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Original Article

Risk Factors for Bloodstream Infections due to Extended-spectrum β -lactamase-producing *Escherichia coli*Un-In Wu^{a†}, Ching-Shiang Yang^{b†}, Wan-Chin Chen^a, Yee-Chun Chen^a, Shan-Chwen Chang^{a,b*}^aDepartment of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan.^bGraduate Institute of Clinical Pharmacy, National Taiwan University College of Medicine, Taipei, Taiwan.

BACKGROUND/PURPOSE: The risk factors for production of extended-spectrum β -lactamases (ESBLs) have rarely been studied for bloodstream infections of *Escherichia coli* alone. A case-control study was undertaken to identify the risk factors associated with bloodstream infections caused by ESBL-producing *E. coli*.

METHODS: From January 1, 2005 to June 30, 2007, all patients with a confirmed diagnosis of bloodstream infection caused by ESBL-producing *E. coli* were reviewed. Each patient was matched with one control subject who experienced ESBL-negative *E. coli* bacteremia during the same study period.

RESULTS: Of the 97 patients diagnosed with ESBL-producing *E. coli* bacteremia, six were excluded owing to incomplete follow-up and missing data. Comparisons were made between 91 patients and their controls. Multivariate analysis identified urinary catheterization [odds ratio (OR)=6.21, 95% confidence interval (CI)=1.91-20.25; $p=0.003$], prior exposure to antibiotics (OR=2.93, 95% CI=1.18-7.30; $p=0.021$) and previous treatment with oxyimino-cephalosporins (OR=5.16, 95% CI=1.03-25.79; $p=0.046$) as independent predictors for bloodstream infection by ESBL-producing *E. coli*. Conversely, patients classified as having a community-acquired infection were less likely to acquire bacteremia caused by ESBL-producing *E. coli* than those caused by non-ESBL-producing *E. coli* (OR=0.22, 95% CI=0.09-0.57; $p=0.002$).

CONCLUSION: More judicious use of antimicrobial agents, especially oxyimino-cephalosporins, and avoidance of urinary catheterization may decrease the possibility of ESBL-producing *E. coli* bacteremia in hospitalized patients.

KEYWORDS: bacteremia, bloodstream infection, case-control study, *Escherichia coli*, extended-spectrum β -lactamase, risk factor

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Introduction

Extended-spectrum β -lactamases (ESBLs) are plasmid-mediated bacterial enzymes that are able to hydrolyze oxyimino- β -lactams (broad-spectrum cephalosporins and aztreonam). The marked increase in the incidence of infections due to ESBL-producing *Enterobacteriaceae* in recent years is of great concern, since the therapeutic options for these organisms are limited.^{1,2} The emergence of CTX-M β -lactamases, especially in *Escherichia coli*, has enabled the expansion of this infection in both nosocomial and community settings.³ Furthermore, patients with infections caused by ESBL producers may experience delay in the initiation of appropriate therapy compared with patients with non-ESBL infections.⁴ The subsequent increased risks for clinical failure and death have been shown in several studies.⁵⁻¹⁰ Documenting risk factors and identifying vulnerable patient groups are important for the management and control of severe infections due to ESBL-producing organisms. The risk factors for acquisition of ESBLs have been studied for *Klebsiella pneumoniae*, or multiple infections due to *Enterobacteriaceae* species,¹¹⁻¹⁴ but rarely for *E. coli* alone. Data focusing on ESBL-producing *E. coli* bloodstream infection are scarce.

In Taiwan, the prevalence of ESBLs has risen in the past decade, ranging from 1.5% to 21.9% for various clinical isolates of *E. coli*.¹⁵⁻¹⁷ Although the risk factors for infection by ESBL-producing *K. pneumoniae* and other *Enterobacteriaceae* have been investigated in a few studies,^{18,19} no published data dealing with *E. coli* infection alone is available. The objective of this study was to elucidate the possible risk factors for ESBL production in patients with *E. coli* bacteremia.

Methods

Data collection

This study was conducted at National Taiwan University Hospital, a 2,500-bed major teaching hospital in northern Taiwan that provides both primary and tertiary medical care. From January 1, 2005 to June 30, 2007, patients older than 16 years with at least one positive blood culture of ESBL-producing *E. coli* were reviewed. Only the first bacteremic episode in each patient was included in our analysis. Patients with bloodstream infections due to

non-ESBL-producing *E. coli* during the same period were selected as controls. Each case patient was matched in a 1:1 manner with a control having a positive blood culture of non-ESBL-producing *E. coli* collected on the same day, or a day apart. If more than one positive blood culture of non-ESBL-producing *E. coli* was retrieved on the same day as the case patient, only the one with the most adjacent chart number would be selected as the control. Medical records were reviewed retrospectively, and a standardized case record form was used to collect the demographic data and possible risk factors for ESBL production. These variables included (1) the Charlson comorbidity index;²⁰ (2) duration of hospital stay; (3) acquisition type (community-acquired, healthcare-associated or hospital-acquired); (4) an intensive care unit stay at the time of infection; (5) primary site of infection; (6) invasive procedures; and (7) prior antimicrobial therapy for at least 48 hours within 30 days prior to bacteremia onset.

Bacteriology and antimicrobial susceptibility testing

Strains of *E. coli* were identified by standard microbiologic methods in the microbiology laboratory. Antimicrobial susceptibility testing was performed using the Kirby-Bauer disk diffusion method. Production of ESBL was confirmed using the double-disk synergy test in accordance with the Clinical and Laboratory Standards Institute standards.²¹

Definitions

The date of collection of the first blood culture which yielded *E. coli* was regarded as the date of bacteremia onset. Nosocomial infection was defined as an infection that occurred > 48 hours after admission to the hospital, or an infection that occurred < 48 hours after admission in patients that had been transferred from another hospital. Infection with ESBL-producing *E. coli* detected within the first 48 hours of hospitalization was classified as "community-onset" in accordance with the US Centers for Disease Control and Prevention definition²² and were further classified into community-acquired or healthcare-associated infections (modified from the study of Siegman-Igra et al).²³ The former definition represents truly community-acquired infection, while the latter consists of infections in patients recently discharged (≤ 6 months), infections associated with invasive procedures performed just before, or at the time of, admission and infections in

patients admitted from nursing homes. The primary sites of infection were identified according to the Centers for Disease Control and Prevention definitions.²⁴ Patients were classified as immunosuppressed if neutropenia (defined as $<1,000$ polymorphonuclear neutrophils cells/mm³), hematologic malignancy, corticosteroid therapy (equivalent to >20 mg prednisolone/day) for at least 2 weeks, and/or cancer chemotherapy or radiation therapy were documented within 30 days of the onset of bacteremia. Patients with serum creatinine level >3 mg/dL, or under dialysis, before the onset of bacteremia were considered to have chronic renal insufficiency.

Statistical analysis

All statistical analyses were performed using the SAS software package (version 9.1; SAS Institute Inc., Cary, NC, USA). For univariate analysis, categorical variables were compared using χ^2 or Fisher's exact test and continuous variables were analyzed with Student's *t* test or Mann-Whitney *U* test. A *p* value <0.05 was considered to be statistically significant, and all probabilities were two-tailed. Multivariate analysis was used to identify independent risk factors for ESBL production and was conducted using a stepwise logistic regression method.

Results

During the study period, 1,792 adult inpatients were diagnosed with *E. coli* bacteremia. Of these, 97 (5.4%) were identified as having bloodstream infections caused by ESBL-producing *E. coli*. Six patients were excluded owing to incomplete medical records. The baseline characteristics of the remaining 91 patients and the 91 controls are shown in Table 1. By univariate analysis, case patients had a higher Charlson comorbidity index (3.9 ± 2.5 vs. 2.6 ± 2.1 ; $p < 0.001$) and were more likely to be immunosuppressed (42.9% vs. 26.4% ; $p = 0.019$). The majority of patients in the case group (60.0%) acquired a bloodstream infection in a hospital setting, while control patients (55.0%) were more often classified as having community-acquired bacteremia. The occurrence of the following risk factors was also significantly more frequent in the case group: prolonged hospital stay, admitted to the intensive care unit during the onset of bacteremia, urinary catheterization, placement of gastrostomy/nasogastric tube or central

venous catheters, and mechanical ventilation. Although only borderline statistical significance was observed, case patients experienced primary bacteremia more frequently than control subjects (28.6% vs. 16.5% ; $p = 0.051$), whereas urinary tract infection was more likely to be reported in the control group (51.6% vs. 37.4% ; $p = 0.053$). A significantly higher proportion of case patients had been exposed to antimicrobial agents within 30 days prior to the onset of bacteremia (63.7% vs. 17.6% ; $p < 0.001$), and oxyimino-cephalosporins (29.7%) were the most frequently used antimicrobial agents (Table 2). Multivariate logistic regression analysis showed that the independent risk factors associated with ESBL-production were urinary catheterization [odds ratio (OR) = 6.21, 95% confidence interval (CI) = 1.91–20.25; $p = 0.003$] and previous antimicrobial therapy during 30 days prior to bacteremia onset (OR = 2.93, 95% CI = 1.18–7.30; $p = 0.021$), with oxyimino-cephalosporins being associated with the highest risk compared with other antimicrobial agents (OR = 5.16, 95% CI = 1.03–25.79; $p = 0.046$). Conversely, community-acquired infection (OR = 0.22, 95% CI = 0.09–0.57; $p = 0.002$) was a negative predictor for ESBL production (Table 3).

Discussion

Early identification of ESBL production is becoming increasingly important in terms of appropriate treatment and effective infection control in hospitals. Our study confirms that patients with urinary catheterization and previous use of antimicrobial agents, especially oxyimino-cephalosporins, are at risk of acquiring bloodstream infection due to ESBL-producing *E. coli* compared with non-ESBL-producing *E. coli* bacteremia, a result similar to that in previous reports.^{25–27} In previous studies, prior exposure to fluoroquinolone was also identified as a potential risk factor.^{26,28} Although this factor was not revealed as an independent risk factor for acquiring ESBL-producing *E. coli* bacteremia by multiple analysis in the present study, fluoroquinolone was the second most frequently used class of antibiotics (25.3%) before bacteremia onset in our case group. This may partially explain the low susceptibility rate of the ESBL-producing *E. coli* to fluoroquinolone (38.5%) in our hospital (data not shown).

It should be noted that, unlike the situations observed in other multidrug resistant bacteria, underlying diseases,

Table 1. Characteristics and potential risk factors associated with bloodstream infection caused by extended-spectrum β -lactamase-producing *Escherichia coli*^a

Variable	Case group (n=91)	Control group (n=91)	Unadjusted OR (95% CI)	p
Demographic				
Age (yr) ^b	65.1±17.1	62.6±17.8	-	0.194
Sex, male	51 (56)	40 (44)	0.62 (0.34-1.10)	0.103
Comorbidities				
Charlson comorbidity score ^b	3.9±2.5 (0-10)	2.6±2.1 (0-8)	-	<0.001
Diabetes mellitus	22 (24.2)	23 (25.3)	0.94 (0.48-1.85)	0.864
Chronic renal insufficiency	18 (19.8)	10 (11.0)	2.00 (0.87-4.60)	0.100
Liver cirrhosis	14 (15.4)	18 (19.8)	0.74 (0.34-1.59)	0.436
Immunosuppression	39 (42.9)	24 (26.4)	2.09 (1.12-3.91)	0.019
Type of infection				
Community-acquired	8 (8.8)	50 (55.0)	0.08 (0.03-0.18)	<0.001
Healthcare-associated	29 (31.9)	22 (24.2)	1.47 (0.76-2.81)	0.248
Hospital-acquired	54 (60.0)	19 (20.9)	5.68 (2.94-10.98)	<0.001
Primary site of infection				
Urinary tract	34 (37.4)	47 (51.6)	0.56 (0.31-1.01)	0.053
Intra-abdominal	22 (24.2)	23 (25.3)	0.94 (0.48-1.85)	0.860
Primary bacteremia	26 (28.6)	15 (16.5)	2.03 (0.99-4.15)	0.051
Others	9 (9.9)	6 (6.6)	1.56 (0.53-4.56)	0.420
Risk factors				
Prolonged hospital stay (> 14 days)	34 (37.4)	9 (9.9)	5.43 (2.42-12.20)	<0.001
ICU stay	13 (14.3)	1 (1.1)	1.92 (1.92-117.27)	0.001
Gastrostomy/nasogastric tube	29 (31.9)	10 (11.0)	3.79 (1.72-8.36)	<0.001
Urinary catheterization	32 (35.2)	6 (6.6)	7.68 (3.02-19.53)	<0.001
Indwelling central venous line	45 (49.5)	14 (15.4)	5.38 (2.67-10.86)	<0.001
Mechanical ventilation	15 (16.5)	1 (1.1)	17.76 (2.29-137.59)	<0.001

^aData presented as n (%) or mean±standard deviation (range); ^bMann-Whitney U test. OR=Odds ratio; CI=confidence interval; ICU=intensive care unit.

e.g. diabetes mellitus, liver cirrhosis and chronic renal insufficiency, were not shown to increase the risk for acquiring bloodstream infections of ESBL-producing *E. coli*. This is consistent with previous studies which demonstrated that antibiotic selective pressure, rather than individual comorbidities, was the most important factor in the emergence of ESBL-producing isolates.^{12,26,28-31} Furthermore, hospitals and other health-care institutions remain the major settings for spreading these multidrug resistant strains according to our study. These findings strongly support the implementation of effective strategies to limit the use of extended-spectrum antibiotics and the use of invasive

procedures, including the insertion of a urinary catheter, to control the spread of ESBL-producing *E. coli*.

Although community-acquired infections (OR=0.22, 95% CI=0.09-0.57; *p*=0.002) were a negative predictor of ESBL production, it is still a matter of concern that 8.8% of case patients were classified as having strictly defined community-acquired infections, and the proportion seems to be increasing in our hospital (9% in 2006 vs. 12% in 2007). In fact, the emergence of ESBL-producing *E. coli* in the community has been increasingly recognized as a global problem in recent years.³²⁻³⁴ The majority of cases were attributed to isolates harboring CTX-M type β -lactamases,³⁵

Table 2. Prior exposure to various classes of antimicrobial agents^a

Antibiotic agent/class	Case group (n=91)	Control group (n=91)	p
Previous antimicrobial therapy	58 (63.7)	16 (17.6)	<0.001
First/Second generation cephalosporins (non-cephamycin)	9 (9.9)	5 (5.5)	0.410
Oxyimino-cephalosporins	27 (29.7)	3 (3.3)	<0.001
Cephameycin	5 (5.5)	4 (4.4)	1.000
Carbapenem	15 (16.5)	2 (2.2)	0.001
Fluoroquinolone	23 (25.3)	5 (5.5)	<0.001
β-lactam/β-lactamase inhibitor	16 (17.6)	4 (4.4)	0.008
Penicillin	2 (2.2)	1 (1.1)	1.000
Monobactam	1 (1.1)	0 (0)	1.000
Glycopeptide	12 (13.2)	3 (3.3)	0.028
Others	15 (16.5)	7 (7.7)	0.069

^aData presented as n (%).

Table 3. Multivariate analysis of risk factors for bloodstream infection caused by extended-spectrum β-lactamase-producing *Escherichia coli*^a

Independent risk factor	Adjusted OR (95% CI)	p
Indwelling urinary catheter	6.21 (1.91–20.25)	0.003
Previous antimicrobial therapy	2.93 (1.18–7.30)	0.021
Prior use of oxyimino-cephalosporin	5.16 (1.03–25.79)	0.046
Community-acquired infection	0.22 (0.09–0.57)	0.002

^aMultiple logistic regression model (n=182); percentage of concordant pairs=79.3%; percentage of discordant pairs=8.7%; adjusted generalized $R^2=0.488$; Deviance goodness-of-fit test, $p=0.525>0.05$ (df=6); Pearson goodness-of-fit test, $p=0.780>0.05$ (df=6); and Hosmer and Lemeshow goodness-of-fit test, $p=0.891>0.05$ (df=6). OR=Odds ratio; CI=confidence interval.

a fact which has also raised considerable concern in hospital settings.³⁶ In many countries, including Taiwan, CTX-M enzymes have become the most prevalent ESBLs among *E. coli* isolates.^{3,37,38} In our study population, none of the patients classified as having community-acquired infections were exposed to antimicrobial agents within the 30 days prior to the onset of bacteremia. In a recent study by Kang et al, no predisposing factor was identified in up to 57% of patients having community-onset bloodstream infections caused by ESBL-producing *E. coli*.³⁹ The paucity of

identifiable risk factors for the acquisition of ESBLs poses a great challenge for clinical therapeutics and infection control in this specific population.

There are limitations in our present study. First, the possible coproduction of AmpC enzymes in strains of *E. coli* might result in false negative tests for the detection of ESBLs using standard Clinical and Laboratory Standards Institute methods.^{17,37} Second, pulsed-field gel electrophoresis was not performed to determine the genetic similarities between all of the identified ESBL-producing *E. coli*. Consequently, we may have underestimated the possibility of clonal spread of these resistant isolates within the hospital. Finally, our study was conducted at a single tertiary care hospital and our results may not reflect those at other institutions with different epidemiologies.

In conclusion, the incidence of ESBL-producing *E. coli* bacteremia may be reduced by curtailing the use of oxyimino-cephalosporins and avoiding urinary catheterization. Although hospitals remain the major settings in which ESBL-producing *E. coli* bacteremia occur, the emergence of ESBL-producing organisms in the community warrants further investigation of the epidemiology and risk factors within this population.

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