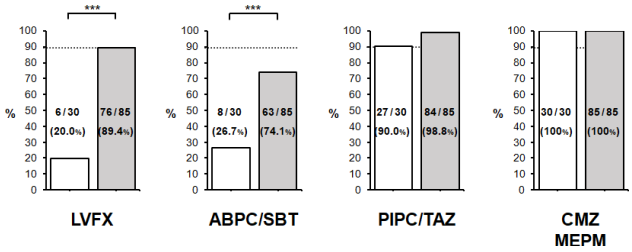

Figure 1: Antibiograms against ESBL-producing and non-ESBL-producing *E. coli*. The results of drug susceptibility tests of 5 antimicrobial drugs that had been relatively frequently administered to inpatients with suspected bacteremia at our hospital are presented. White: ESBL group, Grey: Non-ESBL group. LVFX: Levofloxacin, ABPC/SBT: Ampicillin/Sulbactam, PIPC/TAZ: Piperacillin/Tazobactam, CMZ: Cefmetazole, MEPM: Meropenem, ***p<0.001.

Antimicrobial drugs administered for empiric therapy

In the two groups, 3rd-generation cephalosporins had been the most frequently administered for empiric therapy (14 vs. 36 patients, respectively), followed by β-lactamase inhibitor-containing penicillin (7 vs. 22 patients, respectively) and carbapenem (6 vs. 19 patients, respectively). Effective antimicrobial drugs had been selected for 15 (50%) of the 30 patients in the ESBL group; MEPM 6, PIPC/TAZ 5, sulbactam/cefoperazone (SBT/CPZ) 2, CMZ 1 and LVFX 1. The percentage was significantly lower than that in the non-ESBL group (100%, all 85 patients) (p=0.0001) (Figure 2a). Ineffective antimicrobial drugs, cftriaxone CTRX, cefotaxime CTX, ABPC/SBT, and LVFX, had been administered to 9, 3, 2, and 1 patient, respectively.

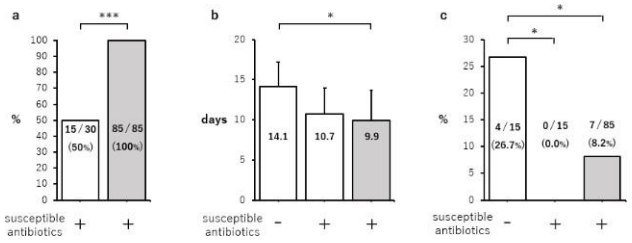

Figure 2: (a) Rate of patients to whom effective antimicrobial drugs had been administered for empiric therapy, (b) Total antimicrobial drug administration period for patients to whom ineffective or effective antimicrobial drugs had been administered for empiric therapy (c) 30-day mortality among the above patients. White: ESBL group, Grey: Non-ESBL group, *p<0.05, ***p<0.001.

Total antimicrobial drug administration period

In patients treated using ineffective antimicrobial drugs for empiric therapy, the total antimicrobial drug administration period was expected to be long. We compared the total antimicrobial drug administration period among 3 groups: 15 patients to whom ineffective antimicrobial drugs had been administered (ineffective-ESBL group), 15 to whom effective antimicrobial drugs had been administered (effective-ESBL group), and 85 to whom all effective antimicrobial drugs had been administered (non-ESBL group) (Figure 2b). In the non-ESBL group, the total administration period was 9.9 ± 3.7 days. It was 10.7 ± 3.2 days for 15 effective-ESBL group, demonstrating no difference with non-ESBL group. However, it was 14.1 ± 3.1 days for 15 ineffective-ESBL group, being significantly longer than that in the non-ESBL group (p=0.03).

Outcome

As shown in Table 1, no difference was observed on 30-day mortality between ESBL and non-ESBL groups. However, all 4 patients who died were in the ineffective-ESBL group; the mortality rate (26.7%) was significantly higher than that in the non-ESBL group (p=0.04) (Figure 2c). The mean period during which ineffective antimicrobial drugs had been administered for empiric therapy was 3.5 ± 1.0 days for surviving patients and 3.8 ± 1.3 days for those who died; there was no difference.

DISCUSSION

We investigated the characteristics of bacteremia caused by ESBL-producing *E. coli* at our hospital. The most frequently infected focus was the urinary tract. Most patients were hospitalized or had a history of admission to geriatric health care facilities, or intravenous antimicrobial drug injection. These are known risk factors for ESBL-producing bacteria [6]. We considered these to be important items for suspecting ESBL-producing bacteria at the time of history taking. It has been reported that most ESBL-producing bacteria are carried through the intestinal tract, Nakane K et al. [7] conducted a follow-up survey involving 52 patients from whom ESBL-producing *E. coli* was isolated from the stool, and reported that this type of bacteria was isolated over 3 months to ≥ 2 years. Therefore, to prevent its prevalence in hospitals or geriatric health care facilities, strategies to prevent contact infection must be established.

Regarding drug susceptibility, many strains of ESBL-producing *E. coli* were resistant to LVFX, as previously reported for the correlation between the rate of ESBL-producing strains and LVFX resistance [8]. On the other hand, many strains of non-ESBL-producing *E. coli* were also resistant to LVFX. In the Antimicrobial Resistance AMR action plan, it is recommended that the fluoroquinolone resistance rate of *E. coli* be reduced to ≤ 25% as an index of the outcome. Considering this, it may be necessary to promote the correct use of LVFX.

The enzymatic activity of ESBL is inhibited by CVA or sulbactam, and it cannot decompose cephamycins or carbapenems. However, in this study, the rate of ABPC/SBT-resistant ESBL-producing *E. coli* was markedly high, consistent with previous studies in Japan and other countries [9-11]. Furthermore, ≥ 90% of the strains was susceptible to PIPC/TAZ, and all strains were susceptible to CMZ and MEPM. One study reported the efficacy of cephamycins for bacteremia related to ESBL-producing *E. coli* [12], and another suggested the efficacy of carbapenems [13]. However, carbapenemase-producing bacteria are of concern, and whether carbapenems should be used for all ESBL-producing bacterial infections is controversial. Mitsuboshi S et al. [14] reported that the patients with bacteremia caused by ESBL-producing bacteria, aged ≥ 85 years were significantly more like to receive a carbapenem than their younger counterparts. They suggested that advanced age was not associated with higher 30-day mortality in patients with bacteremia caused by ESBL-producing bacteria and should not be a criterion for the selection of antibiotic therapy. Concerning PIPC/TAZ, one study reportedthat their effects were similar to those of carbapenems [15], whereas another study reported contrary findings [16]. Although carbapenem is the 1st choice for bacteremia due to ESBL-producing *E. coli*, we consideredthat PIPC/TAZ and CMZ are good candidates for empiric therapy based on the results of antibiograms at our hospital.

Antimicrobial drugs effective against ESBL-producing *E. coli* had not been administered for empiric therapy to 50% of the subjects. Characteristic of our hospital, CTRX had been selected for many patients, partially due to the prevalence of urinary tract infection. The appearance of ESBL was found to be correlated with the Antimicrobial Use Density (AUD) of 3rd/4th generation cephalosporins, especially CTRX [17]. Therefore, the correct use of CTRX must be promoted. Furthermore, the administration of ineffective antimicrobial drugs resulted in a significantly prolonged total antimicrobial drug administration period and poor prognosis. These results suggest that the initial selection of antimicrobial drugs for ESBL-producing *E. coli* may shorten the administration period and induce favorable outcome, although these remains to be clarified further.

Based on this study, ESBL-producing bacteria must be considered in patients in whom bacteremia is suspected due to urinary tract infection with a history of admission to geriatric health care facilities, admission to hospitals, or intravenous antimicrobial drug injection.The selection of antimicrobial drugs for empiric therapy based on the antibiograms at each hospital or status of the antimicrobial drug is important and inhibiting a reduction in activities of daily living (ADL) by shortens the administration days.

CONCLUSION

As future treatment strategies, individual clinicians must recognize ESBL-producing bacteria, and it may be necessary for an infection control team to prepare a manual for empiric therapy and promote the early initiation of antimicrobial drug therapy through the execution of blood culture rounds. Also, a test method to detect ESBL-producing bacteria in the early phase should be developed.

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CONFLICT OF INTEREST

All authors confirm that there are no conflicts of interest to declare.

REFERENCES

1. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. Clin Microbiol Rev. 2005;18:657-686.
2. Hayakawa K, Nagamatsu M, Mezaki K, Sugiki Y, Kutsuna S, Takeshita N, et al. Epidemiology of extended-spectrum beta-lactamase (ESBL) producing E. coli in Japan: characteristics of community-associated versus healthcare-associated ESBL E. coli. J Infect Chemother. 2017;23:117-119.
3. Namikawa H, Yamada K, Fujimoto H, Oinuma KI, Tochino Y, Takemoto Y, et al. Clinical characteristics of bacteremia caused by extended-spectrum beta-lactamase-producing E. coli at a tertiary hospital. Intern Med. 2017;56:1807-1815.
4. Ramphal R, Ambrose PG. Extended-spectrum beta-lactamases and clinical outcomes: current data. Clin Infect Dis. 2006;42:S164-S172.
5. Haruki Y, Hagiya H, Haruki M, Sugiyama T. Clinical characteristics and outcome of critically ill patients with bacteremia caused by extended-spectrum β-lactamase-producing and non-producing E. coli. J Infect Chemother. 2018;24:944-947.
6. Shitrit P, Reisfeld S, Paitan Y. Extended-spectrum beta-lactamase-producing enterobacteriaceae carriage upon hospital admission: prevalence and risk factors. J Hosp Infect. 2013;85:230-2.
7. Nakane K, Kawamura K, Goto K, Arakawa Y. Long-term colonization by bla (CTX-M)-harboring E. coli in healthy Japanese people engaged in food handling. Appl Environ Microbiol. 2016;82:1818-27.
8. Yokota S, Sato T, Okubo T, Ohkoshi Y, Okabayashi T, Kuwahara O, et al. Prevalence of fluoroquinolone-resistant E. coli O25:H4-ST131 (CTX-M-15-non producing) strains isolated in Japan. Chemotherapy. 2012;58:52-9.
9. Nakagawa S, Hisada H, Nomura N. Antimicrobial activity of several drugs against extended-spectrum beta-lactamase positive enterobacteriaceae isolates in gifu and aichi prefecture. Jpn J Antibiot. 2013;66:251-64.
10. Hawser SP, Bouchillon SK, Hoban DJ, Badal RE, Hsueh PR, Paterson DL. Emergence of high levels of extended-spectrum-beta-lactamase-producing gram-negative bacilli in the Asia-pacific region: data from the study for monitoring antimicrobial resistance Trends (SMART) program, 2007. Antimicrob Agents Chemother. 2009;53:3280-3284.
11. Spanu T, Luzzaro F, Perilli M, Amicosante G, Toniolo A, Fadda G, et al. Occurrence of extended-spectrum beta-lactamases in members of the family enterobacteriaceae in Italy: implications for resistance to beta-lactams and other antimicrobial drugs. Antimicrob Agents Chemother. 2002;46:196-202.
12. Matsumura Y, Yamamoto M, Nagao M, Komori T, Fujita N, Hayashi A, et al. Multicenter retrospective study of cefmetazole and flomoxef for treatment of extended-spectrum-β-lactamase-producing E. coli bacteremia. Antimicrob Agents Chemother. 2015;59:5107-13.
13. Kang CI, Kim SH, Park WB, Lee KD, KiBHb, Kim EC, et al. Bloodstream infections due to extended-spectrum beta-lactamase-producing E. coli and Klebsiella pneumoniae: risk factors for mortality and treatment outcome, with special emphasis on antimicrobial therapy. Antimicrob Agents Chemother. 2004;48:457-4581.
14. Mitsuboshi S, Tsuruma N, Watanabe K, Takahashi S, Ito A, Nakashita M, et al. Advanced age is not a risk factor for mortality in patients with bacteremia caused by extended-spectrum β-lactamase-producing organisms: a multicenter cohort study. Jpn J Infect Dis. 2020.
15. Rodríguez-Baño J, Navarro MD, Retamar P, Picon E, Pascual A. β-Lactam/β-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum β-lactamase-producing E. coli: a post hoc analysis of prospective cohorts. Clin Infect Dis. 2012;54:167-174.
16. Harris PNA, Tambyah PA, Lye DC, Mo Y, Lee TH, Yilmaz M, et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with E. coli or Klebsiella pneumoniae bloodstream infection and ceftriaxone resistance. JAMA. 2018;320:984-994.
17. Skrlin J, Vrca VB, Marusic S, Crncec MC, Mayer L. Impact of ceftriaxone de-restriction on the occurrence of ESBL-positive bacterial strains and antibiotic consumption. J Chemother. 2011;23:341-344.