Original Article

Risk factors for bacteremia due to extended-spectrum beta-lactamase-producing *Escherichia coli* in a Turkish hospital

Onur Kaya, Fusun Zeynep Akcam, Ibak Gonen, Onur Unal, Tennure Ceylan

Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey

Abstract

Introduction: Bloodstream infection caused by extended-spectrum beta-lactamase (ESBL)-producing pathogens has become a serious concern worldwide. The purpose of this study was to identify risk factors for bacteremia due to ESBL-producing *Escherichia coli* in a Turkish hospital.

Methodology: We retrospectively reviewed the medical records of patients with *E. coli* bacteremia in a tertiary care centre from January 2007 to October 2011. Data from patients such as demographic features, underlying conditions, and antibiotic exposure were analysed.

Results: A total of 113 patients with bacteremia due to *E. coli* were included and data from patients with ESBL-producing *E. coli* (case patients) were compared to those with non-ESBL-producing *E. coli* (control patients). The frequency of ESBL producers was 38.9% (44/113). Exposure to fluoroquinolones and cephalosporins, history of intra-abdominal surgery intervention, and presence of central venous catheteter and urinary catheteter were more frequently detected among case patients ($P < 0.05$). Independent risk factors for bacteremia due to ESBL-producing *E. coli* were exposure to fluoroquinolones (OR 13.39, 95% CI 1.28-140.03) and cephalosporins (OR 3.48, 95% CI 1.03-11.74).

Conclusions: Previous use of fluoroquinolone and cephalosporin in patients with bacteremia caused by *E. coli* increased the risk for ESBL-producing strains.

Key words: risk factors; *Escherichia coli*; bacteremia; extended-spectrum beta-lactamase

J Infect Dev Ctries 2013; 7(7):507-512. doi:10.3855/jidc.2788

(Received 12 June 2012 – Accepted 19 September 2012)

Introduction

Extended-spectrum beta-lactamases (ESBLs) are a heterogeneus group of enzymes responsible for the resistance of enterobacteria to broad-spectrum beta-lactam antibiotics. These enzymes were first identified in Germany in 1983 [1]. During the past two decades, antimicrobial-resistant strains producing ESBLs have emerged among the Enterobacteriaceae, especially among *Escherichia coli* and *Klebsiella pneumoniae* [2]. ESBLs inactivate cephalosporins, monobactams and penicillins, while ESBL-producing microorganisms are also often resistant to fluoroquinolones and aminoglycosides [2,3]. Infections caused by ESBL-producing microorganisms have limited treatment options, and when treated with inappropriate empirical therapy they are associated with increased mortality [4]. Therefore, identification of risk factors that are predictive of resistance to empirically prescribed antimicrobials should facilitate attempts to define more effective management strategies for serious infections [5]. We aimed to evaluate the risk factors for ESBL-producing bacteremia and the impact of ESBL production on outcome in patients with *E. coli* bacteremia.

Methodology

This retrospective study was conducted at Suleyman Demirel University Research Hospital, Isparta, which is a 550-bed medical centre facility located in Southern Turkey. Hospital records were searched to identify all adult inpatients ($\geq$ 18 years old) diagnosed with bloodstream infection caused by ESBL-producing and non-ESBL-producing *E. coli* strains between January 2007 and October 2011. Cases of bloodstream infections caused by ESBL-positive/negative *E. coli* in at least one blood culture specimen from a patient with systemic inflammatory response syndrome (*e.g.*, fever, tachycardia, tachypnea, and leukocytosis) were considered. Each patient was included as a case patient only once. The date of the first positive blood culture was regarded as the date of bacteremia onset. If *E. coli* strains were

isolated on multiple occasions, only the first episode of infection was considered. Controls were identified among hospitalized patients with bloodstream infection who were infected with ESBL-negative *E. coli* during the same period. Antimicrobial susceptibility testing and ESBL confirmatory testing were performed using the disk diffusion method following the recommendations of the Clinical and Laboratory Standards Institute [6]. Hospital-onset bacteremia was considered when the infection occurred more than 48 hours after admission to the hospital, while community-onset bacteremia was defined as infection that occurred less than 48 hours after admission to the hospital. Data obtained included age, sex, underlying conditions, primary source of infection, immunosuppressive treatments, presence of central venous catheteter, presence of urinary catheter, intra-abdominal operation and/or urinary interventions performed within 90 days prior to the episode of bacteremia, antibiotic use, and another hospitalisation within 90 days prior to the episode of bacteremia, intensive care unit stay, and survival.

Statistically analyses were performed using SPSS 15.0 (SPSS, Chicago, USA). All P-values were two-tailed and a P-value of < 0.05 was considered statistically significant. The chi-square test was used to compare dichotomous data unless the cell size was < 5, in which case Fisher's exact test was used. Univariate and multivariate logistic regression (stepwise regression) analyses were used to compare matched cases and controls. Variables found to be significant on univariate analysis were included in the multivariate model. Odds ratios and their 95% confidence intervals were calculated.

The study protocol was approved by the ethics committee of the Suleyman Demirel University, Faculty of Medicine.

Results

During the study period, 113 adult inpatients had bloodstream infection due to *E. coli*. The study included 58 male and 55 female subjects. The most common underlying diseases were solid tumours (n = 35; 30.9%), followed by diabetes mellitus (n = 27; 23.89%) and chronic renal failure (n = 17, 15.04%). The frequency of ESBL producers was 38.9% (44/113). Seventeen patients with bacteremia due to ESBL-producing *E. coli* had community-onset bacteremia (17/44; 38.6%). No significant differences between community- and hospital-onset bacteremia due to ESBL-producing *E. coli* were found in all parameters such as gender, age, underlying diseases and conditions, mortality rate, site of infection, urinary catheter, and prior to antibiotic use in 90 days ($p > 0.05$) (Table 1). Mortality rates of both groups (community-onset and hospital-onset ESBL-producing *E. coli* bacteremia) were similar. The source of most infections of ESBL-producing *E. coli* bacteremia was the intra-abdominal region (n = 18; 40.9%), followed by the urinary tract (n = 13; 29.5%).

Univariate analysis revealed that significant factors associated with bacteremia due to ESBL-producing *E. coli* were presence of urinary catheter, presence of central venous catheter, intra-abdominal surgery within 90 days, prior cephalosporin use in 90 days, and prior fluoroquinolone use in 90 days ($p < 0.05$). Although the mortality rate of ESBL-producing *E. coli* bacteremia group was higher than that of the ESBL-negative *E. coli* bacteremia group, no significant difference was found (Table 2).

Multivariate analysis using a logistic regression model showed that fluoroquinolone and cephalosporin exposure within 90 days were the significant independent factors associated with ESBL-producing *E. coli* bacteremia ($p < 0.05$) (Table 3).

Discussion

Bloodstream infections due to Gram-negative pathogens may be associated with high mortality [7]; therefore, treatment of these infections is important. On the other hand, treatment of infections due to resistant microorganism strains may be more difficult. Clinicians must decide the appropriate antibiotic for the patient; thus determination of these risk factors contributes to empiric antimicrobial treatments for life-threatening infections. In this study, we aimed to identify risk factors for ESBL-producing microorganisms in hospitalized patients with bacteremia.

The source of hospital-onset Gram-negative bacteremia is usually urinary tract infections. Although our results demonstrate that most common infections in hospital-onset ESBL-producing *E. coli* bacteremia is intra-abdominal infection, this was not statistically significant compared to community-onset bacteremia ($p > 0.05$). This situation may be explained by the fact that the majority of cases in both of groups had undergone an intra-abdominal surgery. The source of bacteremia in nearly half of the cases in the community-onset bacteremia group was the urinary tract. Furthermore, the most detected primary infection site was the urinary tract in the ESBL-negative *E. coli* group, whereas the ESBL-producing *E. coli* group involved the intra-abdominal site.

Table 1. Comparison of patients' characteristics with community-onset and hospital-onset bacteremia due to ESBL-producing *E. coli*

	All ESBL (+) *E. coli* (n = 44)	**Community-onset bacteremia (n = 17)**	**Hospital-onset bacteremia (n = 27)**	**p-value***
Male	24	9 (52.9%)	15 (55.6)	0.865
Age		69.17	65.51	0.655
DM	14	7 (41.2%)	7 (25.9%)	0.290
CRF	6	3 (17.6%)	3 (11.1%)	0.662
Hemodialysis	2	1 (5.9%)	1 (3.7%)	1.000
Hematological malignancy	2	2 (11.8%)	0 (0.0%)	0.144
Solid tumour	15	4 (23.5%)	11 (40.7%)	0.241
CLD	4	3 (17.6%)	1 (3.7%)	0.282
COPD	5	3 (17.6%)	2 (7.4%)	0.359
Immunsuppresive treatment	2	1 (5.9%)	1 (3.7%)	1.000
Corticosteroid treatment	2	0 (0.0%)	2 (7.4%)	0.515
Urinary catheter	29	10 (58.8%)	19 (70.4%)	0.431
Prior use of antibiotic within 90 days**	19	5 (35.7%)	14 (58.3%)	0.179
Prior use of cephalosporin within 90 days	12	3 (23.1%)	9 (40.9%)	0.463
Prior use of fluoroquinolone within 90 days	6	2 (15.4%)	4 (18.2%)	1.000
Mortality	16	6 (35.3%)	10 (37.0%)	0.907
Urinary tract source	13	7 (41.2%)	6 (22.2%)	0.180
Intra-abdominal source	18	6 (35.3%)	12 (44.4%)	0.548

ESBL: extended-spectrum beta-lactamase, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, CRF: chronic renal failure, CLD: chronic liver disease, CVC: central venous catheter, ICU: intensive care unit

*statistically significant at $p < 0.05$

**All antibiotics except for cephalosporin and fluoroquinolone

Fluoroquinolone exposure was found to be independently associated with ESBL-producing *E. coli* bacteremia in the present study (p = 0.032, OR 12.85 95 % CI 1.24-132.75). In a prospective study, the use of beta-lactams or fluoroquinolones was detected as an independent risk factor among hospitalized patients for ESBL-producing strains [8]. Previous retrospective case-control studies have also shown similar results [3,4].

Although elongated intensive care unit stay is commonly a risk factor for nosocomial infections due to multidrug resistant microorganisms such as *Acinetobacter baumannii* and ESBL-producing *Escherichia coli*, our results were not consistent with this [9,10] and may be explained by short duration of stay in intensive care unit by our patients.

In the presented study, hospitalization within 90 days before onset of bacteremia infection was not found to be associated with ESBL production. The emergence of this unusual outcome may be connected to some factors such as antimicrobial chemotherapy, invasive procedures and hospitalization duration in our patients.

Prior use of cephalosporins have been identified as a risk factor for ESBL-producing bacteria as well as fluoroquinolones [3,4,11,12]. Use of cephalosporin was associated with an increased risk of ESBL-producing *E. coli* bacteremia by multivariate analysis in the present study (p = 0.044).

Mortality of bloodstream infections caused by ESBL-producing organisms was higher than that of infections caused by ESBL-negative organisms [13,14]. Mortality rates due to ESBL-producing microorganism were found as about 12.1% to 50.9% in several published reports [1,12,15-17]. In the present study, however, the rate of mortality in the ESBL-producing *E. coli* bacteremia group was higher than that of the ESBL-negative *E. coli* bacteremia group ($p > 0.05$); similar underlying conditions in both groups may be the reason for this observation. However, treatments in both groups were not analyzed.

This study has several limitations, one of which is that prior studies have demonstrated that colonization of ESBL-producing microorganisms is a significant factor associated with bacteremia with ESBL-

Table 2. Characteristic of patients with bacteremia due to ESBL-producing *E. coli* versus non-ESBL-producing *E. coli*

	ESBL (+) *E. coli* bacteremia n = 44	**ESBL (-) *E. coli* bacteremia n = 69**	**OR (95% CI)**	**p-value***
Male	24 (54.5%)	34 (49.3%)	1.23 (0.58-2.64	0.585
Age	66.93 (62.42-71.44)	64.12 (60.65-67.58)		0.319
DM	14 (31.8%)	13 (18.8)	2.01 (0.84-4.82)	0.115
CRF	6 (13.6%)	11 (15.9%)	0.83 (0.28-2.44)	0.738
COPD	5 (11.4%)	4 (5.8%)	2.08 (0.53-8.23)	0.308
CLD	4 (9.1%)	6 (8.7%)	1.05 (0.28-3.95)	1.000
Solid tumour	15 (34.1%)	20 (29.0%)	1.27 (0.56-2.85)	0.567
Hematological malignancy	2 (4.5%)	6 (8.7%)	0.50 (0.10-2.60)	0.480
Hemodialysis	2 (4.5%)	3 (4.3%)	1.05 (0.17-6.53)	1.000
Corticosteroid treatment	2 (4.5%)	5 (7.2%)	0.61 (0.11-3.29)	0.704
Immunsuppressive treatment	2 (4.5%)	11 (15.9)	0.25 (0.05-1.19)	0.064
Urinary catheter	29 (65.9%)	24 (34.8%)	**3. 62 (1.63-8.04)**	**0.001**
CVC	20 (45.5%)	13 (19.4%)	**3.46 (1.48-8.08)**	**0.003**
Hospitalization within 90 days	19 (43.2%)	22 (31.9%)	1.62 (0.74-3.55)	0.223
Intra-abdominal surgery within 90 days	8 (18.2%)	2 (2.9%)	**7.44 (1.50-36.93)**	**0.013**
Urinary intervention within 90 days	8 (18.2%)	6 (8.8%)	2.30 (0.74-7.15)	0.144
ICU stay	12 (27.3%)	12 (17.4%)	1.78 (0.72-4.42)	0.210
Prior use of antibiotic within 90 days**	2 (5.3%)	5 (7.5%)	1.45 (0.27-7.87)	1.000
Prior use of cephalosporin within 90 days	12 (34.3%)	7 (10.6%)	**4.40 (1.54-12.56)**	**0.004**
Prior use of fluoroquinolone within 90 days	6 (17.1%)	1 (1.5%)	**13.45 (1.55-116.82)**	**0.007**
Mortality	16 (36.4%)	19 (27.5%)	1.50 (0.67-3.38)	0.322
Urinary tract source	13 (29.5%)	25 (36.2%)	0.74 (0.33-1.66)	0.463
Intra-abdominal source	18 (40.9%)	20 (29.0%)	1.70 (0.77-3.75)	0.191

ESBL: extended-spectrum beta-lactamase, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, CRF: chronic renal failure, CLD: chronic liver disease,
CVC: central venous catheter, ICU: intensive care unit
*statistically significant at $p < 0.05$
**All antibiotics except for cephalosporin and fluoroquinolone

Table 3. Risk factors on multivariate analysis for bacteremia due to ESBL-producing *E. coli*

Risk Factor	p-value*	OR (95%-CI)
Presence of urinary catheter	0.166	2.34 (0.70-7.76)
Presence of CVC	0.842	1.14 (0.31-4.16)
Intra-abdominal surgery within 90 days	0.067	5.15 (0.89-29.75)
Prior use of cephalosporin within 90 days	**0.044**	**3.48 (1.03-11.74)**
Prior use of fluoroquinolone within 90 days	**0.030**	**13. 39 (1.28-140.03)**

producing isolates. In this retrospective study, we were unable to observe the colonization of ESBL-producing bacteria in the patients' data. The second limitation is that the patients were followed in different clinics; some data was lost for some patients. Therefore, we did not determine these factors to contribute to mortality.

Conclusion

This study showed that community-onset ESBL-producing *E. coli* bacteremia is an important problem for our region. Furthermore, previous uses of fluoroquinolone and cephalosporin are positive risks of ESBL-producing *E. coli* bacteremia.

References

1. Hsieh CJ, Shen YH, Hwang KP (2010) Clinical implications, risk factors and mortality following community-onset bacteremia caused by extended-spectrum beta-lactamase (ESBL) and non-ESBL producing *Escherichia coli*. J Microbiol Immunol Infect 43: 240-248.
2. Paterson DL (2006) Resistance in Gram-negative bacteria: Enterobacteriaceae. Am J Infect Control 34 (5 Suppl 1): S20-28.
3. Doernberg SB, Winston LG (2012) Risk factors for acquisition of extended-spectrum beta-lactamase-producing *Escherichia coli* in an urban county hospital. Am J Infect Control 40: 123-127.
4. Freeman JT, McBride SJ, Nisbet MS, Gamble GD, Williamson DA, Taylor SL, Holland DJ (2012) 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: e371-374.
5. Tumbarello M, Sali M, Trecarichi EM, Leone F, Rossi M, Fiori B, De Pascale G, D'lnzeo T, Sanguinetti M, Fadda G, Cauda R, Spanu T (2008) Bloodstream infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli*: risk factors for inadequate initial antimicrobial therapy. Antimicrob Agents Chemother 52: 3244-3252.
6. Clinical and Laboratory Standards Institue (CLSI) (2010) Performance standards for antimicrobial susceptibility testing: 20th informational supplement. Twentieth informational supplement. M100-S20.
7. Stryjewski ME, Boucher HW (2009) Gram-negative bloodstream infections. Int J Antimicrob Agents 34(Suppl 4): S21-25.
8. Rodriguez-Bano J, Navarro MD, Romero L, Muniain MA, Cueto M, Galvez J, Perea EJ, Pascual A (2008) Risk-factors for emerging bloodstream infections caused by extended-spectrum beta-lactamases-producing *Escherichia coli*. Clin Microbiol Infect 14: 180-183.
9. Sheng WH, Liao CH, Lauderdale TL, Ko WC, Chen YS, Liu JW, Lau YJ, Wang LH, Liu KS, Tsai TY, Lin SY, Hsu MS, Hsu LY, Chang SC (2010) A multicenter study of risk factors and outcome of hospitalized patients with infections due to carbapenem-resistant *Acinetobacter baumannii*. Int J Infect Dis 14: e764-769.
10. Quirante OF, Cerrato SG, Pardos SL (2011) Risk factors for bloodstream infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*. Braz J Infect Dis 15: 370-376.
11. Wu UI, Yang CS, Chen WC, Chen YC, Chang SC (2010) Risk factors for bloodstream infections due to extended-spectrum beta-lactamase-producing *Escherichia coli*. J Microbiol Immunol Infect 43: 310-316.
12. Kang CI, Chung DR, Ko KS, Peck KR, Song JH; Korean Network for Study of Infectious Diseases (2012) Risk factors for infection and treatment outcome of extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* bacteremia in patients with hematologic malignancy. Ann Hematol 91: 115-121.
13. Trecarichi EM, Tumbarello M, Spanu T, Caira M, Fianchi L, Chiusolo P, Fadda G, Leone G, Cauda R, Pagano L (2009) Incidence and clinical impact of extended-spectrum beta-lactamase (ESBL) production and fluoroquinolone resistance in bloodstream infections caused by *Escherichia coli* in patients with hematological malignancies. J Infect 58: 299-307.
14. Tumbarello M, Spanu T, Sanguinetti M, Citton R, Montuori E, Leone F, Fadda G, Cauda R (2006) Bloodstream infections caused by extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*: risk factors, molecular epidemiology, and clinical outcome. Antimicrob Agents Chemother 50: 498-504.
15. Wang SS, Lee NY, Hsueh PR, Huang WH, Tsui KC, Lee HC, Wu CJ, Chang CM, Huang CC, Huang CF, Ko WC (2011) Clinical manifestations and prognostic factors in cancer patients with bacteremia due to extended-spectrum beta-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae*. J Microbiol Immunol Infect 44: 282-288.
16. Kang CI, Song JH, Chung DR, Peck KR, Ko KS, Yeom JS, Ki HK, Son JS, Lee SS, Kim YS, Jung SI, Kim SW, Chang HH, Ryu SY, Kwon KT, Lee H, Moon C, Shin SY; Korean Network for Study of Infectious Diseases (2010) Risk factors and treatments outcomes of community-onset bacteraemia caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. Int J Antimicrob Agents 36: 284-287.

17. Lee JA, Kang CI, Joo EJ, Ha YE, Kang SJ, Park SY, Chung DR, Peck KR, Ko KS, Lee NY, Song JH (2011) Epidemiology and clinical features of community-onset bacteremia caused by extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*. Microb Drug Resist 17: 267-273.

Corresponding author
Onur Kaya
Department of Infectious Diseases and Clinical Microbiology
Faculty of Medicine
Suleyman Demirel University
Isparta, Turkey
Telephone: +90 246 211 9325
Fax: +90 246 237 02 40
Email: onurkaya@sdu.edu.tr

Conflict of interests: No conflict of interests is declared.