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Prevalence of Extended-Spectrum Beta-Lactamase Producing Klebsiella: Cross-Sectional Study, 2000-2021

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ABSTRACT

Increasing resistance due to extended-spectrum ß-lactamases (ESBLs) and multiple resistance mechanisms in gram-negative hospital isolates restrict the role of ß-lactam antibiotics in empirical treatment of serious infections. As the prevalence of ESBL producing strains and resistance rates to antimicrobial agents can vary in each center, local surveillance studies are required to guide therapy. In this study, the prevalence of ESBL-K hospitalized population and the change of prevalence through years from 2000 to 2021.

Klebsiella strains isolated between 2000 and 2021 years, were included. 2000 data was collected from two hospitals; one state and private group hospitals. The other whole data were collected only form private group hospitals. ESBL tests were performed according to CLSI and EUCAST guidelines.

ESBL positive Klebsiella strains were mostly commonly isolated from intensive care units and from sputum + tracheal aspirate (%41). Total prevalence of ESBL positive Klebsiella strains were 51.29%. The prevalence of 2000 years was high probably due to the different hospital /patient profile. By excluding the 2000 data, the prevalence were increasing by years; 15.38% at 2001 to 61.50% at 2021.

High prevalence of ESBL in Turkey was increasing by years. Our private hospitals data was lower than the other state hospitals in the Turkey. Different hospital /patient profile could be the reason of low prevalence through precarity level, unnecessarily broad-spectrum antibiotic treatment, environmental contamination, kitchen hygiene and European health tourism. More research must be done to clarify the reason of this differences.

Keywords: Extended-spectrum beta-lactamase producing Kelbsiella, Prevalence of ESBL-K, ESBL

Introduction

Extended-spectrum β-lactamase (ESBL) producing Enterobacteriaceae are an important reason for β-lactam antibiotics treatment failure (1). Asymptomatic carriage often precede infections due to ESBL-producing Enterobacteriaceae (ESBL-E) (2). Potential routes of transmission of ESBL-E to humans are the human-to-human transmission, food chain, direct contact with animals or indirectly via the environment (3).

ESBL-E are emerging worldwide and have been rated by the WHO as high priority pathogens among resistant bacteria (4).

Enterobacteriaceae group bacteria that exhibit resistance to beta-lactams, broad-spectrum beta-lactams, and third-generation cephalosporins are named as ESBL-E. ESBL-E such as TEM-1, TEM-2, SHV-1, and OXA-10 has been predominantly associated with nosocomial outbreaks because of the resistance caused by point mutations and transferred by plasmid. The CTX-M-15 type ESBL-E is the most commonly identified and common in many countries in Europe, Asia, Africa and the United States (5-7). TEM and SHV-type ESBLs are most often found in *Escherichia coli* and *Klebsiella pneumoniae*TEM -lactamases have been found mainly in clinical isolates of *E. coli* (8, 9).

The majority of SHV-type ESBLs are found in strains of *K. pneumoniae*. The SHV-1 β-lactamase is most commonly found in *K. pneumoniae* and is responsible for up to 20% of the plasmid-mediated ampicillin resistance in this species (10, 11).

This study aimed to determine the prevalence for ESBL-producing *Klebsiella* (ESBL-K) in the Turkey hospitalized population and the change of prevalence by years between 2000-2021.

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Materials and Methods

Study Design and Participants: This was a cross-sectional study.

In our study, 35526 *Klebsiella* strains isolated from various clinical samples as an infectious agent between 2000 and 2021 years, were used.

In 2000, *Klebsiella* strains were collected from a goverment hospital, Ankara Training And Research Hospital and a private hospital groups, Acibadem Hospitals. After 2000, *Klebsiella* strains were collected from only Acibadem Hospitals.

Procedures: Initially, susceptibility tests were performed with the VITEK 2 (BioMérieux, France) system and ESBL results were evaluated by expert system of VITEK 2 according to manufacturer's recommendations. When the ESBL results were suspicious, the Double Disc Sinergy Test (DDST) or Combine Disc Test (CDT) were applied as ESBL confirmations tests according to CLSI and EUCAST guidelines (12,13).

To perform these manual tests, bacterial suspension prepared in 0.5 McFarland turbidity was spread to Mueller-Hinton Agar medium by using sterile swab.

In DDST; after placing an amoxicillin clavulanic acid (AMC) (20/10 μg) disc in the centre of the petri dish and placing ceftazidime (CAZ) (30 μg), ceftriaxone (CRO) (30 μg), cefepim (FEP) (30 μg), cefotaxime (CTX) (30 μg), aztreonam (ATM) (30 μg) radially at a distance of 25 mm from AMC's disc circumference, an expansion towards the AMC disk in the inhibition zones around the CAZ, CRO, FEP, CTX or ATM discs or the presence of a non-bacterial synergy area evaluated as ESBL production. In CDT; ceftazidime (CAZ) (30 μg), ceftazidime-clavulanic acid (CCA) (30/10 μg), cefotaxime (CTX) (30 μg), cefotaxime-clavulanic acid (CCT) (30/10 μg) were used. CAZ and CCA discs were placed in the petri dish with 30 mm distance and same procedure was applied to CTX and CCT discs.

Petri dishes were incubated at 35°C for 18 hours and results were evaluated according to EUCAST criteria. 5 mm or more difference between cephalosporin disc and cephalosporin -clavulanate disc was evaluated as ESBL production (12,13).

Results

Demographic informations: Patients included in the study were 0-94 years old and 72% patients were male, 28% female.

ESBL K strains were commonly isolated from intensive care units (30,0%), then respectively; surgical departments (22,0%), hematology-oncology departments (16%), internal medical departments (14%), emergency departments (12,0%) and department of pediatrics (6,0%) (Table1).

The patient sample types that most ESBL-K isolated that ESBL-K strains isolated were sputum and/or tracheal aspirate (%41) , blood (37%)and urine (%22) (Table2).

The number of *Klebsiella* isolated was increasing by years. It was 328 at 2000 and 3978 at 2021.

The number of *Klebsiella* isolated from in-patients was also progressively increasing by years. It was 172 at 2000 and 2678 at 2021

Total prevalence of ESBL positive *Klebsiella* strains were 51.29%.

Year 2000 data was collected from two hospitals groups; one state and private group hospitals. The other whole data were collected only from private group hospitals. The prevalence of ESBL-K (isolated ESBL-*Klebsiella* number from in-patient/ isolated *Klebsiella* number from in-patient **%)** were also increasing by years. But at year 2000, the ratio was similar as 2014. This could be due to diffence at hospital/patient population. By excluding the 2000 data, the ratio was increased from 15.38% at 2001 to 61.50% at 2021 (Table 3).

Discussion

Since possessing bactericidal effect and low side effects, broad-spectrum beta-lactam antibiotics are often preferred. On the other hand, due to increased clinical use of these drugs the resistance to beta-lactamases has been appeared. ESBL-producing strains cause mortality and serious economic losses (14-16).

Since 2000, the prevalence of ESBL-K has been increasing worldwide with large geographical variations (17). Turkey is one of the countries that possess the increased ESBL-K prevalence due to the redundant use of antibiotics [18-20]. In a study published in 2001, it was reported that prevalence of ESBL positivity was reported higher among *K. pneumoniae* than among *E. coli* strains (19).

Our study was set out to obtain a representative sample of the country's general population. In all, 35526 strains were included and the total prevalence was 51.29%, which is comparable to lower than the other studies in the Turkey. But although the ESBL positivity ratio was lower than

Table 1. Distribution of ESBL Positive *Klebsiella* According To Clinical Departments

Departments	ESBL positive ratio %
İntensive care units	30,0
Surgical departments	22,0
Hematology-oncology departments	16,0
Internal medical departments	14,0
Emergency departments	12,0
Department of pediatrics	6,0

Table 2. Distribution of ESBL Positive *Klebsiella* According To The Most Common Patient Sample Types

Sample type	ESBL positive ratio %
Sputum + Tracheal aspirate	41,0
Blood	37,0
Urine	22,0

avarage of the country, it was increasing by every year as expected from 15,0 to 61,0.

Studies have shown that these rates can be variable depending on the country and region. At a multi-center study (MYSTIC) Gur *et al.* found that hospital acquired ESBL-K strains ratio were 40.5% in 2004-2005. In mystic study, already results of the two centers were higher than the other centers. All the hospitals occupied in the study were state hospitals. In our study, 2000 data collected from state and private hospitals were higher than other year's data collected from just private hospitals; similar as MYSTIC study (21).

In the other study published in 2007, Guducuoglu *et al.* reported that ESBL production was 63% in hospitalized patients while this ratio was 30% in outpatients (23). Studies also published at 2000, 2001 and 2009 yr in Turkey present different prevalence ratio 22%, 33% and 44%. When the studies conducted in our country are examined, it is seen that there has been an increase in ESBL production rates over the years (14, 22, 23, 24).

In the European population, the prevalence of ESBL-producing Enterobacterales colonization in the community ranges from 6% to 11%.4, in hospitalized patients has been reported to be as high as 13% in some regions (25, 26). In the study conducted in Germany at 2007-2011 yr, the prevalence of ESBL-K was reported as 13,8%, 15% and 11,7% in two-year periods (2007-2008, 2009-2010 and 2011-2012, respectively) (27).

Known specific risk factors for ESBL-producing bacterial infections are ESBL-E carriage, age >55 years, male sex (for urinary tract infections) (28-30), precarity level (31,32), antibiotic treatment in the past 1–3 months (33-36), particularly broad-spectrum antibiotics (36-40), recent hospitalization (33), other healthcare activities (e.g. urinary catheter), environmental contamination, kitchen hygiene, ESBL-E carriage in poultry, pig and cattle farms and travelling to endemic areas as Africa and Asia (37-43). Other studies reported that the risk of ESBL-E is higher after swimming in freshwater (44, 45). Moreover, agricultural land may be contaminated through the practice of spreading livestock manure (46, 47). ESBL has also been detected in aquatic environments close to healthcare centers. Altogether, these results suggest that the characteristics (agricultural, environmental or healthcare related) of the area where people live can play a major role in the risk of ESBL-producing Klebsiella infections (44-48).

High precarity level, low unnecessary take of antibiotic treatment, high kitchen hygiene, low environmental contamination and high number of foreign patients especially Europian and Balkan states could be the reason of the low ESBL positivity ratio in our study.

Globally, ESBL-E prevalence varies from 2 to 46% between communities from different subregions (49). Every year ESBL-E carriage rates increase worldwide with more than 5% among healthy individuals (49). Also in Europe, an increase in ESBL-E community carriage rates has been documented over the past years (50). Three studies found an ESBL-E prevalence of 4.5–8.6% among healthy individuals. Two of these identified travel to Asia or Africa in the previous 12 months and the use of proton pump inhibitors (PPI's) to be associated with a higher risk for ESBL-E carriage in the community. Other risk factors were the use of antimicrobials, travel to North and

Table 3: The Total Number of İsolated *Klebsiella*, The Number of *Klebsiella* İsolated From In-Patients, The Number and The Prevalence of ESBL-K In-Patients

Year	Isolated Klebsiella number	Isolated Klebsiella number from in-patient	Isolated ESBL-K number from in-patient	Prevalence of ESBL-K %, in-patients
2000	328	172	74	43.02
2001	179	78	12	15.38
2002	229	84	15	17.78
2003	297	89	18	20.22
2004	361	123	27	21.89
2005	461	131	30	23.12
2006	497	138	32	23.18
2007	521	154	38	24.67
2008	721	190	43	22.63
2009	565	202	74	36.63
2010	904	309	75	24.27
2011	1936	590	183	31.01
2012	1642	836	95	11.36
2013	1617	835	265	31.73
2014	2415	1165	478	41.03
2015	2493	1527	852	55.79
2016	2837	1699	986	58.03
2017	2991	1782	968	54.32
2018	3237	1979	1184	59.82
2019	3727	2467	1509	61.17
2020	3590	2380	1451	60.97
2021	3978	2678	1647	61.50
Total	35526	19608	10056	51.29

Latin America, keeping cows, living in the proximity of a mink farm, and owning or having contact with a horse (51-53). In countries with similar ESBL-E community carriage rates as the Netherlands, previous antibiotic use was identified as a predictor in Japan, Germany and France (49, 53, 54). Travel to Asia or Africa and travel to Africa or Greece were identified as predictors for ESBL-E carriage in Swedish and German communities, respectively (54). Overall, studies found a variety of risk factors. Therefore, elucidation of risk factors is needed to identify definitive sources for ESBL-E carriage in the community and to foresee possible public health risks and interventions.

In conclusion, ESBL production rates of ESBL-producing *K. pneumoniae* that cause infections which are expensive and difficult to treat, should be monitored by each center. Furthermore, broad-spectrum beta-lactam antibiotics preferred in the treatment of infections should be used carefully and hospitalized patients should be isolated. Finally we suggest the surveillance work should be done in hospital departments at risk.

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