



Original Research

Trend in Antibiotic Resistance of Extended-Spectrum Beta-Lactamase-Producing *Escherichia Coli* and *Klebsiella Pneumoniae* Bloodstream Infections

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Abstract

Objectives: Extended-spectrum beta-lactamases (ESBLs) have been detected more frequently in members of the *Enterobacteriaceae* family, particularly *Escherichia coli* and *Klebsiella pneumoniae*. Infections caused by ESBL-producing bacteria are often resistant to treatment with various antibiotic classes and accompanied by increased complication risks, mortality, and costs. In this study, blood culture results were analyzed to determine the change in the ESBL production rate and antibiotic susceptibilities in *E. coli* and *K. pneumoniae* isolates over a period of 3 years.

Methods: The results of blood cultures sent to our laboratory between February 2014 and August 2016 were examined retrospectively. Repeat isolates from the same patient were not included when antibiotic susceptibility rates and clinical distributions were calculated. BD Bactec FX automated blood culture system (Becton Dickinson, Sparks, MD, USA) was used to examine the blood cultures. Matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany) was used to identify microorganisms. For antibiotic susceptibility tests (AST) and ESBL detection Kirby Bauer disk diffusion method or Phoenix automated system (Becton Dickinson, Sparks, MA, USA) was used. When the AST results were evaluated, Clinical and Laboratory Standards Institute breakpoints were used for 2014 and 2015, and European Committee on Antimicrobial Susceptibility Testing breakpoints were used for 2016.

Results: During the 3-year period, 224 (35%) of 632 *E. coli* and 137 (31%) of 439 *K. pneumoniae* isolates were determined to be ESBL-producers. The ESBL-positive isolate percentage for *E. coli* and *K. pneumoniae* for 2014, 2015, and 2016 was 23%, 36%, 48% and 23%, 32%, 37%, respectively. The increase in ESBL was statistically significant for both *E. coli* ($p<0.001$) and *K. pneumoniae* ($p=0.011$). ESBL-positive *E. coli* and *K. pneumoniae* strains were most sensitive to carbapenem-class antibiotics, amikacin, and colistin. While there was no meropenem-resistant strain, 5 (3.3%) ertapenem-resistant and 1 (0.7%) imipenem-resistant ESBL *E. coli* strains were detected. The ESBL *K. pneumoniae* strain resistance rate to ertapenem, imipenem, and meropenem was 12%, 11.2%, and 11.1%, respectively. The resistance rates of *K. pneumoniae* strains to ertapenem, imipenem, meropenem, and piperacillin-tazobactam increased significantly over the study period ($p<0.001$).

Conclusion: Monitoring ESBL rates and the antibiotic susceptibility of *E. coli* and *K. pneumoniae* strains of bloodstream infections is of the utmost importance in guiding empiric antibiotic therapies and patient management.

Keywords: Blood culture; extended-spectrum beta-lactamase; resistance.

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Despite advances in treatment and supportive care, bloodstream infections (BSIs) continue to be one of the most important causes of morbidity and mortality in hospitalized patients. BSIs caused by multiple-drug-resistant microorganisms are becoming more widespread and have become a severe threat to public health. Monitoring of resistance profiles of these microorganisms is critical in terms of combating antimicrobial resistance.^[1] In recent years, the incidence of BSIs caused by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* isolates has increased and associated with higher treatment failure and mortality rates comparing BSIs caused by ESBL-negative isolates.^[2-4]

ESBLs cause resistance through hydrolyzing all cephalosporins, aztreonam, and penicillins, except cephamycins. ESBL-producing strains are also frequently resistant to antibiotics that are not beta-lactam, albeit the resistance to carbapenems is still rare.^[5] The excessive and inappropriate use of carbapenem in clinical practice might accelerate the emergence of carbapenem-resistant bacteria. Since carbapenem-resistant *Enterobacteriaceae* isolates are also resistant to many other antibiotics and considered virulent pathogens, serious precautions should be taken to prevent their spread.^[6]

This study aimed to determine the rate of ESBL-positive *Escherichia coli* and *Klebsiella pneumoniae* strains isolated from blood cultures over three years period, and their susceptibilities to various antibiotics, as well as the distribution among clinics.

Methods

From February 2014 to August 2016, we analyzed blood cultures results retrospectively. We excluded repeated isolates from the same patient in the calculation of antibiotic susceptibility and distribution rates among clinics. The blood cultures were incubated in a BD Bactec FX 200 automated blood culture system (Becton Dickinson, Sparks, MD, USA). When blood culture bottles gave a positive signal, they were taken out from the instrument, broth medium in the bottle was used for a smear preparation for Gram stain and subcultured on blood agar (5% sheep blood) and chocolate agar plates. We identified bacteria colonies with Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) (MALDI Biotyper, Bruker Daltonics, Bremen, Germany). Antibiotic susceptibility tests (AST) were performed using a Phoenix 100 ID/AST automated system (Becton Dickinson, Sparks, MD, USA) or the Kirby Bauer disc diffusion method.

In this study, amikacin, gentamicin, ceftazidime, cefepim, ceftriaxone, piperacillin-tazobactam, ampicillin-sulbactam, trimethoprim-sulfamethoxazole, ciprofloxacin,

imipenem, meropenem, and ertapenem susceptibilities were evaluated for three years; amoxicillin-clavulanic acid and colistin susceptibility were evaluated for 2016. Presence of ESBL was determined by the Phoenix instrument or double disc synergy test. For intermediate/resistant isolates, resistance to carbapenems was confirmed by E-test (BioMerieux, France). AST results were interpreted according to Clinical and Laboratory Standards Institute (CLSI) recommendations for 2014-2015 and European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines for 2016.^[7,8]

SPSS for Windows, Version 15.0 (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis. Descriptive statistics were calculated as numbers and percentages for categorical variables. Trends in the rates of the categorical variable over the years have been tested with the Mantel-Haenszel linear-by-linear association. Statistical significance was accepted as $p < 0.05$.

Results

A total of 632 *E. coli* and 439 *K. pneumoniae* strains were isolated and 34% of these isolates were ESBL-positive. 224 (35%) *E. coli* isolates and 137 (31%) *K. pneumoniae* isolates were ESBL-producer. The distribution of ESBL-positive *E. coli* and *K. pneumoniae* strains by years was determined to be 23%, 36%, 48% and 23%, 32%, 37% for 2014, 2015, and 2016 respectively. The increase over the years was statistically significant for both *E. coli* ($p < 0.001$) and *K. pneumoniae* ($p = 0.011$).

ESBL-positive *E. coli* and *K. pneumoniae* isolates were found most susceptible to amikacin, meropenem, imipenem, and ertapenem respectively. Highest resistance rate was found in ceftriaxone, cefepime, trimethoprim-sulfamethoxazole, and ciprofloxacin (Table 1).

Evaluation of carbapenem-resistance revealed that one of the ESBL-positive *E. coli* strains (0.7%) was resistant to imipenem, while 5 (3.3%) of these strains were resistant to ertapenem. There was no meropenem resistant *E. coli* strain. Resistance rates of ESBL-positive *K. pneumoniae* to imipenem, ertapenem, and meropenem was 11.2%, 12%, and 11.1%, respectively. There was no significant difference in the resistance rates of ESBL-positive *E. coli* isolates to any antibiotics evaluated in the study over the years. Resistance rates of *K. pneumoniae* isolates to imipenem, meropenem, ertapenem, and piperacillin-tazobactam were significantly increased ($p < 0.001$) (Table 1).

Distribution of ESBL-producing strains according to clinics are shown in the Table 2. ESBL-producing strains were most often identified in emergency services (28.1%), followed by the intensive care unit (ICU) (26.5%), pediatric clinics (19.4%), and adult internal medicine clinics (16.2%) (Table 2).

Table 1. Resistance to antibiotics seen over time in extended-spectrum beta-lactamase-positive strains of *E. coli* and *K. pneumoniae*

	ESBL (+) <i>E. coli</i>									ESBL (+) <i>K. pneumoniae</i>										
	2014			2015			2016			p	2014			2015			2016			p
	S	I	R	S	I	R	S	I	R		S	I	R	S	I	R	S	I	R	
AMC	-	-	-	-	-	-	15	0	85	*	-	-	-	-	-	-	5	0	95	*
TZP	62	25	13	64	14	22	64	7	29	0.084	35	52	13	45	19	36	25	2	73	<0.001
SAM	10	35	55	13	18	69	33	0	67	0.479	8	13	79	0	21	79	0	0	100	0.066
Cefoxitin	84	3	3	84	9	7	82	0	18	0.161	92	4	4	92	0	8	62	0	38	0.003
Ceftazidime	33	13	54	26	13	61	6	19	75	0.030	12	21	67	6	6	88	0	2	98	0.001
Ceftriaxone	0	0	100	0	0	100	4	0	96	0.138	4	0	96	6	0	94	0	0	100	0.476
Cefepime	21	4	75	8	4	88	10	1	89	0.137	4	0	96	8	0	92	7	10	83	0.101
Amikacin	100	0	0	98	2	0	100	0	0	*	100	0	0	89	11	0	85	10	5	0.216
Gentamicin	62	0	38	53	0	47	59	0	41	0.992	54	0	46	46	0	54	37	0	63	0.192
Ciprofloxacin	25	8	67	30	4	66	34	1	65	0.892	42	0	58	43	9	48	30	10	60	0.572
SXT	39	0	61	39	0	61	37	0	63	0.804	21	0	79	22	3	75	13	2	85	0.524
Imipenem	96	0	4	100	0	0	100	0	0	0.152	100	0	0	97	0	3	75	0	25	<0.001
Meropenem	100	0	0	100	0	0	100	0	0	*	100	0	0	97	0	3	75	0	25	0.001
Ertapenem	92	9	8	96	0	4	96	1	3	0.448	96	4	0	97	0	3	73	0	27	<0.001
Colistin	-	-	-	-	-	-	99	0	1	*	-	-	-	-	-	-	80	0	20	*

AMC: Amoxicillin/clavulanic acid; ESBL: Extended-spectrum beta-lactamase; I: Intermediate; R: Resistant; S: Sensitive; SAM: Ampicillin sulbactam; SXT: Trimethoprim/sulfamethoxazole; TZP: Piperacillin/tazobactam.

Table 2. Distribution of blood culture extended-spectrum betalactamase-positive isolates according to clinic

	2014 (n=48)	2015 (n=92)	2016 (n=113)
Emergency	14	19	38
Pediatric intensive care	4	17	17
Adult intensive care	8	12	19
Adult clinics	4	20	17
Pediatric clinics	17	15	17
General surgery	1	3	1
Urology	0	5	7
Other surgical clinics	0	1	7

Discussion

Multiple drug-resistant bacteria are increasingly being isolated from BSIs. Data on the resistance profiles of resistant microorganisms are critical to helping clinicians choose the appropriate treatment and to combat against antimicrobial resistance which is an important public health problem.

^[9] Infections caused by ESBL-producing strains increase mortality, hospital stay and costs.^[10]

In our study, over the three-year period 35% of *E. coli* and

31% of *K. pneumoniae* strains isolated from blood cultures sent from various clinics to our laboratory were identified as ESBL-positive strains. In previous studies, it has been reported that ESBL-positivity rates vary according to countries and regions. In a multicentre study conducted in our country, ESBL-producing rates in *E. coli* and *K. pneumoniae* were 42% and 41.4% in hospital isolates respectively.^[11]

Various studies carried out on blood culture isolates in Turkey reported ESBL rates between 26.2% to 44% for *E. coli*,^[12-16] and 24% to 61.4% for *K. pneumoniae*.^[12, 13, 15] In some studies performed in Africa, the ESBL rates of BSI *E. coli* and *K. pneumoniae* isolates were 54.5% to 72.7% and 66.7% to 82.5%, respectively;^[17-19] these rates in Far Eastern countries were 18.5% to 55.5% and 16.5% to 55.7%, respectively.^[20, 21] In a national surveillance study including 2017 hospitals in Germany, healthcare-associated infections due to ESBL-positive *Enterobacteriaceae* between 2007-2011, was investigated in two-year periods (2007-2008, 2009-2010 and 2011-2012); rates of ESBL- positive *E. coli* strains for each two-year periods were 10.8% 15% and 17.5% and *K. pneumoniae* strains were 13.8%, 15% and 11.7%. According to the data in the same study, the increase in rates of ESBL-positive *Enterobacteriaceae* between 2007 and 2012 were found to be statistically significant in surgical site infections (from 11.46% to 15.38%), urinary tract infections

(from 9.36% to 16.56%) and lower respiratory tract infections (from 11.91% to 14.70%). In BSIs, ESBL-positive *E. coli* rate was 12.9% in 2007-2008 and reached up 21.3% in 2011-2012 period but this increase was not statistically significant. The rate of ESBL-positive *K. pneumoniae* in BSIs was 17% in the first two-year period, and decreased to 15.7% in the last two-year period of the study.^[22] In our study, it was determined that the increase in rate of ESBL-positivity over the years in *E. coli* and *K. pneumoniae* strains isolated from BSIs was statistically significant.

ESBL-producing bacteria are known to be isolated more often from hospital-acquired bacteremia. Ndir et al.^[19] reported that 11.6% of ESBL-positive *Enterobacteriaceae* isolates in blood culture were isolated from community-acquired bacteremia and 88.4% from hospital-acquired bacteremia. A study from Turkey reported 61.4% of ESBL-producing *E. coli* strains were isolated from hospital-acquired infections.^[16] Antibiotic resistance rates are particularly high in ICUs. Yilmaz et al.^[23] found ESBL-positivity rates of *E. coli* 56% and *K. pneumoniae* 63% in blood culture isolates of ICUs patients with hospital-acquired infections. Sağlam et al.^[14] reported that 37.8% of ESBL-positive *E. coli* strains were isolated from blood cultures of patients hospitalized in ICUs.

In our study, although ESBL-positive isolates were not defined as hospital-acquired or community-acquired; it was determined that 28.1% of these strains were isolated from patients hospitalized in emergency services, 26.1% of from ICUs and 45.8% from other clinics. The high rate of ESBL-positivity in admissions to the emergency department suggested that antibiotics should be carefully selected for empirical treatment of community-acquired infections. Previous use of third-generation cephalosporins and fluoroquinolones has been reported to increase the risk of community-acquired infection with ESBL-producing strains.^[10]

ESBL-positive strains, comparing to ESBL negative ones, are more resistant to other antibiotic groups besides beta-lactam antibiotics, and treatment of infections caused by ESBL-positive strains continue to be problematic.^[24, 25]

Although carbapenems are the most effective agents in the treatment of infections caused by ESBL-producing bacteria, frequent and inappropriate use of them may cause emerging resistance to these antibiotics.^[6]

In a study conducted in our country between the years 2005 and 2009, the rate of imipenem, meropenem, and ertapenem resistance in ESBL-positive *E. coli* and *Klebsiella* strains isolated from BSIs was found 5.7%, 1.9%, and 2.4%, respectively.^[26] In another study, ESBL-positive *E. coli* strains isolated from various clinical samples were not resistant to imipenem or meropenem. However ertapenem resistance rate was found 0.8% in ESBL-positive *E. coli* strains and car-

bapenem resistance rate in *K. pneumoniae* isolates was 3.6% for all three antibiotics.^[27]

In several studies from Europe, the resistance rate of *E. coli* strains isolated from BSIs was found to range between 3.2% and 6.7% for meropenem, 1.6% and 6.5% for imipenem. In one of these studies, resistance to meropenem and imipenem was not detected in *K. pneumoniae* isolates, in another study, the resistance rate was 65.1% for meropenem and 67.5% for imipenem.^[3, 9] In a 10-year study including 77.618 blood cultures in India, carbapenem and piperacillin-tazobactam resistance was monitored in *E. coli* and *K. pneumoniae* strains, the increase in resistance rate of these antibiotics over years was not statistically significant for *E. coli*, but it was significant for *K. pneumoniae*. In that study, the increase in resistance rate was interpreted as result of increasing in ESBL-positive prevalence and replacement of third-generation cephalosporins with carbapenems and piperacillin-tazobactam in treatment of severe infections.^[28]

In our study, the rate of resistance to imipenem, meropenem, ertapenem, and piperacillin tazobactam in ESBL-positive *E. coli* and *K. pneumoniae* strains isolated from blood cultures was 0.7%, 0%, 3.3%, 23.7% and 11.2%, 11.1% 12%, and 45.5%, respectively. Increasing in the resistance rate over the years for all antibiotics was statistically significant for *K. pneumoniae* ($p < 0.001$), whereas it was not significant for *E. coli*. It has been reported that inappropriate empirical treatment increases mortality rates in invasive infections caused by ESBL-producing strains.^[10]

Considering the ESBL rates in our hospital, the use of carbapenem or amikacin in empirical treatment and de-escalation according to AST results may be good practice in gram-negative bacteremia expected patients.

There are some limitations of this study. Due to the study was retrospective, we could not evaluate the duration of hospital stay or patient transfers between ICU and other services, and hospital and community-acquired infections could not be classified.

Molecular methods were not used to determine resistance mechanisms of multidrug resistant isolates.

In conclusion, this study is one of the rare studies including large number of blood culture isolates in our country. *E. coli* and *K. pneumoniae* strains isolated from blood cultures in our hospital, had high ESBL and carbapenem resistance rates which increased significantly over the years. Our study is important in terms of guiding empirical treatment of BSIs caused by *E. coli* and *K. pneumoniae*. Considering the increasing carbapenem resistance in *Klebsiella* spp., revising the initial treatment would be appropriate as soon as AST results are available.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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