BLOODSTREAM INFECTIONS CAUSED BY EXTENDED-SPECTRUM BETA-LACTAMASE PRODUCING ENTEROBACTERIACEAE AT A TERTIARY CARE HOSPITAL IN SLOVAKIA

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Abstract
Introduction: Extended-spectrum-β-lactamase producing strains of *Enterobacteriaceae* (ESBL-E) are a significant cause of bloodstream infections (BSI) in hospitalized patients and are a leading cause of death. The objective of this study was to evaluate risk factors and outcome for BSI caused by ESBL- E.
Methods: A hospital-based study was conducted from January 1, 2013 to December 31, 2014 at tertiary care hospital in Trnava. All patients with a confirmed BSI caused by ESBL-E were reviewed. Cases included 115 patients with ESBL-producing *Enterobacteriaceae* and 94 cases with non-ESBL-producing *Enterobacteriaceae*.
Results: The incidence rate of ESBL-E BSI was 0.4 cases/1000 patient-days (95% CI: 0.3-0.5 cases per 1000 patient-days). Multivariate analysis identified prior exposure to antibiotics (OR 2.23; 95%CI 1.06-4.73; P=0.04), previous treatment with fluoroquinolones (OR=4.43; 95%CI 1.13-17.32; P=0.03) and hospital – acquired BSI (OR=8.68; 95%CI 2.99-25.25; P<0.0001), and healthcare-associated BSI (OR=7.89; 95% 2.83-21.98; P<0.0001) as independent predictors for bloodstream infection by ESBL-E. Inadequate initial antibiotic therapy was more frequent in ESBL-E BSI than in non-ESBL (78.3% versus 14.9%, P<0.0001). ESBL-E BSI was associated with higher case-fatality rate than in non-ESBL-E BSI (28.7% versus 16.0%, P=0.03). Inadequate initial antibiotic therapy was more frequent in ESBL-positive BSI than ESBL-negative BSI (94.2% versus 5.7%, p<0.0001). ESBL-positive BSI was associated with higher case-fatality rate than ESBL-negative BSI (54.8% versus 15.4%, p<0.001).
Conclusions: The study revealed that incidence of BSI caused by ESBL - E was relatively high in our setting with a high case fatality rate. Our findings suggest that the use of antibiotics, especially fluorochinolones and hospital acquired BSI increases the risk of acquiring such infections. Control of ESBL-E spread is an emergency and could be achieved with better stewardship of antibiotic use, especially for empirical therapy and application of infection prevention and control measures.

Keywords: Bloodstream infection. Extended-spectrum beta-lactamase producing *Enterobacteriaceae*. Risk factor. Inadequate initial antibiotic therapy. Case-fatality rate

1 Introduction

In the last twenty years, antimicrobial resistance especially extended-spectrum β-lactamases (ESBLs) have spread among *Enterobacteriaceae* [1]. Extended-spectrum beta-lactamases producing *Enterobacteriaceae* (ESBL-E) are of major concern since infections caused by these resistant strains are associated with prolonged hospital stay and increased case-fatality rate [2-4]. Bloodstream infections caused by extended-spectrum beta-lactamases producing *Enterobacteriaceae* (ESBL-E BSI) are of major concern in clinical practice because of limited therapeutic options effective to treat them. Extended-spectrum β-lactamases have been increasingly described worldwide, not only in the nosocomial, but also in the community setting [5]. Selection of empiric treatment modalities is an increasing challenge and carbapenems are often regarded as a major antibacterial drug for these infections. Indeed it increases the rise and spread of carbapenemase-producing *Enterobacteriaceae* [6] and the rate of subsequent multidrug-resistant bacteria-related infections [7-8]. Patients with severe infections are highly dependent on receiving adequate treatment. For a patient with BSI caused by resistant bacteria, such as an ESBL-producer, administration of an ineffective antibiotic can be lethal. Knowledge of the local epidemiology is therefore very important. Identification of locally relevant risk factors for these infections is essential, both to guide empirical therapy and to design rational preventative strategies. Although numerous risk factors have been described in a variety of geographic settings, but no studies have evaluated specific risk factors in the setting of a tertiary hospital in Slovakia. The aim of this study was to describe the burden of extended-spectrum β-lactamase (ESBL) *Enterobacteriaceae* among patients hospitalized with bloodstream infections, to identify risk factors for ESBL acquisition, and to assess impact on clinical outcomes.

2 Materials and Methods

2.1 Setting and study design

This hospital-based study was carried out in patients hospitalized from January 1, 2013 to December 31, 2014 at the University Hospital in Trnava (618-bed; approx. 25 000 patients per year). All patients older than 18 years old admitted to the hospital for longer than 24 hours were enrolled.Cases were detected by daily review of blood culture results from microbiology laboratory database. A BSI was defined according the ECDC definition as the isolation of a pathogen from ≥ 1 set of blood cultures for a recognised pathogen. All patients with positive blood cultures for *Enterobcteriaceae* were considered eligible. In all patients, only the first episode of bacteremia was included for further analysis. The date of the bloodstream infection onset was the date the first sample yielding an *Enterobacteriaceae* strain was collected. Cases were patients with BSI caused by an *Enterobacteriaceae* and included two subgroups of inpatients: those with ESBL-positive BSI and those with ESBL-negative BSI. ESBL production was detected with the phenotypic confirmatory test.

2.2 Data collection

The clinical records of each patient were reviewed. The following variables were collected: demographic data (age, gender), germs isolated and resistance profile,underlyingcomorbidity, source of bloodstream infections, acquisition of infection, previous hospitalization within 3 months, prior antibiotic use, surgical and invasive procedures, presence of invasive medical devices during the admission prior to the BSI, response to bloodstream infection (sepsis, severe sepsis, septic shock), parameters for the calculationof scoring systems, length of stay (LOS),antibiotics prescribed empirically and targeted therapy andin-hospital mortality.

Acquisition of BSI were classified according to the criteria used by Friedman et al. [5] as hospital acquired BSI, healthcare-associatedor community-acquired infections.Source of bloodstream infections was classified asprimary (bloodstream infection of unknown origin or catheter-related) and secondary BSI (the same microorganism was isolated from another infection site).

The severity of illness was evaluated by Pitt bacteriemia Score and by the Acute Physiology and Chronic Health Evaluation (APACHE II) score and failure of organs were evaluated by the Sequential Organ Failure Assessment (SOFA) scale on the day of first positive blood culture. The Charlson score was used as the measure of comorbid illness [9] and McCabe & Jackson classification scheme were used for categorize the severity of underlying diseases [10]. Antibiotic therapy was defined as empirical if prescribed initially before susceptibility test results were available. Empirical antibiotic therapy was considered inadequate when the initial antibiotic drug prescribed was not active against the pathogen causing the infection. All patients were followed from admission to discharge or in-hospital death.

2.3 Statistical analysis

All analysis was performed using statistical program R-project. Contingency data were analyzed by the two-tailed χ^2 test or Fisher's exact test, and continuous data were analyzed by Student's *t* test or MannWhitney U test. The significance of differences in proportions was assessed by the χ^2 test. The 95% test-based confidence intervals (95% CIs) were calculated to determine the significance of the odds ratios (OR). Multivariate analysis was used to identify independent risk factors for ESBL production and was conducted using a stepwise logistic regression method. Differences in survival were analyzed with the Kaplan-Meier method with the use of log-rank test. A p value < 0.05 was considered to be statistically significant.

2.4 Ethical considerations

The medical and legal board of Trnava Hospital approved this hospital-based study and the study protocol. All data collected were anonymized prior to analysis and in accordance with the Helsinki Declaration.

3 Results

During the study period we analyzed 209 cases of BSI due to *Enterobacteriaceae*. The incidence of BSI caused by *Enterobacteriaceae* was 5.3 cases/1000 addmission (95% CI: 5.0–5.6 cases per 1000 addmision) and incidence density was 0.7 cases/ 1000 patients – days (95% CI: 0.7-0.8 cases per 1000 patient-days). Among the 209 BSI episodes due to *Enterobacteriaceae*, 204 were monomicrobial and 5 contained two different *Enterobacteriaceae*. Predominant *Enterobacteriaceae* was *E. coli* (49.1%), *Klebisella spp.* (27.1%), followed by Proteus mirabilis (13.1%). The overall in-hospital case fatality rate among patients with *Enterobacteriaceae* was 22.4%. In the most frequent isolates of *E. coli* and *Klebsiella spp.* case-fatality rates were 15.2% and 31.0% (Table 1).

Overall 115 (55.0%) cases of BSI due to *Enterobacteriacea* were ESBL producers (ESBL-E BSI) and 94 were non-ESBL. ESBLs were produced by 74.1% (43) of *Klebsiella spp.* isolates, 46.7% (49) of *E. coli* isolates, 64.3% (18) of *Proteus mirabilis* isolates and 43.8% (7) *Enterobacter spp*. The incidence of ESBL-E BSI was 2.9 cases/1000 addmission (95% CI: 2.2-3.7 cases per 1000 addmission) and incidence rate of ESBL-E BSI was 0.4 cases/1000 patient-days (95% CI: 0.3-0.5 cases per 1000 patient-days).

Table 1 *Aetiology of bloodstream infections due to Enterobacteriacea and case fatality rate*

	Total	**Case fatality rate**
Enterobacteriaceae	**214**	22.4%
Escherichia coli	105 (49.1%)	15.2%
Klebsiella spp.	58 (27.1%)	31.0%
Proteus mirabilis	28 (13.1%)	28.6%
Enterobacter spp.	16 (7.5%)	31.3%
Serratia spp.	2 (0.9%)	0.0%
Morganella morganii	3 (1.4%)	33.3%
Yersenia spp.	1 (0.5%)	0.0%
Salmonella enteritidis	1 (0.5%)	100%

Table 2 gives an comparison of BSI caused by ESBL-E and non-ESBL E. Univariate analysis showed that risk factors for ESBL-E were surgery (OR=4.33; $_{95CI}$ 1.89-9.90; P=0.0005), presence of central venous catheter (OR=2.34; $_{95CI}$ 1.28-4.29; P=0.006), nasogastric tube (OR=2.30; $_{95CI}$ 1.12-4.70; P=0.02), presence of urinary catheter (OR=3.02; $_{95CI}$ 1.70-5.35; P=0.0005), total parenteral nutrition (OR=4.20; $_{95CI}$ 1.17-15.10; P=0.03), previous hospitalization (OR=4.2; $_{95CI}$ 1.17-15.10; P=0.0003), prior antibiotic use (OR=4.68; $_{95CI}$ 2.54-8.62; P<0.0001), exposure of fluoroquinolones (OR=5.32; $_{95CI}$ 1.76-16.05; P=0.003), hospital acquired BSI (OR=9.78; $_{95CI}$ 4.28-22.36; P<0.0001) and HAI-BSI (OR=5.85; $_{95CI}$ 2.32-14.79; P=0.0002).

Table 2 *Risk factors associated with BSI caused by ESBL-Enterobacteriaceae*

Enterobacteriaceae N= 209/Univariate analysis

Characteristic	**ESBL N=115 n (%)**	**Non-ESBL N=94 n (%)**	**Unadjusted odds ratio (95% CI)**	**P-value**
Age (mean±SD)	66.5±13.32	68.2±12.54	0.99 (0.96-1.02)	0.62
Gender (Male)	64 (55.7%)	41 (43.6%)	1.62 (0.94-2.81)	0.08
Underlying disease				
Diabetes mellitus	53 (46.1%)	47 (50.0%)	0.85 (0.50-1.48)	0.57
Chronic respiratory disease	29 (25.2%)	20 (21.3%)	1.25 (0.65-2.39)	0.50
Chronic renal failure	33 (28.7%)	22 (23.4%)	1.32 (0.70-2.46)	0.39
Chronic liver disease	5 (4.3%)	4 (4.3%)	1.02 (0.27-3.92)	0.97
Malignancy	26 (22.6%)	20 (21.3%)	1.08 (0.56-2.09)	0.82
Hypertension	70 (60.9%)	66 (70.2%)	0.67 (0.37-1.18)	0.16
Ischemic heart disease	42 (36.5%)	37 (39.4%)	0.89 (0.51-1.55)	0.67
Trauma	9 (7.8%)	3 (3.2%)	2.57 (0.68-9.80)	0.17
Charlson comorbidity score (median, IQR)	3 (1-5)	2 (1-4)	0.97 (0.80-1.16)	0.7
McCabe classification				
Nonfatal	77 (67.0%)	73 (77.7%)	1	
Ultimately fatal	25 (21.7%)	17 (18.1%)	1.39 (0.70-2.79)	0.35
Rapidly fatal	13 (11.3%)	4 (4.3%)	3.08 (0.96-9.88)	0.06
Risk factors				
Corticosteroid use	11 (9.6%)	10 (10.6%)	0.89 (0.36-2.19)	0.80
Immunosuppressive therapy	18 (15.7%)	16 (17.0%)	0.90 (0.43-1.89)	0.79
Invasive procedure	19 (16.5%)	13 (13.8%)	1.23 (0.57-2.65)	0.59
Surgery	33 (28.7%)	8 (8.5%)	4.33 (1.89-9.90)	**0.0005**
Mechanical ventilation	29 (25.2%)	14 (14.9%)	1.93 (0.95-3.91)	0.07
Central venous catheter	48 (41.7%)	22 (23.4%)	2.34 (1.28-4.29)	**0.006**
Nasogastric tube	31 (27.0%)	13 (13.8%)	2.30 (1.12-4.70)	**0.02**
Urinary catheter	66 (57.4%)	29 (30.9%)	3.02 (1.70-5.35)	**0.0002**
Total parenteral nutrition	14 (12.2%)	3 (3.2%)	4.20 (1.17-15.10)	**0.03**
Admitted in hospital within 3 months	50 (43.5%)	18 (19.1%)	4.20 (1.17-15.10)	**0.0003**
Prior antibiotic use	66 (57.4%)	21 (22.3%)	4.68 (2.54-8.62)	<**0.0001**
Prior antibiotic use				
Beta-lactam + beta-lactamase inhibitors	3 (2.6%)	1 (1.1%)	2.49 (0.25-24.35)	0.43
Cephalosporins	10 (8.7%)	5 (5.3%)	1.70 (0.56-5.14)	0.35
Fluoroquinolones	22 (19.1%)	2 (2.1%)	5.32 (1.76-16.05)	**0.003**
Beta-lactams+ fluoroquinolones	10 (8.7%)	2 (2.1%)	4.38 (0.94-20.50)	0.06
Fluoroquinolones + cephalosporins	6 (5.2%)	3 (3.2%)	1.67 (0.41-6.86)	0.45
Acquisition of infection				
Community-acquired (CA)	9 (7.8%)	39 (41.5%)	1	-
Hospital acquired (HA)	79 (68.7%)	35 (37.2%)	9.78 (4.28-22.36)	<**0.0001**
Healthcare-associated (HAI)	27 (23.5%)	20 (21.3%)	5.85 (2.32-14.79)	**0.0002**

Table 3 showed that patients with ESBL-E BSI were more likely have to BSI related to central venous catheter (OR=2.34; $_{95CI}$ 1.28-4.29; P=0.006) and secondary BSI to surgical site (OR=8.86; $_{95CI}$ 1.11-70.48; P=0.04).

Table 3 *Source of BSI caused by ESBL-Enterobacteriaceae*

Enterobacteriaceae N= 209

Source of BSI	**ESBL N=115 n (%)**	**Non-ESBL N=94 n (%)**	**Unadjusted odds ratio (95% CI)**	**P-value**
BSI related to CVC (CRI3-CVK)	48 (41.7%)	22 (23.4%)	2.34 (1.28-4.29)	**0.006**
BSI related to PVC	0 (0.0%)	1 (1.1%)	-	-
Unknown origin	15 (13.0%)	13 (13.8%)	0.93 (0.42-2.08)	0.87
S-PUL (lower respiratory tract)	25 (21.7%)	11 (11.7%)	2.09 (0.97-4.52)	0.06
S-UTI (urinary tract)	52 (45.2%)	53 (56.4%)	0.64 (0.37-1.11)	0.11
S-SSI (surgical site)	10 (8.7%)	1 (1.1%)	8.86 (1.11-70.48)	**0.04**
S- DIG (pri infekcii tráviaceho traktu)	1 (0.9%)	4 (4.3%)	0.20 (0.02-1.79)	0.15
S-SST (skin and soft tissue)	2 (1.7%)	3 (3.2%)	0.54 (0.09-3.28)	0.51
S-OTH (other)	3 (2.6%)	5 (5.3%)	0.48 (0.11-2.05)	0.32

Multivariate logistic regression analysis showed that the independent risk factors associated with ESBL-production were previous antimicrobial therapy prior to BSI onset (OR 2.23; $_{95\%CI}$ 1.06-4.73; P=0.04), with fluoroquinolones being associated with the highest risk compared with other antimicrobial agents (OR=4.43; $_{95\%CI}$ 1.13-17.32; P=0.03) and hospital – acquired BSI (OR=8.68; $_{95\%CI}$ 2.99-25.25; P<0.0001), and healthcare-associated (OR=7.89; $_{95\%}$ 2.83-21.98; P<0.0001) (Table 4).

Table 4 *Multivariate analysis of risk factors for BSI caused by ESBL –Enterobacteriaceae*

Multivariate analysis

Risk factors	**Adjusted odds ratio (95% CI)**	**P-value**
Previous antimicrobial therapy	2.23 (1.06-4.73)	**0.04**
Prior use of fluoroquinolones	4.43 (1.13-17.32)	**0.03**
Acquisition		
Hospital - acquired (HA)	8.68 (2.99-25.25)	**<0.0001**
Healthcare-associated (HAI)	7.89 (2.83-21.98)	**<0.0001**

Patients with ESBL-E BSI were more likely to have severe sepsis or septic shock (53.0% versus 38.3%, P=0.03) and significantly higher APACHE II score (median 24 [17.3-31] versus median 22 [16-26.5], P= 0.047) and SOFA score (median 7 [5-11] versus median 6 [4-9]) than non-ESBL-E BSI. Inadequate initial antibiotic therapy was more frequent in ESBL-EBSI than non-ESBL-E BSI (78.3% versus 14.9%, P<0.0001). ESBL-E BSI was associated with higher case-fatality rate than non-ESBL-E BSI (28.7% versus 16.0%, P=0.03). The 28-day mortality rate for the ESBL-BSI group was 27.8%, whereas that of non-ESBL was 12.8% (P = 0.01) (Table 5). The survival curve also shows that the ESBL-BSI group had a lower probability of survival than the non-ESBL BSI group (log rank=0.02) (Figure 1).

Table 5 *Systematic response to BSI caused by ESBL - Enterobacteriaceae and outcome*

	ESBL N=115; n (%)	**Non-ESBL N=94; n (%)**	**P-value**
Systematic response to BSI			
Sepsis	54 (47.0%)	58 (61.7%)	**0.03**
Severe sepsis or septic shock	61 (53.0%)	36 (38.3%)	
APACHE II score (median,IQR)	24 [17.3-31]	22 [16-26.5]	**0.047[1]**
Pitt bacteriemia score (median,IQR)	2 [1-5.5]	1 [1-4]	0.06[1]
SOFA score (median,IQR)	7 [5-11]	6 [4-9]	**0.03[1]**
Outcome			
Inadequate empirical antibiotic treatment	90 (78.3%)	14 (14.9%)	**<0.0001**
Case -fatality rate (total) %	33 (28.7%)	15 (16.0%)	**0.03**
7-day mortality rate (%)	19.1%	9.6%	0.08
28-day mortality rate (%)	27.8%	12.8%	**0.01**

[1] Mann–Whitney U test

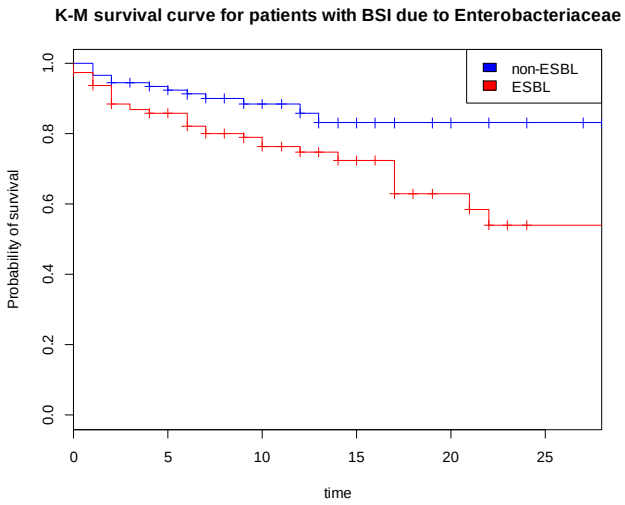

Fig. 1 *Survival curve using the Kaplan-Meier method for patients with BSI due to ESBL-Enterobacteriaceae compared to those with non-ESBL (Log rank = 0,02).*

4 Discussion

Our analysis showed that independent risk factors for ESBL-E BSI acquisition were previous antibiotic therapy (OR=2.23), previous fluoroquinolones use (OR=4.43), hospital acquisition (OR=8.68) and healthcare-associated acquisition of BSIs (OR=7.89). Also several studies identified recent antibiotic therapy as a risk factor for ESBL-producing *Enterobacteriaceae* BSIs, with odds ratios ranging from 1.9 to 11.81 [11-15]. When single antibiotic classes were analyzed, previous fluoroquinolones has also been reported as an independent risk factor for ESBL-E BSIs [13-18]. Other studies also show that the hospital acquisition and healthcare-associated acquisition of BSIs have been recognized as more likely to occur in ESBL-producing *Enterobacteriaceae* BSIs [1,12,14,19] and community-acquired infection has been negative predictor for ESBL production [15]. The next factor independently associated with ESBL-producing *Enterobacteriaceae* BSIs found in several studies was previous hospitalization. In particular, a prolonged length of hospital stay [1,11-12,14] and previous stay in an ICU was found to increase the risk up to 35.7 times [20-21]. Important group of risk factors associated with ESBL- E BSI includes previous invasive procedures and presence of invasive devices, especially urinary catheterization [14-16,19] and central venous catheters [17,22]. In our study, invasive inputs such as central venous catheters and permanent urinary catheter were noted as significant in a univariate analysis. In our study, the lethality of ESBL-E patients was 28.7% and was significantly higher than that of non-ESBL (28.7% vs. 16.0%, P = 0.04). In the studies the mortality rate for patients with ESBL-E BSI ranged from 8.1 to 43.6% and was significantly higher than in non-ESBL-E BSI [11,14,16,19,23]. One of the most frequently reported risk factors for mortality in patients with ESBL-E BSI is the inadequacy of initial antimicrobial therapy, which was found in our study in 78.3%. Meta-analysis showed that the mortality is fivefold higer in the ESBL group than in non-ESBL group [24]. The inadequacy of initial antimicrobial therapy has been assessed in several study and this factor was independently associated with mortality with OR ranging from 2.1 to 14.9 [13-14,16,19, 23, 25-26]. Any delay in the initiation of adequate antibiotic therapy is potentially lethal for patients with ESBL - E BSIs.

5 Conclusion

Knowledge of risk factors and of factors facilitating adverse outcome can improve the efficacy of empirical treatment. Documenting risk factors and identifying vulnerable patient groups are important for the management and control of severe ESBL-E BSI. The impact of antibiotic treatment on the dissemination and persistence of resistant bacteria cannot be underestimated. For antibiotics to be potent also in the future, promoting rational antibiotic use in all sectors minimizes the selective pressure for resistant bacteria. New treatment options can buy us time to address this important issue. Beside monitoring and judicious usage of antibiotics, periodic surveillance of antibiotic resistance patterns would go a way in addressing some of the problems associated with ESBL. Efective and racionale antibiotic treatment is in turn dependent on the development of faster diagnostic tools. The important is that microbiology laboratories rapidly detect ESBL-producing pathogens for early initiation of adequate antibiotic therapy and the intervention for infection control.

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