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Original article

Prevalence and risk factors of infections caused by extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae

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ABSTRACT

Objective: To study the clinical characteristics and associated risk factors of infections caused by extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae.
Methods: A case–control study at a large university hospital in Japan, comparing patients who were infected or colonized with ESBL-producing Enterobacteriaceae (n = 212) and non-ESBL-producing Enterobacteriaceae (n = 2089) in 2010–2013. Data were collected from medical charts, retrospectively. Multivariate logistic regression analysis was used to explore risk factors of ESBL-producing Enterobacteriaceae (*Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Proteus mirabilis*) infection or colonization for each pathogen, respectively.
Results: ESBL-producing Enterobacteriaceae [*E. coli* (n = 113), *K. oxytoca* (n = 46), *K. pneumoniae* (n = 41), *P. mirabilis* (n = 12)] were taken from patients were identified in 1409 outpatient and 892 inpatients. Infection or colonization caused by ESBL-producing Enterobacteriaceae was considered to be hospital-acquired, healthcare-associated and community-acquired in 60.4%, 17.9% and 21.7% patients, respectively. Independent risk factors for ESBL-producing Enterobacteriaceae infection or colonization were male sex, cerebrovascular disease, intubation/tracheostomy, major surgery within 60 days ($p < 0.001$). Moreover, antimicrobial usage (more than 4 days) during preceding 60 days, especially aminoglycoside, oxazolidinone, tetracycline, fluoroquinolone, trimethoprim/sulfamethoxazole, and second- and fourth-generation cephalosporin were risk factors ($p < 0.001$). However, acquisition location of infection (hospital-acquired and community-onset) was not a risk factor ($p > 0.05$).
Conclusion: The problem of ESBL production is no longer limited to hospital-acquired infections. The presence of chronic illness, such as cerebrovascular disease, and recent antimicrobial use were independent risk factors for ESBL-producing Enterobacteriaceae infection or colonization.

1. Introduction

As the prevalence of extended-spectrum β-lactamase (ESBL)-producing bacteria has increased worldwide sharply over the last decade, production of ESBL is increasingly important cause of resistance in gram-negative bacteria throughout the world [1–4]. The first ESBL was identified in Germany in 1983 [5]; ESBL are capable of degrading the β-lactam ring of most of the penicillins and cephalosporins [5,6].

ESBL-encoding plasmids frequently bear resistance genes for additional antimicrobial classes, such as sulfonamides, aminoglycosides, and fluoroquinolones [7,8]. Herein, treatment options for infections due to these multidrug-resistant organisms are therefore limited, and initial empirical therapy is often ineffective and associated with increases mortality. Consequently, infection by

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ESBL producers has been associated with increased mortality, prolonged hospitalization, and rising medical costs [9–11].

Additionally, it is not surprising that gram-negative bacteria that produce these ESBL are increasingly implicated as causes of community-onset infection [12–14]. The problem of ESBL-production is no longer limited to hospital-acquired infections.

Therefore, early recognition of patients who are at risk for infection with ESBL-producing bacteria is necessary to guide empirical treatment and to apply preventive measures to limit the dissemination of infection [15,16]. The aim of this study was to assess risk factors for infection or colonization with ESBL-producing Enterobacteriaceae.

2. Materials and methods

2.1. Study design and patients

The study population consisted of 2301 patients, including inpatients and outpatients, from whom Enterobacteriaceae was isolated at least once between 1 January 2010 and 30 June 2013 at Aichi Medical School University Hospital, a 955-bed tertiary care facility. We performed a detailed retrospective investigation of the clinical features of these patients, and extracted microbiological data for *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Proteus mirabilis* that were identified in clinical cultures. In cases in which any bacterial cultures were tested twice or more in this period in the same patients, we selected the case at the time of initial isolation of *Enterobacteriaceae*. The same patients were included more than once only if relevant species were identified at least six months apart.

This study was approved by Ethics Committee of the Faculty of Aichi Medical University, Japan (12-131).

2.2. Data collection

For each patient, the following putative risk factors were collected from the clinical records: age, gender, medical complication, and invasive procedure such as urinary catheter, intubation/tracheostomy, naso-gastric tube, central venous catheter, intravenous catheter, drain, artificial organ, and hospital admission during preceding two months, use of an antimicrobial agent for more than 4 days in the preceding 60 days [17], a major operation (any surgical procedure that involved anesthesia or mechanical ventilation) within 60 days. We investigated the history of antimicrobials usage with medical chart. Those for whom previous antimicrobial use could not be ascertained were excluded from the study. History of following associated diseases was documented: sepsis, cancer, cardiovascular disease, cerebrovascular disease, diabetes, diseases of the nervous system, psychiatric disorder, respiratory ailment, digestive system disease, urological diseases, skin and musculoskeletal disease, and blood dyscrasia. Antimicrobial susceptibility of the Enterobacteriaceae isolates was also recorded.

Sites of acquisition of the organisms (community-onset or hospital-acquired), risk factors were also investigated in this study. Community-onset was defined outpatients or within 48 h of hospitalization, while hospital-acquired was defined hospital admission after 48 h or more. Moreover, the case in community-onset was classified as community-acquired and nursing and healthcare-associated.

Healthcare-associated infections were classified in accordance with the Japanese Respiratory Society [18]. Any of the following criteria were considered as healthcare-associated infections (i) resident of an extended care facility or nursing home; (ii) person who has been discharged from a hospital within the preceding 90 days; (iii) an elderly or disabled person who is receiving nursing care; (iv) person who is receiving regular endovascular treatment as an outpatient (dialysis, antimicrobial therapy, chemotherapy, immunosuppressive therapy).

2.3. Screening and confirmation of ESBL production

ESBL expression was screened with the disc diffusion method on Mueller–Hinton agar using cefotaxime, ceftazidime cefpodoxime and ceftriaxone with and without clavulanic acid (10 mg), as recommended by the Clinical and Laboratory Standards Institute (CLSI), and each set of samples was tested with CLSI quality control strains *E. coli* ATCC 25922 and *K. pneumoniae* ATCC 700603.18 (M100-S21).

2.4. Antimicrobial susceptibility testing

All Enterobacteriaceae isolated from patients were tested for antimicrobial susceptibility. The minimum inhibitory concentration (MIC) was measured by the broth microdilution method based on the CLSI recommendations [19].

2.5. Statistical analysis

Patients were divided into two groups: the ESBL-positive group and the ESBL-negative group (non-ESBL), and categorical features of each group were compared respectively. Statistical analyses were performed using the χ^2-test, Fisher's exact test to compare categorical variables, and the *t*-test for comparing the age of patients in both groups. $p < 0.05$ was considered significant.

Univariate analyses were performed separately for each of the variables. Variables with a *p* value of <0.1 in the univariate analysis were candidates for multivariate analysis using a backward elimination method. Analysis of risk factors was performed according to species. All tests were 2-tailed, and a $p < 0.05$ was considered significant in the multivariable model. The odds ratio was calculated with a confidence interval (CI) of 95%. SPSS software package version 11.0.1J (LEAD Technologies, Inc) was used for statistical analysis.

3. Results

3.1. Patient population

During the study period, 168 blood cultures, 1182 urine cultures, 381 sputum cultures, 180 pus cultures and 390 others were taken from 1409 outpatients and inpatients ≦48 h of admission and 892 inpatients >48 h of admission to Aichi Medical School University hospital. Of the 2301 patients, 212 patients (9.2%) were detected as infected or colonized with an ESBL-producing Enterobacteriaceae during study period. One hundred twenty eight (60.4%) of the 212 patients yielding ESBL producers were male (Table 1). Ages ranged from 0 to 97 years (median: 63). Onset of infection caused by the ESBL-producing Enterobacteriaceae was considered to be hospital-acquired, community-acquired and nursing and healthcare-associated in 128 (60.4%), 46 (21.7%) and 38 (17.9%) patients, respectively (Table 1).

3.2. Epidemiological analysis

The 2301 episodes represented 1413 *E. coli*, 223 *K. oxytoca*, 543 *K. pneumoniae* and 122 *P. mirabilis*, including 212 ESBL producers (9.2%; 113 *E. coli*, 46 *K. oxytoca*, 41 *K. pneumoniae* and 12 *P. mirabilis*). Species distribution of ESBL-producing and non-ESBL-producing Enterobacteriaceae isolates were shown in Fig. 1. *E. coli* was the most frequent microbial isolated in both groups. However, the