A Retrospective Analysis of Risk Factors and Patient Outcomes of Bloodstream Infection with Extended-Spectrum β-Lactamase-Producing Escherichia coli in a Chinese Tertiary Hospital

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Objective: The present study assessed risk factors and patient outcomes of bloodstream infection (BSI) caused by extended-spectrum β-lactamase (ESBL)-producing Escherichia coli (E. coli).

Methods: A retrospective study was performed to analyze risk factors and patient outcomes of BSI caused by extended-spectrum β-lactamase-producing Escherichia coli (ESBL-EC) in one Chinese tertiary hospital over a 7.5-year period. The clinical characteristics of patients infected with ESBL-producing and non-ESBL-producing E. coli were compared. Predictors of 30-day mortality in patients with E. coli BSI were also identified in our study.

Results: The results of drug sensitivity showed that quinolones, aminoglycosides, β-lactam/β-lactamase inhibitor combinations (BLICs) and trimethoprim/sulamethoxazole exhibited significant differences between the ESBL and non-ESBL groups. Of the 963 patients with E. coli BSI, 57.6% developed ESBL-EC. Multivariate analysis showed that biliary tract infection (BTI) [P<0.001, OR (95% CI): 1.798 (1.334–2.425)], urinary tract obstructive disease [P=0.001, OR (95% CI): 2.106 (1.366–3.248)], surgery within 3 months [P=0.002, OR (95% CI): 1.591 (1.178–2.147)], hospitalization within 3 months [P=0.001, OR (95% CI): 2.075 (1.579–2.725)], ICU admission [P=0.011, OR (95% CI): 1.684 (1.124–2.522)] and history of cephalosporin use [P=0.006, OR (95% CI): 3.097 (1.392–6.891)] were statistically significant. In mortality analysis, aCCI≥2 [P=0.016, OR (95% CI): 2.453 (1.179–5.103)], gastrointestinal catheterization [P=0.004, OR (95% CI): 2.525 (1.334–4.782)] were significantly associated with 30-day mortality. According to Kaplan-Meier survival analysis, we found that in SOFA≤2 group and SOFA≥3 group, the mortality rate of patients treated with BLICs were lower than that of carbapenems (P<0.05).

Conclusion: This study showed that BTI, urinary tract obstructive disease, surgery within 3 months, hospitalization within 3 months, ICU admission and cephalosporin exposure were independent risk factors for the emergence of ESBL-EC BSI. Analysis of risk factors for 30-day mortality revealed that the factors independently associated with a higher risk of mortality were aCCI≥2, gastrointestinal catheterization. Compared to carbapenems, the BLICs had preferable effect to treat patients with ESBL-EC BSI. Notably, patients with severe illness were inclined to use carbapenems, which affected the analysis results. Therefore, we suggest that BLICs could be recommended to treat mild patients with ESBL-EC bacteremia.

Keywords: Escherichia coli, extended-spectrum beta-lactamase, bloodstream infection, risk factors, carbapenems
Introduction

*Escherichia coli* (E. coli) is one of the most common microorganisms causing intra-abdominal, urinary system and bloodstream infection (BSI). According to the data of the European Antimicrobial Resistance Surveillance Network from 2002 to 2009, *E. coli* is the distinctly dominant BSI-causing pathogen. In South Korea, surveillance network data in 2016–2017 showed that *E. coli* was the predominant pathogenic bacteria. A Belgian study in 2000–2014 also showed a gradual increase in *E. coli* infections. There is no doubt that *E. coli* infection has become a major health crisis attracting worldwide attention.

Bacterial resistance, particularly the emergence of extended-spectrum β-lactamase (ESBL), is an unavoidable and urgent problem worldwide. The emergence of ESBL mediates drug resistance to cephalosporins and greatly increases medical costs. *E. coli* is one of the major species of ESBL-producing family *Enterobacteriaceae*, and studies demonstrated that the infection rate of extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-EC) is increasing annually. In China, the prevalence rate of ESBL-EC is up to 53.6% ESBL-EC BSI has been increasing sharply, which greatly increases the medical burden. However, risk factors and outcomes associated with ESBL-EC BSI are not well established. The present study investigated the prevalence and some specific risk factors associated with ESBL-EC bacteremia and outcomes of patients infected with *E. coli*.

Materials and Methods

Study Design and Population

This retrospective, case–control study was performed at the Clinical Laboratory of the Second Affiliated Hospital of Nanchang University, which is a tertiary university hospital with 2400 patient beds in Jiangxi, China. We included all people with *E. coli* BSI from January 2012 to June 2019. Only the first bacteremic episode of each patient was included (Figure 1).

Data Collection

All data were collected from electronic medical records, including demographics and health-care history (admission diagnoses, history of chronic illness, antibiotic usage, hospital exposures, mortality, and collection time of first positive blood culture). The age-adjusted Charlson Comorbidity Index (aCCI) and sepsis-related organ failure assessment (SOFA) scores were calculated at the time of BSI onset.

Definitions

*E. coli* bloodstream infection was defined as at least one positive blood culture together, while presenting the following at least two criteria: 1) body temperature was higher than 38 °C or lower than 36 °C; 2) heart rate exceeded 90 beats per minute; 3) respiratory rate exceeded 20 breaths per minute; 4) the peripheral blood cell count showed an increase above 10 × 10^3/L or a decrease below 4 × 10^3/L. Nosocomial infection was defined as an infection that occurred >48h after admission to the hospital. The onset of infection was the time of sample collection. Empirical antibiotic therapy referred to antibiotics chosen after the patient had infection symptoms. Appropriate empirical antibiotic therapy as defined by the antimicrobials is active in vitro.

Antimicrobial Susceptibilities

*E. coli* isolates were identified using the VITEK 2 Compact system (bioMérieux, France) or MALDI-TOF MS (bioMérieux, France), and antimicrobial susceptibilities were determined in vitro using VITEK-2 Compact AST-N16 (bioMérieux, France) or a Kirby–Bauer test. Drug sensitivities refer to the Clinical and Laboratory Standards Institute (CLSI) standards. Screening for ESBL production was performed using a combination disc method according to CLSI protocols using cefotaxime and cefazidime alone or in combination with clavulanic acid.

Statistical Analysis

For categorical variables, the *χ*^2^ test or Fisher’s exact test was used. In risk factor analysis, candidate variables with a *P* value <0.1 in a univariate model were included and then further determined in a forward stepwise logistic regression model. We used cox regression analysis to evaluate the survival in patients with bloodstream infection with *E. coli*. The Kaplan–Meier product-limit method was used to estimate the survival distribution function. Nonparametric (log-rank) tests were used to compare survival functions in different groups. All analyses were performed using SPSS (version24.0) software. In all analyses, *P* value≤0.05 was considered significant.

Results

Microbiological Characteristics of *E. coli*

During the 7.5-year study period, a total of 980 patients with *E. coli* BSIs were included. According to drug
sensitivity test results, isolates were the highest sensitive to carbapenem, followed by furantoin and piperacillin/tazobactam. Compared the antimicrobial susceptibility profiles, we found that quinolones, aminoglycosides (except amikacin), β-lactam/β-lactamase inhibitor combinations (BLICs) and trimethoprim/sulfamethoxazole showed significant differences between the ESBL and non-ESBL groups. Of these drugs, amoxicillin/clavulanate and piperacillin/tazobactam showed more resistance in the non-ESBL groups. There was no difference between the resistance of carbapenem in ESBL and non-ESBL groups (Table 1).
Demographic Characteristics of Patients with E. coli BSI

In the 980 patients, 17 cases of carbapenem-resistant E. coli BSI were excluded. The median age was 61 years (IQR: 51–72), and the female account for 54.1% (521/963). Nosocomial infection occurred in 49.9% (481/963), and most patients (33.2%) had hypertension, followed by biliary tract infection (BTI) (30.5%). A total of 24.1% (232/963) had antimicrobial exposure within 30 days. Among these patients, the proportion of patients who received BLICs antibiotic treatment was the highest. In all isolates, 57.6% (555/963) isolates were ESBL-producing organisms. All data are shown in Table 2.

Risk Factors for ESBL-Producing E. coli BSI

Table 2 shows the risk factors of ESBL-producing E. coli. In univariate analysis, female, diabetes, BTI, urinary tract obstructive disease, gastrointestinal catheterization, surgery within 3 months, hospitalization within 3 months, intensive care unit (ICU) admission, history of cephalosporin use and history of BLICs use were incorporated into multivariate analysis. After adjusting the confounding factors via logistics regression analysis, BTI [P<0.001, OR (95% CI):1.798 (1.334–2.425)], urinary tract obstructive disease [P=0.001, OR (95% CI):2.106 (1.366–3.248)], surgery within 3 months [P=0.002, OR (95% CI):1.591 (1.178–2.147)], hospitalization within 3 months [P<0.001, OR (95% CI):2.075 (1.579–2.725)], ICU admission [P=0.011, OR (95% CI):1.684 (1.124–2.522)] and history of cephalosporin use [P=0.006, OR (95% CI):3.097 (1.392–6.891)] were independent risk factors of ESBL-producing E. coli BSI.

Risk Factors of 30-Day Mortality in Patients with ESBL-Producing E. coli BSI

In the risk factor analysis for mortality, 47 patients who died within 48h were excluded, and 42 patients who were treated with antibiotics for less than 48h were excluded. The 30-day mortality rate was 9.0%. In cox regression analysis, adjusting for ESBL production, central venous catheterization, urinary catheterization, nosocomial infection and appropriate empirical antibiotic therapy, aCCI>2 [P=0.016, OR (95% CI): 2.453 (1.179–5.103)], gastrointestinal catheterization [P=0.004, OR (95% CI):2.525 (1.333–4.782)] were significantly associated with 30-day mortality (Table 3). ESBL-positive E. coli did not impact the mortality rate. To evaluate the efficacy of antibiotics in the treatment of ESBL-positive patients, we divided all ESBL-positive patients into SOFA score <2 and SOFA score ≥2 group. According to the therapy of different antibiotics in ESBL-positive patients, a Kaplan-Meier survival analysis is presented in Figure 2.

Discussion

In this study, we retrospectively analyzed the clinical characteristics of ESBL-producing and non-ESBL-producing E. coli BSI. We found that ESBL-EC was often more resistant to quinolones, aminoglycosides (except amikacin) and trimethoprim/sulfamethoxazole, which is consistent with other studies.9-11 The reason may be that plasmids carrying genes encoding ESBL also often carry other drug-resistant genes

| Antimicrobial | Overall (n=980) | ESBL-Positive E. coli (n=563) | ESBL-Negative E. coli (n=417) | \( \chi^2 \) | P value |
|--------------|----------------|-----------------------------|-----------------------------|---------|---------|
| Cefoxitin    | 17.5% (127/724) | 17.0% (70/412)             | 18.3% (57/312)             | 0.201   | 0.654   |
| Ciprofloxacin| 52.9% (462/874)| 70.5% (341/484)            | 31.0% (121/390)            | 134.745 | <0.001  |
| Levofloxacin | 51.0% (499/978)| 67.2% (377/561)            | 29.3% (122/417)            | 137.818 | <0.001  |
| Gentamicin   | 39.1% (382/977)| 45.8% (257/561)            | 30.0% (125/416)            | 24.926  | <0.001  |
| Amikacin     | 2.5% (24/974)  | 3.6% (20/558)              | 1.0% (4/416)               | 6.821   | 0.09    |
| Macrodantin  | 1.8% (16/891)  | 2.8% (14/496)              | 0.5% (2/395)               | 6.690   | 0.01    |
| Tobramycin   | 11.1% (99/893) | 15.3% (76/498)             | 5.8% (23/395)              | 19.907  | <0.001  |
| Meropenem    | 2.5% (2/81)    | 3.3% (2/61)                | 0.0% (0/20)                | -       | 0.565   |
| Imipenem     | 1.6% (16/974)  | 1.2% (7/561)               | 2.2% (9/413)               | 1.277   | 0.258   |
| Amoxicillin/Clavulanate | 16.1% (102/633) | 13.1% (45/344) | 19.7% (57/289) | 5.125 | 0.024 |
| Piperacillin/Fosfomycin | 3.1% (30/971) | 1.6% (9/558) | 5.1% (21/413) | 9.510 | 0.002 |
| Ampicillin/Sulbactam | 56.1% (143/255) | 70.0% (105/150) | 36.2% (38/105) | 28.665 | <0.001 |
| Trimethoprim/Sulfamethoxazole | 51.1% (499/976) | 56.9% (320/562) | 43.2% (179/414) | 17.914 | <0.001 |
| Characteristics                                      | ESBL Negative (n=408) | ESBL Positive (n=555) | Univariate Analysis | Multivariate Analysis |
|------------------------------------------------------|-----------------------|-----------------------|---------------------|----------------------|
|                                                      |                       |                       | **P value** | **OR (95% CI)** | **P value** | **OR (95% CI)** |
| Female                                               | 239                   | 282                   | 0.017    | 0.730 (0.564–0.945) | Not selected | Not selected   |
| Median age (IQR)                                     | 61 (52–72)            | 61 (50–71)            | 0.317    | 0.996 (0.987–1.004) | -          | -              |
| Pre-existing medical conditions                      |                       |                       |          |                  |            |                |
| Hypertension                                         | 139                   | 181                   | 0.636    | 0.937 (0.714–1.228) | -          | -              |
| Diabetes                                             | 85                    | 88                    | 0.047    | 0.716 (0.515–0.996) | Not selected | Not selected   |
| Biliary tract infection                              | 100                   | 194                   | 0.001    | 1.655 (1.244–2.201) | <0.001     | 1.798 (1.334–2.425) |
| Pancreatitis                                         | 17                    | 17                    | 0.363    | 0.728 (0.367–1.443) | -          | -              |
| Liver disease                                        | 56                    | 79                    | 0.822    | 1.043 (0.721–1.509) | -          | -              |
| Gastrointestinal disease                             | 41                    | 55                    | 0.943    | 0.985 (0.643–1.508) | -          | -              |
| Urinary tract obstructive disease                   | 37                    | 83                    | 0.007    | 1.763 (1.169–2.658) | 0.001      | 2.106 (1.366–3.248) |
| Chronic kidney disease                               | 26                    | 35                    | 0.967    | 0.989 (0.585–1.671) | -          | -              |
| Leukemia                                             | 17                    | 13                    | 0.112    | 0.552 (0.265–1.149) | -          | -              |
| Solid tumor                                          | 104                   | 124                   | 0.256    | 0.841 (0.624–1.134) | -          | -              |
| Invasive procedure or device                         |                       |                       |          |                  |            |                |
| Central venous catheterization                      | 49                    | 80                    | 0.280    | 1.234 (0.843–1.806) | -          | -              |
| Urinary catheterization                             | 59                    | 101                   | 0.124    | 1.316 (0.927–1.868) | -          | -              |
| Gastrointestinal catheterization                    | 18                    | 47                    | 0.015    | 2.005 (1.146–3.506) | Not selected | Not selected   |
| Surgery within 3 months                              | 100                   | 190                   | 0.001    | 1.603 (1.205–2.134) | 0.002      | 1.591 (1.178–2.147) |
| Hospitalization within 3 months                     | 138                   | 278                   | <0.001   | 1.964 (1.508–2.557) | <0.001     | 2.075 (1.579–2.725) |
| Nosocomial infection                                 | 193                   | 288                   | 0.160    | 1.202 (0.930–1.552) | -          | -              |
| ICU admission                                        | 43                    | 91                    | 0.010    | 1.665 (1.130–2.453) | 0.011      | 1.684 (1.124–2.522) |
| Antimicrobial exposure within 30 days                |                       |                       |          |                  |            |                |
| Penicillin                                           | 9                     | 12                    | 0.963    | 0.980 (0.409–2.348) | -          | -              |
| Cephalosporin                                        | 8                     | 36                    | 0.002    | 3.468 (1.594–7.544) | 0.006      | 3.097 (1.392–6.891) |
| BLICs                                                | 31                    | 67                    | 0.024    | 1.670 (1.068–2.609) | Not selected | Not selected   |
| Fluoroquinolone                                      | 19                    | 33                    | 0.383    | 1.294 (0.725–2.311) | -          | -              |
| Carbapenem                                           | 6                     | 11                    | 0.553    | 1.355 (0.497–3.694) | -          | -              |

encoding quinolones, aminoglycosides and trimethoprim/sulfamethoxazole.12

Our study found that BTI was an independent risk factor for ESBL-EC BSI. Gut luminal bile has anti-inflammatory, endotoxin-binding, bacteriostatic, mucosal-trophic, epithelial-tight-junction-maintaining, and gut motility-regulating effects.13 BTI could lead to the deficiency of intestinal bile, resulting in excessive growth of intestinal flora, translocation of microflora and entry of endotoxin into the portal vein and systemic circulatory system.14,15 Studies also found that intestinal microbiota imbalance led to a large number of pathogen colonization, which caused the spread of drug resistance genes (including genes encoding ESBL).16,17 This pathway is likely the major reason for the increase of ESBL caused by BTI. Besides, most of these patients underwent biliary stent implantation. Invasive treatment leads to damage to the intestinal mucosal epithelium and results in bacterial translocation, which may also be another reason for the increase of ESBL.18 Obstructive diseases of the urinary system were also an important risk factor for ESBL-EC BSI. Urinary tract infections are the major sources of bacteremia, and E. coli is the most common bacteria isolated from urine specimens.19,20 In recent years, antibiotic-resistant E. coli in urinary tract infections is increasing, predominantly ESBL-EC.21 Therefore, we need to be highly vigilant for serious bloodstream infections caused by urinary tract infection bacteria entering the bloodstream.

Exposure to cephalosporins, hospitalization and surgical history was closely related to the production of ESBL, which suggests that recent medical treatment behavior may accelerate the spread of ESBL. We speculated that the spread of ESBL was closely related to the relevant medical institutions, and many asymptomatic patients may become carriers and disseminators of ESBL for the related health-care behavior. ICU admission was also a risk factor for ESBL-EC.
Table 3 Analysis of Risk Factors for 30-Day Mortality in Patients with *Escherichia coli* Bloodstream Infections

| Characteristics                              | Survival (n=795) | Nonsurvival (n=79) | Multivariate Analysis |
|----------------------------------------------|------------------|-------------------|-----------------------|
| aCCI score > 2                              | 623              | 71                | P value | OR (95% CI) |
| ESBL-producing *E. coli*                    | 463              | 45                | 0.016   | 2.453 (1.179–5.103) |
| Central venous catheterization              | 101              | 13                | Not selected |        |
| Urinary catheterization                     | 120              | 21                | 0.070   | Not selected |
| Gastrointestinal catheterization            | 47               | 11                | 0.004   | 2.525 (1.333–4.782) |
| Nosocomial infection                        | 391              | 41                | 0.846   | Not selected |
| Appropriate empirical antibiotic therapy    | 715              | 72                | 0.840   | Not selected |

BSI. We speculated that patients admitted to ICU use a variety of antibiotics for a long time, which caused the increase in the horizontal transfer of ESBL genes.

According to multivariate analysis, aCCI > 2 and gastrointestinal catheterization were relatedly associated with day 30 mortality. Research demonstrated that enteral nutrition significantly reduced the infection rate and mortality of patients compared with parenteral nutrition. Our data showed that most of the patients who underwent gastrointestinal catheterization were in critical condition. Therefore, it is reasonable to assume that the increased mortality in patients with gastrointestinal catheterization was more likely associated with their own underlying diseases. The production of ESBL did not affect the 30-day mortality of patients.

Many studies confirmed that carbapenem was effective or an optimal scheme for treating ESBL-EC. However, carbapenem resistance has increased gradually. Studies found that BLICs, especially novel BLICs, have shown excellent in vitro susceptibilities to ESBL-EC. Treatment of ESBL-producing strains with BLICs could alleviate potential antibiotic selective pressure and resistance of carbapenems. We estimated the single antibiotic regimen with BLICs or carbapenems in 30-day mortality. Among the patients isolated with ESBL-positive strains, a total of 294 patients received BLICs or carbapenems alone, of which 214 received BLICs and others received carbapenems. In SOFA score < 2 group and SOFA score ≥ 2 group, the mortality rate of patients receiving BLICs all showed lower than that of patients received carbapenems (Figure 2). BLICs had preferable effect to mild-severity patients. But it does not means carbapenems were ineffective. In fact, carbapenems were part of antibiotic therapy for severe gram-negative infections and might therefore just indicate patients with a higher grade of severity of illness and, thus, increased mortality (Table 4). Furthermore, our study was a single-center retrospective analysis, which means that selection bias and sample size would impact our results.

![Figure 2](https://example.com/image.png)

**Figure 2** Kaplan–Meier 30-day survival estimates: (A) patients (SOFA score < 2) treat with carbapenem and BLICs antibiotics (p=0.008); (B) patients (SOFA score ≥ 2) treated with carbapenem and non-carbapenem antibiotics (p=0.044).
Table 4 The Patients Treated with Single Regimens in Different SOFA Score Groups

| SOFA Score | Total | Received BLICs | Received Carbapenems |
|------------|-------|----------------|----------------------|
|            |       | Survival       | Nonsurvival          | Survival       | Nonsurvival          |
| <2         | 85    | 98.5%(64/65)   | 1.5%(1/65)           | 90%(18/20)     | 10%(2/20)            |
| 2–6        | 135   | 95.2%(99/104)  | 4.8%(5/104)          | 96.8%(30/31)   | 3.2%(1/31)           |
| 7–9        | 43    | 90%(27/30)     | 10%(3/30)           | 76.9%(10/13)   | 23.1%(3/13)          |
| ≥10        | 31    | 86.7%(13/15)   | 13.3%(2/15)          | 62.5%(10/16)   | 37.5%(6/16)          |

In conclusion, this study found that BTI, urinary tract obstructive disease, surgery within 3 months, hospitalization within 3 months, ICU admission and exposure to cephalosporin were independent risk factors of ESBL-EC BSI. In patients with BSI of E.coli, aCCl score >2 and indwelling gastrointestinal tube were important risk factors for 30-day mortality. Moreover, BLICs could recommended to treat mild-severity patients.

Data Sharing Statement
All the data are from the database of the second affiliated Hospital of Nanchang University. The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

Ethics Statement
Informed consent was acquired from each participant included in the study. This study was approved by the Second Affiliated Hospital of Nanchang University Medical Research Ethics Committee (No. Review-2011-011).

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Disclosure
The authors have no conflicts of interest to disclose.

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