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Extended-spectrum β-lactamase-producing *E. coli* septicemia among rectal carriers in the ICU

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Abstract

The aim of this study was to identify risk factors for extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* (*E coli*) bloodstream infection (BSI) among carriers hospitalized between March 2011 and June 2016 at the ICU of the West China Hospital.

The cases were patients with at least 1 episode of ESBL-producing *E coli* BSI within 1 week after a positive rectal swab. Controls were selected randomly 1:2 among ESBL-producing *E coli* rectal carriers who did not develop BSI.

Among 19,429 ICU patients, 9015 (46.4%) had a positive rectal swab for ESBL-producing *E coli*. Of them, 42 (0.5%) were diagnosed with ESBL-producing *E coli* BSI. The in-hospital mortality was higher for the BSI patients compared with controls (19.1% vs. 6.0%, $P = .031$). In the past 72 hours, patients in case group were more likely to use penicillin (odds ratio [OR] = 12.076; 95% confidence interval [CI]: 1.397–104.251, $P = .02$), cephalosporin (OR = 6.900; 95% CI: 1.493–31.852, $P = .01$), and carbapenem (OR = 5.422; 95% CI: 1.228–23.907, $P = .03$) as compared to patients in control group. Also, when compared to patients in control group, patients in case group were likely to stay for a longer time in ICU before positive rectal swab test (OR = 1.041, 95% CI: 1.009–1.075, $P = .01$) and have higher maximum body temperature before positive rectal swab (OR = 8.014; 95% CI: 2.408–26.620, $P = .001$).

Bacteremia owing to ESBL-producing *E coli* was associated with high antimicrobial exposure, hospital stay, and maximum body temperature.

Abbreviations: BC = blood culture, BSI = bloodstream infection, CI = confidence interval, *E coli* = *Escherichia coli*, ESBL = extended-spectrum β-lactamase, ICU = intensive care unit, IQR = interquartile range, ROC = receiver-operating characteristics, UCs = urine cultures.

Keywords: Bacteremia, BSI, ESBL-producing *E coli*, rectal

1. Introduction

Extended-spectrum β-lactamase (ESBL) bacteria are rapidly emerging worldwide.[1–6] Recent reports from the CHINET surveillance network for bacterial resistance showed that the prevalence of ESBL-producing *Escherichia coli* (*E coli*) was 53.6% in China,[7] posing a serious threat to public health.[8] ESBL-producing *E coli* is resistant to penicillin, cephalosporin, and monobactam, and is also commonly resistant to fluoroquinolone and cotrimoxazole.[9–11]

E coli is one of the most common ESBL-producing species and the common most cause of bloodstream infection (BSI).[12–14] The patients admitted to the intensive care unit (ICU) are in a poor health condition and often they will have lowered immunity. Therefore, this results in high rates of nosocomial infections.[15] ESBL-producing *E coli* BSIs are associated with higher mortality, longer ICU stay, and higher costs compared with BSI caused by non-ESBL-producing bacteria.[16,17]

There are 2 steps in the development of BSI (colonization and infection) and few clinical studies have investigated the 2 steps separately, leaving obscure the infection step of already colonized patients.[18] Unfortunately, the epidemiology of ESBL-producing *E coli* is complex because it is difficult to identify bacterial colonization before infection. Indeed, most previous studies used non-ESBL-producing *E coli* carriers as controls.[19–21] Therefore, identifying patients with ESBL-producing *E coli* as well as the factors associated with infection are of paramount importance for the patients and physicians.[19–21]

There are some studies about ESBL-producing *E coli* colonization and risk factors for ESBL-producing *E coli* BSI[8–11], but the factors associated with ESBL-producing *E coli* BSI among rectal ESBL-producing *E coli* carriers in the ICU are poorly known. Therefore, this study aimed to identify risk factors for ESBL-producing *E coli* BSI among rectal ESBL-producing *E coli* carriers in the ICU. Rectal carriers were selected because rectal cultures are routinely used at our institution for patients in the ICU. This study may provide physicians with useful information to improve therapeutic approaches and improve the control rate of nosocomial infections in the ICU.

2. Materials and methods

2.1. Study design and population

This was a retrospective nested case-control study performed at the ICU of West China Hospital, a 4800-bed tertiary teaching

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hospital that has a 220-bed adult ICU and a 20-bed pediatric ICU. Both adult and pediatric patients hospitalized from March 2011 to June 2016 and with a ESBL-producing *E coli*-positive rectal swab were included. Before receiving the results of drug sensitivity, the patients were treated based on the physicians' experience. The treatment approaches were then changed according to the results of antibiotics sensitivity.

The cases consisted of patients with at least 1 episode of ESBL-producing *E coli* BSI within 1 week after a positive rectal swab (which is a routine test at our ICU), to reduce the probability that the infection came from a different source than the rectum. Each BSI patient was included only once at the time of first ESBL-producing *E coli* isolation from BCs. Control samples were selected randomly at a ratio 1:2 among ESBL-producing *E coli* rectal carriers who did not develop BSI. The 2 controls were selected with a time window of ±1 week from each case of BSI to minimize seasonal variations of *E coli* infection.[22]

This study was approved by the review board of the West China Hospital, Sichuan University. All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The need for individual consent was waived by the committee because of the retrospective nature of the study.

2.2. Data collection

Data were collected from the Hospital Information System, an electronic medical chart system. Demographic data, underlying condition, body temperature for 1 week before positive rectal swab, ICU stay before the studied event period, history of hospitalization within the last 3 months, blood analysis within 2 weeks before the studied event period, previous antimicrobial exposure (within 3 months and 72 hours before the positive rectal swab), antibiotics prescription during the studied event period, invasive procedures or devices (including central vein catheterization, urinary catheter, gastric catheter, tracheotomy, invasive ventilation, surgery, thoracentesis, and abdominocentesis) before the studied event period, and in-hospital mortality were analyzed.

2.3. Definitions

Rectal carriers were defined as patients with ESBL-producing *E coli* isolated from a rectal swab but without symptoms and signs of invasive infection. ESBL-producing *E coli* BSI was defined as BSI documented by at least one BC positive for an ESBL-producing *E coli* strain and clinical signs of systemic inflammatory response syndrome.[23] The studied event period was considered from the first positive rectal swab to death or hospital discharge. Antibiotics use' density, as defined by the World Health Organization, was calculated as the value of number of patients using antibiotics per 100 days-person.

2.4. Microbiology

Rectal swabs were inoculated on a chromogenic agar plate (ChromID ESBL plate; bioMerieux, Marcy l'Étoile, France) containing cefpodoxime as a selective agent. BCs were incubated using the BacTAlert automated system (Alert 3D; BioMerieux, Hazelwood, MO). The Vitek 2 Compact automated system (BioMerieux, Hazelwood, MO) was used for the identification of *E coli* isolates.

2.5. Statistical analysis

Continuous data were expressed as mean ± standard deviation if normally distributed, or as median and interparticle ranges (IQR) if non-normally distributed, based on the Kolmogorov-Smirnov test. The *t* test or the Mann-Whitney *U* test was used to analyze the continuous variables, as appropriate, whereas the χ^2 or the Fisher exact test was used for categorical variables. Binary logistic regression (backward conditional) was used to select the factors associated with BSI, and the enter method was used to correct the final model. Variables with *P* values $<.05$ in the univariate analyses were included in the multivariate model. The goodness of fit of the regression equation was assessed by the Hosmer-Lemeshow test. ROC curves were used to verify whether the regression model could discriminate low- versus high-risk BSI patients among ESBL-producing *E coli* carriers. Statistical analysis was performed using SPSS 21.0 (IBM, Armonk, NY). Two-sided *P* values $<.05$ were considered statistically significant.

2.6. Data availability

All data generated or analyzed during this study are included in this article.

3. Results

3.1. Characteristics of the patients

During the study period, 19,429 ICU patients were screened for multidrug-resistant bacteria. Among them, 9015 (46.4%) had a positive rectal swab for ESBL-producing *E coli*. Of them, 42 (0.5%) were diagnosed with ESBL-producing *E coli* BSI. The BSI patients were compared with 84 randomly selected ESBL-producing *E coli* rectal carriers without documented BSI during hospitalization (Fig. 1).

In the BSI group, blood culture (BC) revealed that 17 (40.5%) patients had multipathogen infection in addition to ESBL-producing *E coli*, including non-ESBL-producing *E coli* bacteria (n=13, 31.0%), fungus (n=2, 4.8%), and non-ESBL-producing *E coli* bacteria concomitant with fungus (n=2, 4.8%).

Table 1 shows that there were no significant differences for age, sex, previous 3-month hospitalization, and previous 2-week blood analysis between the patients with BSI and controls (all $P>.05$). BSI patients had higher maximum body temperature (39.7 ± 0.8 vs. 38.4 ± 0.8°C, $P<.001$) 1 week before positive rectal swab, longer stay in the ICU before positive rectal swab test (median of 24 vs. 8.5 days, $P=.007$), and higher frequency of urinary infection (33.3% vs. 16.7%, $P=.034$). Among the patients with urinary infection, the BSI group included 5 patients with positive *E coli* urine cultures (UCs) within 1 week before positive BC, and one had a positive *E coli* UC 5 months after BSI.

3.2. Mortality

The in-hospital mortality rate was higher for the patients with BSI compared to controls (19.1% vs. 6.0%, $P=.031$) (Table 1).

3.3. Antibiotics exposure

Patients with ESBL-producing *E coli* BSI had been more frequently exposed to previous β-lactam antibiotics than controls ($P=.001$ for previous 3 months and $P=.002$ for previous 72 hours). After ESBL-producing *E coli* BSI diagnosis, 35 of 42 (83.3%) patients were administrated carbapenem for therapy

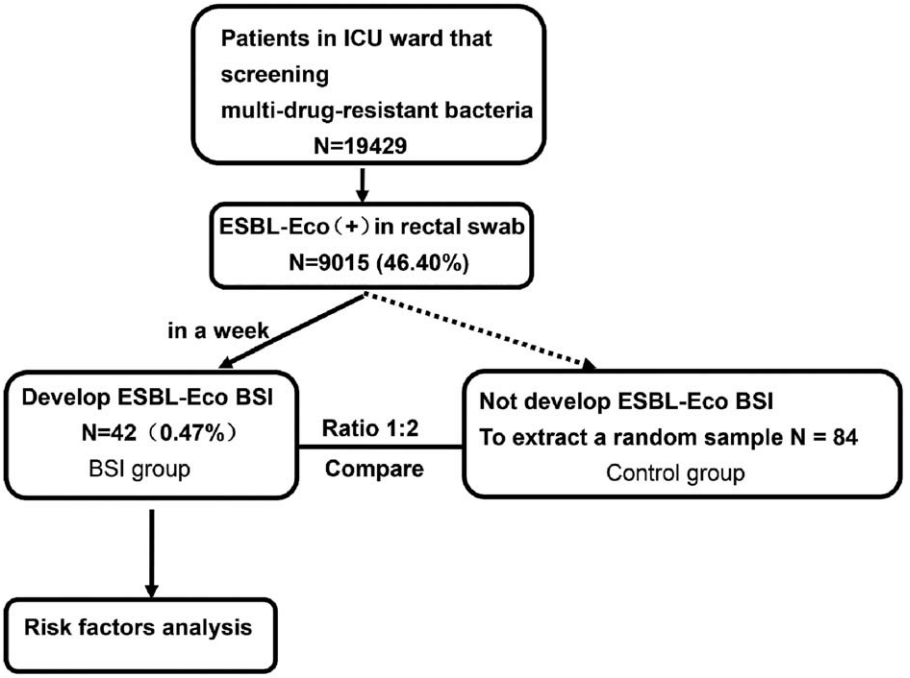

Figure 1. Patients flowchart.

Table 1

Characteristics of the patients.

	BSI N = 42	Controls N = 84	*P*
Demographic data			
Age[†], y, median (IQR)	48 (60)	43 (56)	.736
Males[‡], n (%)	26 (61.9)	55 (65.5)	.693
Female[‡], n (%)	16 (38.1)	29 (34.5)	
Maximum body temperature[§] (°C), mean ± SD	39.7 ± 0.8	38.4 ± 0.8	<.001*
APACHE II Score[†], median (IQR)	23.5 (10)	22 (13)	.665
Previous ICU stay before positive rectal culture[†], days, median (IQR)	24.0 (30.0)	8.5 (12.3)	.007*
Invasive procedures[‡]	42 (100)	84 (100)	1.000
Immunosuppressive agent use[‡]	12 (28.6)	31 (36.9)	.307
Underlying diseases[‡], n (%)			
Solid tumor	3 (7.1)	6 (7.1)	.654
Respiratory diseases	28 (66.7)	51 (60.7)	.515
Circulatory diseases	9 (21.4)	25 (29.8)	.321
Digestive diseases (except pancreatitis)	20 (47.6)	38 (45.2)	.800
Pancreatitis	9 (21.4)	13 (15.5)	.407
Urinary diseases	14 (33.3)	14 (16.7)	.034*
Nervous diseases	3 (7.1)	2 (2.4)	.332
Trauma	4 (9.5)	5 (6.0)	.480
Post-operation[‡]	10 (23.8)	12 (14.3)	.184
Previous hospitalization: 3 mo[‡], n (%)			
Yes	18 (42.9)	42 (50.0)	.298
No	12 (28.6)	28 (33.3)	
Unknown	12 (28.6)	14 (16.7)	
Previous blood analysis, 2 weeks[‡], median (IQR)			
WBC (10^9 cells/L)	9.1 (7.2)	10.4 (6.8)	.567
Neutrophil % (percentage of WBC)	84.1 (18.2)	82.9 (21.2)	.737
CRP, mg/L	79.9 (151.9)	76.0 (155.3)	.231
PCT, ng/mL	2.4 (23.7)	2.5 (8.8)	.437
IL-6, pg/mL	132.9 (252.6)	82.44 (247.4)	.277
Death[‡]	8 (19.1)	5 (6.0)	.031*

CRP = C-reactive protein, ICU = intensive care unit, IL-6 = interleukin-6, IQR = interquartile range, PCT = procalcitonin, WBC = white blood cell.

* $P < .05$.

† Mann-Whitney *U* test;

‡ χ^2 or the Fisher exact test.

§ *t* Test.

Table 2

Antibiotic use between the case and control groups[†].

	BSI N = 42	Controls N = 84	*P*
Previous antibiotic use: 3 mo, n (%)			
Total number of users	30 (71.4)	33 (39. 3)	.001[*]
Penicillin	11 (26.2)	5 (6.0)	.001[*]
Cephalosporin	14 (33.3)	9 (10.7)	.002[*]
Fluoroquinolone	2 (4.8)	5 (6.0)	1.000
Carbapenem	16 (38.1)	6 (7.1)	<.001[*]
Others	14 (33.3)	24 (35.7)	.583
Previous antibiotic use: 72 h, n (%)			
Total number of users	27 (64.3)	29 (34.5)	.002[*]
Penicillin	9 (21.4)	4 (4.8)	.010[*]
Cephalosporin	14 (33.3)	12 (14.3)	.013[*]
Fluoroquinolone	5 (11.9)	3 (3.6)	.116
Carbapenem	10 (23.8)	9 (10.7)	.053
Aminoglycoside	0 (0.0)	1 (1.2)	1.000
Glycopeptide	5 (11.9)	3 (3.6)	.116
Others	4 (9.5)	4 (4.8)	.439
Antibiotic use during the studied event period, n (%)			
Total number of users	42 (100)	72 (85.7)	.008[*]
Penicillin	20 (47.6)	37 (44.1)	.704
Cephalosporin	22 (52.4)	41 (48.8)	.705
Fluoroquinolone	8 (19.1)	19 (22.6)	.645
Carbapenem	35 (83.3)	29 (34.5)	<.001[*]
Aminoglycoside	4 (9.5)	2 (2.4)	.095
Glycopeptide	18 (42.9)	17 (20.2)	.008[*]
Others	10 (2.8)	23 (27. 4)	.667

[*] $P < .05$. Statistical Analysis,
[†] χ^2 or the Fisher exact test.

since 38 of 42 (90.5%) ESBL *E coli* strains from case group patients were sensitive to carbapenems (Table 2). Within the 72 hours before positive rectal swab and during their hospitalization for BSI, the antibiotics use' density of the patients with BSI was higher than in controls (Fig. 2).

3.4. Multivariate analysis

The factors with *P* values <.05 in univariate analyses including maximum body temperature, urinary diseases, previous ICU stay, previous 3 months' penicillins use, previous 3 months' cephalosporins use, previous 3 months' carbapenems use, previous 72 hours' penicillins use, previous 72 hours' cephalosporins use, previous 72 hours' carbapenems were added into the multivariate logistic regression analysis. As compared to patients in control group, patients in case group were more likely to use penicillin (odds ratio [OR] = 12.076; 95% confidence interval [CI]: 1.397–104.251, $P = .02$), cephalosporin (OR = 6.900; 95% CI: 1.493–31.852, $P = .01$), and carbapenem (OR = 5.422; 95% CI: 1.228–23.907, $P = .03$) in the past 72 hours. Also, patients in case group were likely to stay for a longer time in ICU before positive rectal swab test (OR = 1.041, 95% CI: 1.009–1.075, $P = .01$) and have higher maximum body temperature before positive rectal swab (OR = 8.014; 95% CI: 2.408–26.620, $P = .001$) when compared with patients in control group (Table 3). The Hosmer-Lemeshow test ($P = .375$) showed that the model displayed acceptable goodness of fit. The pseudo-R^2 (Nagelkere) was 0.675.

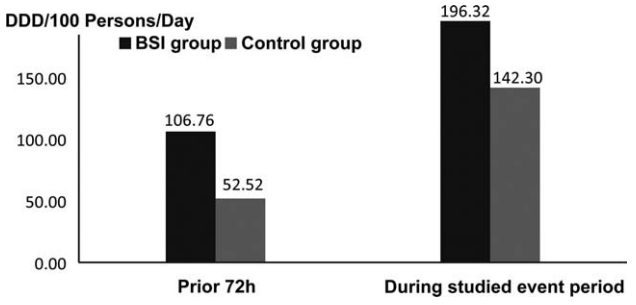

Figure 2. Antibiotics use' density in the previous 72-hour period and during the studied event period between the case and control groups. DDD = defined daily dose, as defined by WHO.

3.5. Receiver-operating characteristic curve analysis

The receiver-operating characteristics (ROC) curve analysis suggested that the predictive value of the regression model to discriminate low-risk from high-risk patients had an area under the curve of 0.933 (95% CI: 0.882–0.983, $P < .0001$).

4. Discussion

The factors associated with ESBL-producing *E coli* BSI among ESBL-producing *E coli* rectal carriers in the ICU are poorly known. The aim of the present study was to identify factors associated with ESBL-producing *E coli* BSI among ESBL-producing *E coli* carriers in the ICU. The use of β-lactam antibiotics and high body temperature were independently associated with BSI occurrence in ESBL-producing *E coli* rectal carriers. Bacteremia owing to ESBL-producing *E coli* was associated with high mortality rates.

This retrospective nested case-control study reports for the first time in a Chinese population that 0.5% of the ESBL-producing *E coli* rectal carriers developed BSI. This rate is smaller than that of a Spanish study that showed a rate of ESBL-producing *E coli* BSI of 3.5%.[24] The in-hospital mortality rate of patients with ESBL-producing *E coli* BSI among ESBL-producing *E coli* rectal carriers in the ICU was 19.1%, which was much higher than the mortality reported by a previous study on other ESBL-producing bacteria (9.6%),[25] but lower than that of the Spanish study, which showed a mortality of 50.9% for ESBL-producing *E coli* and ESBL-producing *Klebsiella pneumoniae*, taken together.[24]

In the present study, the subjects were ESBL-producing *E coli* rectal carriers hospitalized in the ICU and were therefore high-risk patients because of their severe condition and compromised immune status. Previous studies showed that procalcitonin (PCT) levels had high predictive value for bacteremia,[26,27] but this factor showed no association with BSI in the present study. A meta-analysis suggested that the diagnostic performance of PCT for bacteremia in emergency departments is moderate,[28] possibly because PCT is also associated with non-infectious diseases.[29,30]

Table 3

Multivariate logistic regression analysis.

	OR	95% CI	*P*
Previous penicillins use: 72 h	12.076	1.397–104.251	.024
Previous cephalosporins use: 72 h	6.900	1.493–31.852	.013
Previous carbapenems use: 72 h	5.422	1.228–23.907	.026
Previous ICU stay	1.041	1.009–1.075	.012
Maximum body temperature	8.014	2.408–26.620	.001

CI = confidence interval, ICU = intensive care unit, OR = odds ratio.

In the present study, among all ESBL-producing *E coli* rectal carriers, the antibiotics use' density of patients with BSI was much higher than that in non-BSI patients. In addition, BSI patients among ESBL-producing *E coli* rectal carriers in case group are more likely to use β-lactam antibiotics in the past 72 hours as compared to patients in control group. These results are supported by a Spanish study that showed that the previous use (within 3 months) of >2 different classes of antimicrobials was associated with a higher risk of BSI by ESBL-producing *E coli*.[24] Another Spanish study showed that a previous use of cephalosporin and carbapenem was associated with ESBL-producing *E coli* BSI.[31] Rodriguez-Bano et al[32] showed that ESBL-related BSI patients were more exposed to β-lactam antibiotics or fluoroquinolone. Tumbarello et al[33] showed that previous exposure to antimicrobials in general was associated to ESBL-producing strains. Therefore, we can hypothesize that under the pressure of large-spectrum β-lactam antibiotics and antibiotics in general, enteric normal flora becomes imbalanced and may cause ESBL-producing *E coli* BSI. There is a possibility that β-lactam antibiotics were not able to kill ESBL-producing *E coli* effectively, but they might have killed other β-lactam-sensitive bacteria. Consequently, the dysbiosis resulted in ESBL-producing *E coli* entering the blood stream and causing infection. Nevertheless, additional studies are necessary to address this point. In addition, it must be stressed that the different classification systems of antibiotics use may lead to different results and risk factors, as previously suggested.[34]

The factors observed in the present study were consistent with some published studies of BSI caused by ESBL-producing bacteria.[33,35–38] Nevertheless, the present study focused on factors of ESBL-producing *E coli* infection among patients already colonized by the bacteria, while many previous studies focused on the colonization step, which does not necessarily progress to infection. Previous studies reported that the presence of invasive devices, older age, and longer stay in hospital were risk factors for BSI caused by ESBL-producing bacteria,[37–39] but the presence of invasive devices and older age were not found to be associated with BSI in the present study. At the West China Hospital, invasive devices are routinely used in practically all patients in the ICU wards and this factor could not be analyzed. Regarding age and hospital stay, all patients in the ICU are usually weak and with low immunity, not only the oldest ones. In addition, all ICU patients are with severe conditions at the start. Therefore, there may be some differences in BSI occurrence between ICU and general wards. On the other hand, the present study showed that ICU stay before positive rectal swab was associated with BSI caused by ESBL-producing bacteria, as supported by previous studies, albeit in various bacteria, patient populations, and sites of infections (blood, pneumonia, among others).[37–41] Longer hospital stay increases the likelihood of being exposed to contamination and the risk of infection.

In the present study, 5 patients with urinary infection owing to *E coli* ultimately developed ESBL-producing *E coli* BSI (11.9% of the patients with ESBL-producing *E coli* BSI), but this number was too small to perform any reliable statistical analysis. Nevertheless, urinary infection could be a risk factor for BSI, as previously observed.[42] As is well known, high temperature is a consequence of infections and a mean to combat them. In the present study, high temperature was independently associated with ESBL-producing *E coli* BSI, but the retrospective nature of the study prevents any case-to-effect analysis.

There are some limitations to the present retrospective study. First, the number of BSI patients was small, representing only a small proportion of all ESBL-producing *E coli* carriers. These results should be validated with prospective multi-center studies. Second, antibiotic records may not completely represent the outpatient antibiotics use, antibiotics use in other hospitals, or life-time history of antibiotics use, which might bias the data. Third, homology between ESBL-producing *E coli* in the rectum and ESBL-producing *E coli* in the blood was not tested and it is unknown whether BSIs were caused by the same strain of ESBL-producing *E coli*. Fourth, the selection plates for ESBL selection contained cefpodoxime, which has been reported to be a highly efficient screening antibiotic, which could bias the population of bacteria.[43,44] Finally, in some patients, BSI was caused by non-ESBL-producing *E coli* pathogens; whether this was caused by contamination of the samples or weaken state of the patients leading to opportunistic infections warrants further study. Unfortunately, because of the small sample size, reliable subgroup analyses were not possible.

In conclusion, BSI patients among ESBL-producing *E coli* rectal carriers were more likely to use β-lactam antibiotics and had higher body temperature as well as longer hospital stay as compared to the patients in control group. The mortality rates increased when ESBL-producing *E coli* rectal carriers developed bacteremia. A predictive model with these variables may be useful to identify patients at low- versus high risk of ESBL-producing *E coli* BSI and avoid overuse of broad-spectrum antibiotics or pay special attention to the ICU patients who have a high body temperature. Nevertheless, further studies are needed to validate those results.

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