THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2018.60352
Med Bull Sisli Etfal Hosp 2019;53(1):70–75

Research Article

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. A BD Bactec FX automated blood culture system (Becton Dickinson and Company, Franklin Lakes, NJ, USA) was used to examine the blood cultures. Matrix-assisted laser desorption ionization-time of flight mass spectrometry (Product name?; Bruker Daltonics, Inc., Billerica, MA, USA) was used to identify microorganisms. For antibiotic susceptibility tests (AST) and ESBL detection, the Kirby Bauer disk diffusion method or a Phoenix automated system (Becton Dickinson and Company, Franklin Lakes, NJ, 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. pneumonia 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.

Please cite this article as "Bayraktar B, Pelit S, Bulut ME, Aktaş E. Trend in Antibiotic Resistance of Extended-Spectrum Beta-Lactamase-Producing Escherichia Coli and Klebsiella Pneumoniae Bloodstream Infections. Med Bull Sisli Etfal Hosp 2019;53(1):70–75".

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Submitted Date: December 27, 2017 **Accepted Date:** January 11, 2018 **Available Online Date:** March 25, 2019

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

ESBLs hydrolyze all cephalosporins, aztreonam, and penicillins, except cephamycins and induce resistance against this group of antibiotics. Although ESBL-producing strains are resistant to antibiotics that do not contain beta-lactam, resistance to carbapenems is rarely seen.[5] On the other hand, use of excessive and inappropriate carbapenem in clinical practice can accelerate the emergence of carbapenem-resistant bacteria. Since the isolates of carbapenem-resistant *Enterobacteriaceae* are also resistant to many other antibiotics and considered virulent pathogens, serious precautions should be taken to prevent the spread of these microorganisms.[6]

The aim of this study was to determine the ESBL rate in *Escherichia coli* and *Klebsiella pneumoniae* strains isolated from blood cultures and to determine the susceptibilities of ESBL-producing strains to various antibiotics, as well as the distribution among clinics.

Methods

The results of blood cultures sent between February 2014 and August 2016 to the laboratory were analyzed retrospectively. Repeated isolates from the same patient were not included in the calculation of the rate of antibiotic susceptibility or distribution among clinics. The blood cultures were incubated in a BD Bactec FX automated blood culture system (Becton Dickinson and Company, Franklin Lakes, NJ, USA) for 5 days. During this period, 5% sheep blood agar and chocolate agar were cultivated from the bottles signaling bacterial growth and Gram-stained slides were prepared. Matrix-mediated laser desorption ionization-flight time mass spectrometry (MALDI-TOF MS) (Product name?; Bruker Daltonics, Inc., Billerica, MA, USA) and antibiotic susceptibility tests (AST) were performed using a Phoenix automated system (Becton Dickinson and Company, Franklin Lakes, NJ, USA) or the Kirby Bauer disc diffusion method to identify the bacteria.

Amikacin, gentamicin, cefoxitin, ceftazidime, cefepim, ceftriaxone, piperacillin-tazobactam, ampicillin-sulbactam, trimethoprim-sulfamethoxazole, ciprofloxacin, imipenem, meropenem, and ertapenem susceptibilities were evaluated. The presence of ESBL was determined by the Phoenix device or a double disc synergy test. Resistance to carbapenems was confirmed using the Etest (BioMerieux SA, Marcy-l'Étoile, France) with medium-sensitive/resistant isolates. AST results for 2014 and 2015 were evaluated according to Clinical and Laboratory Standards Institute breakpoints, and European Committee on Antimicrobial Susceptibility Testing breakpoints were used to assess the results of 2016.[7, 8]

SPSS for Windows, Version 15.0 (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis. Descriptive statistics of number and percentage were calculated for categorical variables. The trend in the rate of the categorical variables over the years studied was tested using Mantel-Haenszel linear-by-linear association. Statistical significance was accepted as $p<0.05$.

Results

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

In the ESBL-producing strains, AST results were calculated after recurrent strains were eliminated. Among the antibiotics tested during a period of 3 years, ESBL-positive *E. coli* and *K. pneumoniae* isolates were most susceptible to amikacin, meropenem, imipenem, and ertapenem, respectively, while the highest resistance rate was to 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 merapenem. No resistance to meropenem was detected. However, the resistance rate of ESBL-positive *K. pneumoniae* to imipenem, ertapenem, and meropenem was 11.2%, 12%, and 11.1%, respectively. When the change in antibiotic susceptibilities over the study period was examined, it was found that there was no significant difference in the resistance rates of ESBL-positive *E. coli* strains to any antibiotics evaluated. Resistance rates of *K. pneumoniae* strains to imipenem, meropenem, ertapenem, and piperacillin tazobactam were significantly increased ($p<0.001$).

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

	ESBL (+) *E. coli*										ESBL (+) *K. pneumonia*									
	2014			2015			2016				2014			2015			2016			
	S	I	R	S	I	R	S	I	R	p	S	I	R	S	I	R	S	I	R	p
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 beta-lactamase-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

When the distribution of ESBL-producing strains was examined by clinic, it was observed that 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).

Discussion

Multiple drug-resistant bacteria are increasingly being isolated from BSIs. Data on the resistance profiles of resistant microorganisms are very important to help clinicians choose the appropriate treatment and to combat 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, 35% of *E. coli* and 31% of *K. pneumoniae* strains isolated from blood cultures sent from various clinics of our hospital to our laboratory were identified as ESBL-positive strains. The reported rates vary according to the country and region. In a multicenter study conducted in our country, ESBL rates were found to be 42% in hospital-acquired *E. coli* and 41.4% in *K. pneumoniae* isolates.[11]

In various studies conducted with blood culture isolates in our country, the reported rate was 26.2% to 44% for *E. coli*,[12–16] and 24.4% for *K. pneumoniae*.[12, 13, 15] In some studies performed in Africa, the ESBL rate of BSI agents such as *E. coli* and *K. pneumoniae* isolates was found to be 54.5% to 72.7% and 66.7% to 82.5%, respectively.[17–19] In some Far Eastern countries the rate was determined to be 18.5% to 55.5% and 16.5% to 55.7%, respectively.[20, 21] The regional distribution of ESBL-positive *Enterobacteriaceae* responsible for nosocomial infections in Germany between 2007 and 2011 was investigated, and the rate of ESBL-positivity in *K. pneumoniae* strains in 2-year periods (2007-2008,

2009-2010, and 2011-2012) was 10.8%, 15%, and 17.5%, respectively. The corresponding rates for *K. pneumoniae* strains were 13.8%, 15%, and 11.7%, respectively.

In the same study, the data from 2007 to 2012 showed that increases in ESBL-positivity rates in *Enterobacteriaceae* bacteria were 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, the rate of ESBL-positivity in *E. coli* increased from 12.9% in the period of 2007 to 2008 to 21.3% in the period of 2011 to 2012, but this increase was not statistically significant. The rate of ESBL-positivity in *K. pneumoniae* as pathogens of BSIs was 17% in the first 2-year period, and decreased to 15.7% in the last 2-year period studied.[22] In our study, it was determined that the increase in the ESBL-positivity rate 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 nosocomial bacteremia. In a study conducted in Turkey, it was determined that 61.4% of ESBL-producing *E. coli* strains were isolated from nosocomial infections.[16] In particular, antibiotic resistance rates were observed to be higher in ICUs. Yılmaz et al.[23] found an ESBL rate of 56% *E. coli* and 63% *K. pneumoniae* strains isolated from blood cultures of patients with nosocomial infections hospitalized in ICUs. Sağlam et al.[14] reported that 37.8% of ESBL-positive *E. coli* strains in blood cultures were isolated from patients hospitalized in ICUs.

In our study, although ESBL-positive isolates were not defined separately as nosocomial or community-acquired infections, it was determined that 28.1% of these strains were isolated from patients hospitalized in emergency services, 26.1% of them from ICUs, and 45.8% from inpatients in other clinics. The high rate of ESBL-positivity in admissions to the emergency department suggest 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 infection with community-acquired ESBL-producing strains.[10]

ESBL-positive strains are also resistant to beta-lactam antibiotics as well as other antibiotic groups, compared with ESBL-negative strains, and treatment of infections caused by these strains continues to be problematic.[24, 25]

Although carbapenems are among the most effective agents in the treatment of infections caused by ESBL-producing bacteria, frequent and inappropriate use may lead to the development of resistance to these antibiotics.[6] In a study conducted in our country encompassing the years 2005 to 2009, the rate of imipenem, meropenem, and ertapenem resistance in the ESBL-positive *E. coli* and *Klebsiella* isolates obtained from BSIs was found to be 5.7%, 1.9%, and 2.4%, respectively.[26]

In another study conducted in this country, ESBL-positive *E. coli* strains isolated from various clinical samples did not demonstrate imipenem or meropenem resistance. However resistance to ertapenem was found in 0.8% of ESBL-positive *E. coli* strains and the rate of resistance in *K. pneumoniae* isolates was 3.6% for all 3 antibiotics.[27]

In several studies conducted in Europe, the resistance rate of *E. coli* strains isolated from BSIs was found to range between 3.2% and 6.7% for meropenem and 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 of 77,618 blood cultures in India, where the resistance to carbapenem and piperacillin tazobactam was monitored in *E. coli* and *K. pneumoniae* strains, the increase in the resistance rate to these antibiotics over the years was not statistically significant for *E. coli*, but it was significant for *K. pneumoniae*. The increase in the resistance rate in that study was interpreted as a result of ESBL prevalence in third-generation cephalosporins, and these antibiotics were replaced by carbapenems and piperacillin tazobactam in the treatment of serious infections.[28]

In our study, the rate of resistance to imipenem, meropenem, ertapenem, and piperacillin tazobactam caused by ESBL-positive *E. coli* and *K. pneumoniae* strains isolated from blood cultures was 0.7%, 0%, 3.3%, 23.7% and 11.2%, 12%, and 45.5%, respectively. The increase in the resistance rate to all of these antibiotics over the years studied was statistically significant in for *K. pneumoniae* ($p<0.001$), whereas it was not significant for *E. coli*. It has been reported that insufficiency in 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 patients with suspected Gram-negative bacteremia.

There are some limitations of this study. Due to the retrospective nature, we could not evaluate the duration of hospital stay or patient transfers between ICU and other services, and hospital and community-acquired infections were not evaluated separately. In addition, the resistance state of multiple isolated microorganisms was not identified using molecular methods. However, this study is one

of the rare examples in our country of research conducted with a large number of blood culture isolates.

E. coli and *K. pneumoniae* strains isolated from blood cultures in our hospital showed ESBL-positivity and carbapenem resistance rates had increased over the years studied. *E. coli* and *K. pneumoniae* are important factors in the empirical treatment of BSIs. Considering the increased carbapenem resistance in *Klebsiella spp.*, it would be appropriate to review the treatment when AST results are obtained.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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