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Research Article

Antimicrobial Susceptibility Patterns and Extended-Spectrum β-Lactamase Production by *Enterobacterales* in a Tertiary Hospital

Bir Üçüncü Basamak Hastanesinde *Enterobacterales*'ler Tarafından Üretilen Geniş Spektrumlu Beta Laktamazlar ve Antimikrobiyal Duyarlılık Paternleri

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Abstract

Puspose: In this research, we seek to define the extended-spectrum -lactamases (ESBL) producers and patterns of antimicrobial susceptibility of *Enterobacterales* from clinical care patients in the Aksaray province Türkiye, throughout the term from January 2017 to December 2021.

Materıal And Methods: Clinical strains will be isolated and identified for microbiologically. Then *Enterobacterales* isolates antibiotic resistance profiles will be determined, in addition the presence of blaCTX-M gene in these isolates will be investigated by molecular methods.

Results: A total of 1752 clinical strains were initially microbiologically isolated and subsequently identified using VITEK® 2 incoupled with an automated ID and susceptibility system. Following that, the identified and suspected isolates were subjected to PCR application for the presence of blaCTX-M gene. The results showed that more common *Klebsiella pneumoniae (K. pneumoniae*) (43.95%) than other species with low percentages were following *Escherichia coli (E.coli)* (45.89%). The antimicrobial susceptibility pattern was determined to be 86.62% resistant to ampicillin, 76.33% to amoxicillin/clavulanic acid, 64.52% to cefuroxime, 59.14% to trimethoprim/sulfmetaxazol, 59.99% to ceftriaxone, 58.35% to ceftazidime, and 54.39% to ciprofloxacin. 45.49% of the isolates from urine samples showed sensitivity to fosfomycin, nitrofurantoin, imipenem, and amikacin. Based on the suspected species, the frequencies of *E. coli* isolates were detected to be 47.63% positive for ESBL, and of *K. pneumoniae* isolates 61.16%.

Conclusions: Overall, we detected that the bacteri of ESBL-producing *E. coli* was relatively high. Antimicrobial resistance clearly to be a mixed issue because of the superior consumption of antibiotics in the society and the knowledge from the trend research could be considered as helpfully for a more wide assesment of the antibiotic resistance profiles in the Turkiye provinces.

Keywords: *Enterobacterales*, Antimicrobial resistance, ESBL, bla CTX-M

Öz

Amaç: Bu çalışmada, Ocak 2017-Aralık 2021 döneminde, Aksaray ilinde çeşitli kliniklerden gelen hastalardan elde edilen *Enterobacterales* izolatlarının ürettiği geniş spektrumlu β-laktamaz (GSBL) oranlarının ve antimikrobiyal duyarlılık paternlerinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Laboratuvarda, klinik numunelerden suşlar izole edilecek ve mikrobiyolojik olarak tanımlanacaktır. Daha sonra *Enterobacterales* izolatlarının antibiyotik direnç profilleri belirlenerek, bu izolatlarda blaCTX-M geninin varlığı moleküler yöntemlerle araştırılacaktır.

Bulgular: Çalışma süresince toplam 1752 klinik suş mikrobiyolojik olarak izole edildi ve ardından otomatik bir ID ve duyarlılık sistemi ile birleştirilmiş VITEK® 2 sistemi kullanılarak suşlar tanımlandı. Ardından tespit edilen ve şüphelenilen izolatlara blaCTX-M geninin varlığı için PCR uygulaması yapıldı. Bulgular, *Escherichia coli*'nin (*E.coli*) (%45,89) en yaygın tür olduğunu, bunu *Klebsiella pneumoniae* (*K.pneumoniae*) (%43,95) ve düşük yüzde ile diğer türlerin izlediği görüldü. Antimikrobiyal duyarlılık paterni ampisiline %86,62, amoksisilin/klavulanik aside %76,33, sefuroksime %64,52, trimetoprim/sülfmetaksazole %59,14, seftriaksona %59,99, seftazidime %58,35 ve siprofloksasine %54,39 olarak belirlendi. İdrar örneklerinden elde edilen izolatların %45,49'u fosfomisin, nitrofurantoin, imipenem ve amikasine duyarlılık gösterdi. Şüphelenilen türe göre GSBL sıklığı *E. coli* için %47,63, *K. pneumoniae* için %61,16 olarak bulundu.

Sonuç: Genel olarak, GSBL üreten *E. coli* oranının nispeten yüksek olduğunu bulduk. Antimikrobiyal direnç, toplumdaki yüksek antibiyotik tüketimi nedeniyle karmaşık bir sorun olarak görünmektedir ve mevcut çalışmadan elde edilen bu veriler, Türkiye'de illerdeki antibiyotik direnç profillerinin daha kapsamlı bir şekilde değerlendirilmesi için yardımcı olarak kabul edilebilir.

Anahtar Kelimeler: *Enterobacterales*, Antimicrobial direnç, GSBL, bla CTX-M

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INTRODUCTION

One of the biggest global dangers to public health is antimicrobial resistance. It has asubstantial negative influence on health care systems, as well as, global serious social implications (1). The family of Enterobacterales includes the well-known pathogens which cause nosocomial infections, gastrointestinal infections, septicemia, pneumonia, meningitis, peritonitis and urinary tract infections (2,3). Some members of the family Enterobacterales have acquired resistance against antibiotic agents by a specific resistance mechanism, producing extended spectrum β-lactamase (ESBL) enzymes to hydrolyze oxyimino-cephalosporins and aztreonam(4). Due to this characteristic, extended spectrum β-lactamase (ESBL) enzymes exert a significant impact on antimicrobial therapy. These enzymes have emerged with point mutations in the TEM-1, TEM-2 and SHV-1 genes, which show beta-lactamase activity. While ESBL enzymes originating from TEM and SHV genes were common in the 1980s, they were replaced by CTX-M type enzymes in the 2000s (5). The early CTX-M variants hydrolysed cefotaxime and ceftriaxone efficiently, thus the name cefotaximase. In contrast to the TEM- and SHV-type ESBLs reported to date, the early CTX-M enzymes had limited activity against ceftazidime. However, CTX-M variants with enhanced ceftazidime hydrolytic activity were later described (6). This makes infections caused by pandrug resistant or almost pandrug resistant Gram-negative germs particularly challenging to cure and a growing problem in many healthcare facilities. (7,8). Moreover, *E. coli* and *Klebsiella pneumoniae* (*K. pneumoniae*) have get to resistant to newer third generation cephalosporins, indicating that they are hard-to-treat ESBL producers. Recent worldwide surveys reported increasing proportions of ESBL-producers among *E. coli* (from 9% in 2003 to 18% within 2005–2007) and *K. pneumoniae* (from 14% to 26.2%); there was decreasing susceptibility to third-generation cephalosporins (from 85–90% to 77–82%) (9).

As variations do exist among different countries and regions, the local epidemiological data along with local resistance patterns is essential for the effective management of infections (11).

In Turkey, there have been many clinical studies on ESBL-producing strains of Enterobacterales. However, data from Aksaray province in Central Anatolia are still missing. Therefore, this research was planned to define the antimicrobial susceptibility patterns and to detect the occurrence of ESBL-producers among members of the family Enterobacterales isolated from various clinical care patients admitted to the Aksaray University Training and Research Hospital, Aksaray province, Turkiye.

MATERIALS AND METHODS

The research was carried out between January 2017 to December 2021 in the department of Clinical Microbiology of the Training and Research hospital of the University School of Medicine. The University Training and Research hospital located in middle Anatolian province, Turkey comprises a 500-bed tertiary care facility with approximately 50.000 admissions each year.

Ethics Committee Approval

The territorial ethics committee gave its admission to the study protocol, Faculty of Medicine, Aksaray University. (Committee approval date: 23.06.2022; number 2022/12-13).

Isolation and identification of Enterobacterales species

A total of 1752 clinical samples included urine (n=1002), blood (n=226), catheter (n=92), tracheal secretion (n=315), wound (n=54), sputum (n=30), stool (n=8), tissue (n=19) and sterile body fluids (n=6) were cultured directly onto MacConkey agar and 5% sheep blood agar (Merck, Darmstadt, Germany). Under aerobic situations, all plates were incubated at 37 °C for 24-48 hours.

For each morphologically distinct type of colony per specimen belonging to Enterobacterales, one isolate was selected and tested for gram stain and oxidase reaction using Bactident oxidase test strips (Merck, Darmstadt, Germany), and the oxidase-negative colonies were subcultured onto 5% sheep blood agar for further identification.

All isolates were thereafter identified handling the VITEK®2 compact automated system (bioMérieux), for this purpose, two or three colonies from 5% sheep blood agar were suspended in aqueous 0.45% (wt/vol) NaCl to achieve a turbidity equivalent to 0.5 Mc Farland. The turbidity meter (DensiChek, bioMerieux, Franch) was used for turbidity reading. After that, the isolates were identified using VITEK®2 ID-GNC card according to the manufacturer's instructions.

Determination of antimicrobial susceptibility (AMS)

The AMS was performed using AST-N325 and AST-N327 VITEK® 2 cards comprised of various antibiotics including ampicillin (AM), amoxicillin/clavulanic acid (AMC), amikacin (AN), ceftazidime (CAZ), cefixime (CFM), ciprofloxacin (CIP), ceftriaxone (CRO), cefuroxime (CXM), ertapenem (ETP), fosfomycin (FOS), nitrofurantoin (FT), gentamicin (GM), imipenem (IPM), meropenem (MEM), trimethoprim/sulfmetaxazol (STX), piperacillin/tazobactam (TZP), colistin (CS), cefepime (FEP) and tigecycline (TGC).

Finally, the production of ESBLs was confirmed by disc diffusion method using ceftazidime (30 µg) and cefotaxime (30 µg) discs alone and in combination with clavulanic acid discs according to the Guidelines of EUCAST (13), followed by an in the night incubation at 37°C. The zone of inhibition was evaluated by the criteria described by the Guidelines of EUCAST (13). *E. coli* ATCC 25922 and *K. pneumoniae* ATCC 700603 and were used for ESBL positive and ESBL negative control testing.

Molecular detection of ESBL

A randomly selected number of ESBL-producing *E. coli* (n=30) and *K. pneumonia* (n=15) isolates were further examined for the presence of bla-genes by a specific PCR assay using universal CTX-M primers and the amplification conditions as previously described (14). Total DNA of ESBL-producing isolates was extracted using DNeasy Blood & Tissue Kit (Qiagen, Hilden, Germany) accordingly the manufacturer's instructions. Gel electrophoresis of the PCR products was performed in a 2% agarose gel (Biozym, Hessisch-Oldendorf, Germany). The amplicons were photographed by GelDoc 2000 imaging system (BioRad-USA). Finally, the analysis was carried-out using Image Lab™ Software, Version 5.0 (BioRad). For quality control, *E. coli* strain DSM 22665 harboring a blaCTX-M gene was used as standard ESBL-positive strain for all PCR amplification tests.

Statistical analysis

SPSS for Windows version 26 was used for the statistical analysis of the study subjects' demographic, clinical, and laboratory data. (IBM, USA).

RESULTS

In one year study period, Enterobacterales isolates were recovered from 1752 clinical samples. Different Enterobacterales isolates from clinical samples are displayed in Table 1.

Clinical samples included urine (n=1002), blood (n=226), catheter (n=92), tracheal secretion (n=315), wound (n=54), sputum (n=30), stool (n=8), tissue (n=19) and sterile body fluids (n=6) . The results showed that 898 (51.26%) isolates were beta lactamase positive. The presence ratio per genus was; *E. coli* (n=804; 45.89%), *K. pneumoniae* (n=770; 43.95%), *K. oxytoca* (n=10; 0.58%) *Proteus spp*. (n=43; 2.45%), *Enterobacter spp*. (n=64; 3.65%), *Serratia spp*. (n=28; 1.61%), *Citrobacter spp*. (11; 0.63%), P*rovidencia spp.* (9; 0.50%) and *Morganella morganii* (11; 0.63%) and *Raoultella ornithinolytica* was (2; 0.11%) (Table 2).

Table 1: Percent prevalence of antimicrobial resistance phenotypes in Enterobacterales isolates from different specimens.

Bacterial Species		*E. coli*	*K. pneumoniae*	Other Isolates
Isolate	No.	804	770	178
	(%)	45,89	43,95	10,16
Antibiotics and % of Resistance	AM	73,34	100	88,75
	AMC	58,73	93,79	80,29
	AN	64,35	68,8	10,38
	CAZ	39,23	81,33	45,32
	CIP	28,8	84,49	39,78
	CRO	34,92	90,34	41,91
	CXM	28,94	96,8	85,62
	ETP	4,54	81,5	27,89
	GN	17,43	67,2	31,13
	MEM	2,64	77,68	17,66
	SXT	44,69	79,52	36,28
	TZP	23.45	89,76	29,23
	CFM	52,36	87,48	77,25
	FOS1	24,23	54,42	37,12
	FT1	27,35	74,33	71,26
	IPM	1,25	61,35	22,92
	CO2	1,57	44,9	55,48
	FEP	35,3	83,12	18,8
	TGC2	2,56	31,24	37,44

Abbreviation: AM, ampicillin; AMC, amoxicillin/clavulanic acid; AN, amikacin; CAZ, ceftazidime; CFM, cefixime; CIP, ciprofloxacin; CRO, ceftriaxone; CXM, cefuroxime; ETP, ertapenem; FOS, fosfomycin; FT, nitrofurantoin; GM, gentamicin; IPM, imipenem; MEM, meropenem; STX, trimetoprim/sulfmetaxazol; TZP, piperacillin/tazobactam; CS, colistin; FEP, cefepime; TGC, tigecycline. Antibiotic resistance phenotypes determined based on EUCAST guidelines (EUCAST Clinical Breakpoint Tables 2020)

Table 2: Distribution and percent of the esbl isolates in investigated specimens

Bacterial species	Total no.[1]	ESBL producing isolates	
		No. of isolates (%)	Specimen (*n*)[2]
E. coli	804	383 (47,63)	urine (280), blood (48), catheter (12), tracheal (19), wound (16), sputum (6), sterile body fluids (1), tissue (1)
K. pneumonia	770	471(61,16)	urine (134), blood (144), catheter (12), tracheal (161), wound (9), sputum (9), sterile body fluids (2)
Other isolates	158	44 (27,85)	urine (27), tracheal (12), wound (2), sputum (1), stool (1), catheter (1)
Other isolates (ESBL (-))	24	0	
Total	1752	898 (51,26)	

1. Total number of isolates; - = none
2. Number in parenthesis indicates the number of isolates; ESBL, extended spectrum β-lactamase.

The majority of ESBL-producing isolates were recovered from urine specimens (n=442; 49.11%) followed by blood (n=192; 21.38%), tracheal secretion (n=192; 21.38%), with decreasing isolation rates from wound (n=27; 3.01%), catheter (n=25; 2.79%), sputum (n=16; 1,78%), steril fluid body (n=3; 0.33%), stool (n=1; 0.11%) and tissue(n=1; 0.11%) (Table 3).

Table 3: Clinical samples from which enterobacterales isolates were obtained and ESBL (+) ratios.

Clinical samples	Total samples		ESBL (+) samples	
	n	%	n	%
Urine	1002	57.19	442	49.11
Tracheal secretion	315	17.98	192	21.38
Blood	226	12.90	192	21.38
Catheter	92	5.25	25	2.79
Wound	54	3.08	27	3.01
Sputum	30	1.71	16	1.78
Tissue	19	1.09	1	0.11
Stool	8	0.46	1	0.11
Sterile body fluids	6	0.34	3	0.33
Total	1752	100	898	100

Finally, all selected *E. coli* (n=30) and *K. pneumoniae* (n=15) isolates phenotypically ESBL positive were confirmed with PCR amplification of blaCTX-M gene. The results revealed that 45 ESBL positive isolates were positive with an amplicon size of 585 bp (Figure).

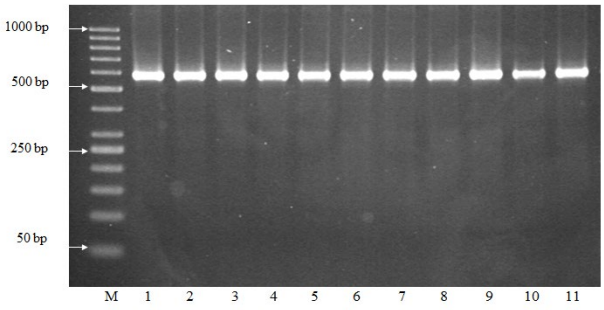

Figure: Typical amplicon of blaCTX-M (585 bp).

M = Marker, Gene Ruler® 50 bp DNA Ladder; 1-10, isolates obtained in this study; 11 = positive control *E. coli* strain DSM 22665 harboring a blaCTX-M gene.

CONCLUSION

A meta-analysis represents the first attempt to assess the prevalence of co-existing ESBL producing *E. coli* and *K. pneumoniae* in animals, humans, and the environment worldwide. Additionally, it was observed that blaCTX−M and blaSHV were the most frequently detected genes in ESBL producing *E. coli* and *K. pneumoniae* infecting animals, humans, and the environment (12).

The CTX-M or cefotaximase known as serine-β-lactamases family pose a substantial clinical challenge because of their capacity to impart resistance to a wide range of β-lactam antibiotics and inhibitors. This characteristic qualifies CTX-M-ases for classification as ESBL (13). In recent years, there have been studies on the epidemiology of CTX-M β-lactamases in the world (14).

Since no data related to the ESBL prevalence in the middle Anatolian region in Turkıye were available, in our hospital, a study was done to determine the prevalence of ESBL among Enterobacterales isolates and their antibiotic susceptibility profile. To the best of our knowledge, this study was the first to documented the prevalence of Enterobacterales that produce ESBLs. and the distribution of antibiotic susceptibly patterns from the specimens of patients in province Aksaray of middle Anatolia region.

In investigation yielded, a total of 1752 Enterobacterales isolates from different specimens were analyzed. The majority were *E. coli* (45.89%) followed by *K. pneumoniae* (43.95%), and other species (10,16%) (Table 1).

Our study emerged that the *E. coli* isolates were resistance to ampicilin (73,34%), amikacin (64,35%), amoxicillin clavulanic acid (58,73%), cefixime (52,36%), sulfometaxazol/trimethoprim (44,69%), ceftazidime (39,23%) respectively. There is a dramatic difference between the study by Gündüz et al and our *E. coli* resistance patterns in terms of amikacin. They found 6% resistance to amikacin (15). A decrease in amikacin resistance in ESBL-producing *E. coli* was observed after 2019 in the study by Beata et al (16). In our study, *K. pneumoniae* isolates showed resistance to ampicilin (100,00%), cefuroxime (96,80%), amoxicillin clavulanic acid (93,79%), ceftriaxone (90,34%), piperacillin/tazobactam (89,76%), cefixime (87,48%) and ceftazidime (81,33%). *K. pneumoniae* strains show a more resistant profile compared to *E. coli* and other Enterobacterales. These results are consistent with the studies of Beata et al. Although *E. coli* is responsible for the majority of infections, *K. pneumoniae* is frequently seen in multidrug-resistant strains (16).

Around the world, ESBL-producing Enterobacterales are becoming more common in urinary tract infections.

In this investigation, the prevalence of ESBL-producing organisms was detected to be 36.3%, with the bulk of ESBL isolates coming from urine samples. (Table 2 and Table 3). Our results indicate that the frequency of ESBL-producing bacteria was remarkably high rate the E. coli isolates (n=280; 73.10%) than the *K. pneumoniae* isolates (n=471, 28.45%) and ESBL-producing *K. pneumoniae* and *E. coli* were isolated most commonly from urine samples (n=280) and (n=134), respectively. Similar to our study, in a study by Şenol et al. 86.55% of the 1041 ESBL-positive samples were urine samples and 70.3% were reported as E. coli (17).

The epidemiological research for ESBL-producing bacteria conducted locally, regionally, nationally, and internationally bacteria in the clinical specimens provide different data (7). In Turkiye, ESBLs has been investigated in different studies performed in various regions, quite different antimicrobial resistance/susceptibility rates have been reported. For example Bülüç et al. (19) reported that ESBL detection rate in various clinical samples including urine samples (37% in all) in Istanbul faculty of medicine; 48% of *K. pneumoniae*, 40% of *K. oxytoca* and 14% of *E. coli* were ESBL positive. Also Karagöz et al. (20) determined the drug resistance of 28 ESBL-

producing *E. coli* isolates acquir from 144 patients hospitalized at the Yüzüncü Yil University Hospital in Van province, Turkey. They reported that all *E. coli* isolated developed resistance by producing ESBLs against oxyimino and non-oxyimino cephalosporins, and penicillin-type antibiotics. Delialioglu et al. (21) proclaimed that ESBL frequencies of *E. coli*, *K. pneumoniae* and *K. oxytoca* and isolates were 18.3, 29.7 and 4.2%, respectively. In addition, Bali et al. (22) verified 94 clinical isolates collected from Gazi University Hospital in Ankara and showed that 69.1% of the Enterobacterales isolates were ESBL-producer. They came to the conclusion that the most prevalent species in the hospitalized patients were ESBL-positive strains of *A. baumannii, E. coli*, , *K. pneumoniae* and *P. aeruginosa*, and that it is crucial to quickly identify these drug-resistant strains in order to treat serious infections. Celik et al. (23) examined the presence of ESBL-producing *E. coli* isolated from patients admitted to the hospital of the Trakya University in the province of Edirne with a community-acquired urinary tract infection.

The interpretation of the study by Doğanay et al. is that although different studies had different resistance rates, there was a change in resistance rates between centres over the years. The effect of the samples from which the isolates were obtained, the clinics and the conditions of patient use on resistance can be attributed to this situation (23).

Eleven isolates of *E. coli* harboring ESBL were identified among 30 *E. coli* isolated from patients admitted with symptoms corresponding to upper urinary tract infection. Furthermore, the selected ESBL-positive isolates were analyzed for blaCTX-M gene by PCR assay. The results showed that all investigated ESBL-producing isolates were observed to carry blaCTX-M, the gene that mediates CTX-M enzyme production. The ESBL mediated by blaCTX-M type β-lactamase genes are undoubtedly the most widespread type produced among species of Enterobacterales worldwide. Several studies in Turkiye have shown that CTX-M-type extended-spectrum -lactamases have appeared in Enterobacterales, together with the genes coding for their production (22).

Over the last two decades, there has been an eightfold surge in the intestinal carriage rate of ESBL *E. coli* within the community. Mitigating its dissemination may necessitate the development of novel therapeutic and public health strategies (24). Kızmaz et al. found that faecal colonisation of ESBL *E. coli* persisted in 15 (23%) of 64 patients after treatment of UTI and that faecal and urine isolates of three (20%) of these patients were in the same phylogenetic class. Faecal colonisation was found to be significantly higher in patients with invasive procedures in the last year (25). These results reveal the spread of ESBL from another point.

An inherent limitation of this study is the relatively small sample size for the CTX-M gene, which may affect the generalisability of the findings to a wider population. Furthermore, the study faced challenges due to the unavailability or unreliability of certain data, imposing restrictions on grouping and analysing for hospital- or community-acquired ESBL strains.

The current study reveals an increasing resistance to third generation cephalosporins in the middle region of Turkıye. The ESBL-producing bacteria disseminates easily through communities where antimicrobial drug consumption is uncontrolled. An adequate and reasonable antibiotic use may lead to reduction due to the selective pressure, and it's possiblity that the resistance bacteria will no longer have a survival benefit. The information from the present study may be useful for a more thorough analysis of the patterns of antibiotic resistance across Turkıye.

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