

EXTENDED-SPECTRUM BETA-LACTAMASE PRODUCING GRAM NEGATIVE BACTERIA IN IRAN:  
A REVIEW

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## Abstract

**Background:** The emergence and spread of extended spectrum  $\beta$ -lactamase (ESBL)-producing Gram-negative bacteria (GNB), particularly in Enterobacteriaceae, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, have increased all over the world. ESBLs are characterized by their ability to hydrolyze  $\beta$ -lactams, early cephalosporins, oxyimino-thiazolyl cephalosporins, and monobactams, but not cephamycins or carbapenems. The rate of nosocomial infections caused by ESBL-producing GNB in Asia Pacific has increased and several studies have identified their prevalence in the region. The aim of this study is to review the prevalence of ESBL-producing GNB in the West Asia and the Middle East with a particular focus on Iran.

**Materials and Methods:** The available evidence from various studies (Microbia and clinical studies, retrieved from the PubMed, and Scopus databases) regarding the ESBL producing Gram negative bacteria in Iran were evaluated.

**Results:** In almost all parts of the country, high resistance has been observed, especially in the central part of Iran. Up to 89.8% *Escherichia coli*, 72.1% *Klebsiella pneumoniae*, 84.2% *Acinetobacter baumannii*, and 83.8% *Pseudomonas aeruginosa* isolates are ESBL positive.

**Conclusion:** The present study showed the increasing prevalence of ESBLs in different regions of Iran, which could be useful to strategic policy towards reducing reduce their prevalence.

**Keywords:** extended-spectrum  $\beta$ -lactamase; antibiotic resistance; *Acinetobacter baumannii*; *Pseudomonas aeruginosa*; Iran.

## Introduction

Infections due to Gram negative bacteria (GNB) are causing morbidity and mortality worldwide, and the production of  $\beta$ -lactamase remains the most important contributing factor to  $\beta$ -lactam resistance (Leylabadlo et al., 2016). Nowadays, the rapid spread of resistance to  $\beta$ -lactam antibiotics among GNB poses a clinical and public health challenge and increasing rates of drug resistance among them is a major concern worldwide (Little et al., 2012). Monobactams, cephalosporins, penicillins, and carbapenems can be hydrolyzed by the enzymes of the  $\beta$ -lactamase group, which renders them microbiologically ineffective (Bush and Mobashery, 1998). In the early 1980s, new family of beta-lactamases named extended-spectrum  $\beta$ -lactamases (ESBLs) were identified introduced that hydrolyze penicillins and expanded-spectrum cephalosporins have emerged (Kliebe et al., 1985). They are effective against  $\beta$ -lactam antibiotics like ceftazidime, ceftriaxone, cefotaxime, and oxyiminomonobactam, but not cephamycins or carbapenems (Bradford, 2001). ESBL production has been associated with Enterobacteriaceae, mostly *Klebsiella pneumoniae* isolated from Intensive care unit (ICU) patients; however, it is found also in community setting (Paterson and Bonomo, 2005) and, more recently, other Gram negative bacteria such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa* (Oliver et al., 2005).

Nowadays, more than 600 ESBL variants have been described, the majority of which belong to the Cefotaxime hydrolyzing capabilities (CTX-M), Sulfhydryl variable (SHV) and Temoneira (TEM) (<http://www.lahey.org/studies/webt.htm>). Most of the detected ESBLs are either of SHV or TEM types and associated with nosocomial infections caused by Gram negative bacteria (Paterson and Bonomo 2005). In the recent years, the spread of CTX-M-producing *E. coli* has been dramatic and they are considered the primary ESBL producers that are always associated with community-acquired infections (Leylabadlo et al., 2015).

Generally, ESBL has been found all over the world; for example, previous studies have reported that the prevalence of ESBL in Europe is higher than the United States, but lower than South America and Asia (Giamarellou, 2005). Asia is almost certainly a part of the world, in which the prevalence of ESBLs is very high among GNBs; however,

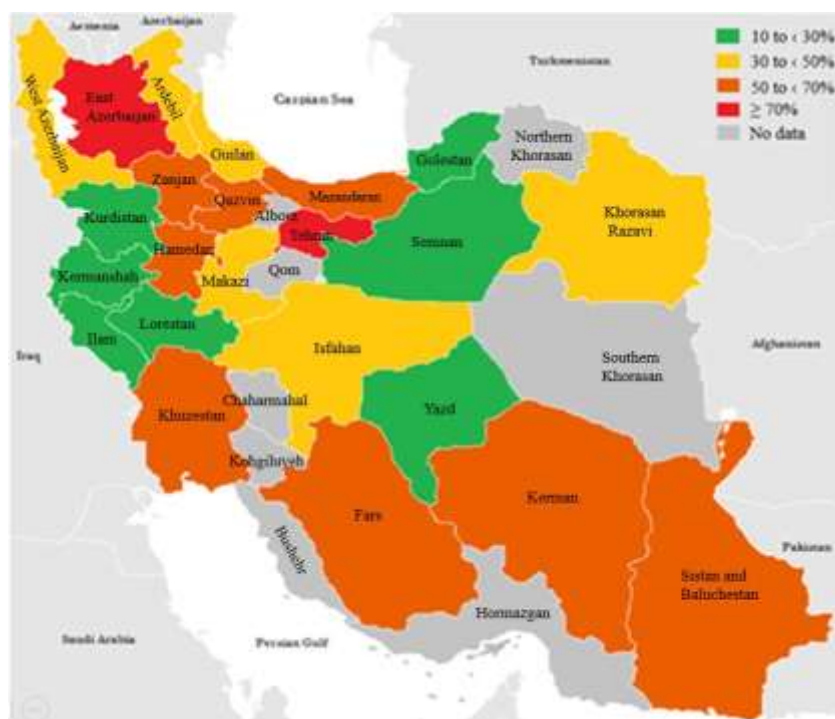
different countries have different prevalence rates (Giamarellou, 2005). The prevalence of ESBL in GNB has been previously reviewed in the countries of Gulf Cooperation Council (GCC) in the West of Asia and the Middle East (Zowawi et al., 2013), but did not include Iran, a country in both the West of Asia and in the Middle East, which also is another Persian Gulf country. Therefore, this review is focused on obtaining Iranian ESBL epidemiology and population structure of ESBL-producing isolates from hospitals and communities. Also, we have attempted to analyze the nature of mobile genetic elements carrying ESBL genes.

## Material and Methods

We conducted a search in the field using the Scopus, PubMed, Google Scholar, and Persian Databases from 2008 to 2016.

### Prevalence of ESBLs-producing GNB in Iran

Iran, a country in the western Asia, is the second largest nation in the Middle East. The country is bordered by Azerbaijan and Armenia in the northwest, Russia and Kazakhstan across the Caspian Sea, Turkmenistan in the northeast, Afghanistan and Pakistan in the east, the Gulf of Oman and the Persian Gulf in the south, and Turkey and Iraq in the west. Iran is divided into five regions with thirty-one provinces and various climatic conditions. For convenience of study, we divided it into five hypothetical parts: Northern (Mazandaran, Guilan, and Golestan Provinces), Southern (Kerman, Khuzestan, Yazd, Fars, Hormazgan, Bushehr, as well as Kohgiluyeh and Boyer Ahmad Provinces), Central (Tehran, Isfahan, Makazi, Zanjan, Semnan, Chaharmahal and Bakhtiari, Qom, Qazvin, and Alborz Provinces), Eastern (Khorasan Razavi, Northern and Southern Khorasan, as well as Sistan and Baluchestan Provinces), and Western (Hamedan, Ilam, Kermanshah, Kurdistan, East Azerbaijan, West Azerbaijan, Lorestan, and Chaharmahal and Bakhtiari Provinces). There are several studies about the prevalence of ESBL-producing bacteria from most provinces in Iran. Nevertheless, in some provinces (Hormazgan, Kohgiluyeh and Boyer Ahmad, Qom, Northern and Southern Khorasan, as well as Bushehr), no reports are available. Spread and prevalence of ESBLs-producing bacteria are shown in Figure 1.



**Figure 1:** Representation of the frequency of ESBL production (no. of tested isolates) and types of ESBLs produced by GNB isolates from Iranian hospitals and communities. Distribution of ESBLs was not available for all the studies reporting prevalence data.

**Northern part of Iran**

In the north of Iran, several surveys have been conducted among ESBL-producing GNB isolates from the community and hospitals. A study in Mazandaran Province, which was carried out at Buali Sina Hospital, revealed that 100 out of 327 uropathogenic *E. coli* (30.5%) were positive for ESBL that were lower in other Asian countries such as India (27%) (Ananthan and Subha 2005). Also, in the same study, TEM gene was the most prevalent one (49%) followed by other genes and about 12% of ESBL-producing isolates were shown to have both TEM and CTX-M genes. In another study from the region, to identify the accompanying Class 1 integrons and ESBLs in the MDR *E. coli* isolates, urine samples were collected (Moghaddam et al., 2015). The isolates were different in the resistance profiles; however, some others had similar resistance profiles. In a recent study, there was a significant correlation between ESBL production and resistance to all types of antibiotics except for piperacillin and ciprofloxacin, and out of eight ESBL positive isolates, seven (87.5%) carried class 1 integrons (Moghaddam et al., 2015). In another study from pediatric patients for ESBL genes, about 30.5% of isolated *E. coli* were ESBL-positive and TEM gene was identified in 49% followed by CTX in 28%, SHV in 44%, VEB in 8%, and GES in 0% of isolates (Rezai et al., 2015).

The analysis of 100 ESBL phenotypes of *A. baumannii* from the clinical samples of some hospitals in Mazandaran Province, representing the molecular pattern of *Acinetobacter* spp., 24% of the isolates were positive, which 79.1% were *bla*<sub>TEM</sub> and 31.5% were *bla*<sub>CTX</sub> (Ahanjan et al., 2014). The prevalence of *bla*<sub>TEM</sub> in this study was the same as reported in China (Jin et al., 2009). In a study from Babol city in Mazandaran during 2011-2012, a high prevalence of  $\beta$ -lactamase-producing *E. coli* was reported in the hospital, having two or three different types of enzymes in a bacterium, the lowest of which was related to Plasmid-Encoded AmpC (pAmpC) enzyme in 20 (7.7%) isolates (Shahandeh et al., 2015). This value was different from Indian study with the prevalence of 48.5% (Nagdeo et al., 2012).

A study in Guilan Province on urine samples revealed that 55% of *E. coli* isolates were resistant to the third and fourth cephalosporins. In a similar study on the urine samples of hospitalized patients and outpatients of Valiasr Hospital, the incidence of ESBL was 38.92% and bacterial isolates had the highest levels of resistance to amoxicillin, cephalixin, and tetracycline (Ranjbar et al., 2014). Another province in the northern part of Iran is Golestan Province. In a study carried out on urine samples of the outpatients, 70 isolates (32.1%) were resistant to cefotaxim and 62 (88.6%) were confirmed as ESBL-producing *E. coli* (NasrolahiOmran et al., 2012). Also, the prevalence of ESBL-producing *E. coli* in Golestan was in the range of the country's average and *bla*<sub>CTX-M</sub> gene was the most common one (NasrolahiOmran et al., 2012).

In general, class A and D as well as AmpC  $\beta$ -lactamases are the most common in the northern part of Iran. The prevalence of ESBLs was between 24 and 56.85% among the samples of both hospitals and the community. Also, this prevalence was 33.77% in the north of Iran on average. The highest rate belonged to a hospital in Babol city in the north of Iran, which was also mentioned in the present work (Table 1).

**Table 1:** Summary of ESBL enzymes and their rates identified in the Iran. All listed studies used phenotypic methods such as double-disk synergy test (DDST) or ESBL Etest

Section and Province	Producing organism	Setting	ESBL genotypes	(%)among ESBL	Reference
<b>Northern part of Iran</b>					
Mazandaran	<i>E. coli</i>	Hospital and Community	TEM, SHV, CTX, VEB	(30.5)	(Rezai et al., 2014)
Mazandaran	<i>A. baumannii</i>	Hospital	TEM, CTX	(24)	(Ahanjan et al., 2014)
Mazandaran	<i>E. coli</i>	Hospital	AmpC	(56.8)	(Shahandeh et al., 2015)
Guilan	<i>E. coli</i>	not specified	CTX-M	(24)	(Hemmati et al., 2015)
Guilan	<i>E. coli</i>	Hospital and Community	Not analyzed	(38.9)	(Ranjbar et al., 2014)
Golestan	<i>E. coli</i>	Community	CTX-M, TEM, SHV	(28.4)	(Nasrolahi et al., 2012)

Southern part of Iran					
<b>Kerman</b>	<i>P.aeruginosa</i>	Hospital		SHV, PER, TEM (34)	(Shakibaie et al., 2008)
<b>Kerman</b>	<i>K. pneumoniae</i> <i>E. coli</i>	Hospital		CTX-M, AmpC (43.8)	(Mansouri et al., 2014)
<b>Kerman</b>	<i>P.aeruginosa</i> <i>A. baumannii</i>	Hospital		CTX-M (59.4)	(Mansouri et al., 2012)
<b>Kerman</b>	<i>P.aeruginosa</i>	Hospital		CTX-M , VEB-1, PER-1, GES-1, OXA-4, OXA-10 (34.1)	(Shacheraghi et al., 2010)
<b>Khuzestan</b>	<i>Enterobacteriac eae</i>	Hospital Community	and	TEM , SHV (30.5)	(Moosavian and Deiham 2012)
<b>Khuzestan</b>	<i>K. pneumoniae</i>	Hospital		CTX-M1 (47.72)	(Khosravi et al., 2013)
<b>Khuzestan</b>	<i>P.aeruginosa</i>	Hospital		PER-1, OXA-10, CTX-M (51.9)	(Farshadzadeh et al., 2014)
<b>Yazd</b>	<i>P.aeruginosa</i>	Hospital		Not analyzed (22)	(Tafti et al., 2014)
<b>Fars</b>	<i>K. pneumoniae</i>	Hospital		TEM, CTX-M (60)	(Ghasemi, Archin et al.)
<b>Fars</b>	Gram negative bacil	Community		TEM, SHV (11.75)	(Kargar et al., 2014)
Central part of Iran					
<b>Tehran</b>	<i>E. coli</i>	Hospital		TEM, SHV (28)	(Pakzad et al., 2011)
<b>Tehran</b>	<i>K. pneumoniae</i>	Hospital Community	and	SHV, CTX-M, TEM , PER (38.5)	(Leila et al., 2010)
<b>Tehran</b>	<i>K. pneumoniae</i>	Hospital Community	and	SHV, TEM, CTX-M (72.1)	(Feizabadi et al., 2010)
<b>Tehran</b>	<i>E. coli</i>	Hospital		SHV, TEM (49)	(Shahcheraghi et al., 2009)
<b>Tehran</b>	<i>E. coli</i>	Community		TEM, SHV (2.7)	(Hosseini et al., 2007)
<b>Tehran</b>	<i>K.spp</i>	Hospital		SHV, TEM, CTX-M (51.6)	(Ghafourian et al., 2010)
<b>Tehran</b>	<i>K. pneumoniae</i>	Hospital Community	and	SHV, TEM, CTX-M (27.45)	(Eftekhar et al., 2012)
<b>Tehran</b>	<i>K. pneumoniae</i>	Hospital		SHV, TEM-1, CTX-M-15 (62.85)	(Ashayeri et al., 2014)
<b>Tehran</b>	<i>E. coli</i>	Hospital		TEM (64)	(Yazdi et al., 2013)
<b>Tehran</b>	<i>E. coli</i>	Hospital		CTX-M-1 (70)	(Peerayeh et al., 2013)
<b>Tehran</b>	<i>E. coli</i>	Hospital		CTX-M, TEM, SHV (20)	(Abdi, 2014)

Tehran	<i>P.aeruginosa</i>	Hospital		TEM, PER-1	(39.2)	(Rafiee et al., 2014)
Tehran	<i>P.aeruginosa</i>	Hospital (children)		AmpC (Not found PER)	(83.3)	(Fazeli et al., 2014)
Tehran	<i>K. pneumoniae</i>	Hospital Community	and	CTX-M-15, OXA-48	(57.5)	(Hashemi et al., 2014)
Tehran	<i>K. pneumoniae</i>	Hospital		OXA-48 (first report)	not specified	(Azimi et al., 2014)
Tehran	<i>Shigella</i>	Hospital		CTX-M-15, CMY-1	not specified	(Tajbakhsh et al., 2012)
Tehran	Gram negative bacil	Hospital		CTXM	(29.09)	(Vali et al., 2014)
Tehran	<i>P.aeruginosa</i>	Hospital		CTX-M-15	P (31.91)	(Hallajzadeh et al., 2014)
Tehran	<i>A. baumannii</i>	Hospital		PER-1, VEB-1	A (21.42)	(Fallah et al., 2014)
Tehran	<i>Acineto.spp</i>	Hospital		TEM, SHV	(84.2)	(Sharif et al., 2014)
Tehran	<i>E. coli</i>	Hospital Community	and	TEM, CTX-M	(51)	(Goudarzi, 2014)
Tehran	<i>E. coli</i>	Hospital		SHV	not specified	(Dallal et al., 2013)
Esfahan	<i>K. pneumoniae</i> <i>E. coli</i>	Hospital Community	and	TEM, SHV	(89.8)	(Gholipour et al., 2014)
Esfahan	<i>P.aeruginosa</i>	Hospital		GES-2, SHV-5, CTX-M-1	(18.75)	(Tavajjohi et al., 2011)
Esfahan	<i>P.aeruginosa</i>	Hospital		OXA-10	(8.1)	(Golshani and Sharifzadeh 2013)
Markazi	<i>Enterobacteriac eae</i>	Hospital Community	and	CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9	not specified	(Safari et al., 2013)
Qazvin	<i>E. cloacae</i>	Hospital		Not analyzed	(44)	(Peymani et al., 2014)
Zanjan	<i>E. coli</i> (EAEC)	Hospital Community	and	TEM, CTX-M	(55.7)	(Khoshvaght et al., 2014)
Semnan	<i>E. coli</i> <i>K. pneumoniae</i>	Community		Not analyzed	(52.7)	(Moghadas, 2009)
<b>Eastern part of Iran</b>						
Khorasan	<i>E. coli</i>	Hospital		CTX-M,TEM, SHV	(18.1)	(Moghaddam et al., 2012)
Khorasan	<i>E. coli</i> <i>Klebsiella</i>	Hospital Community	and	SHV,TEM	(33.3)	(Zaniani et al., 2012)
Khorasan	<i>Enterobacteriac eae</i>	Hospital Community	and	CTX-M-15	not specified	(Moghaddam et al., 2014)

<b>Sistan baluchestan</b>	<i>K. pneumoniae</i> <i>P.aeruginosa</i>	Hospital	TEM, CTX-M	K (66.6) P (13.3)	(Saeidi et al., 2014)
<b>Sistan baluchestan</b>	<i>P.aeruginosa</i>	Hospital	TEM, VEB-1, PER-1, SHV	(6.89)	(Bokaeian et al., 2015)
<b>Western part of Iran</b>					
<b>Hamedan</b>	<i>P.aeruginosa</i>	Hospital	PER-1, VEB	(58.3)	(Alikhani et al., 2014)
<b>Hamedan</b>	<i>A. baumannii</i>	Hospital	TEM, SHV	(7)	(Safari et al., 2015)
<b>Ilam</b>	<i>K.oxytoca</i>	Hospital	Not analyzed	(25)	(Ghafouryan et al., 2010)
<b>Kermanshah</b>	<i>E. coli</i>	Community	Not analyzed	(24.5)	(Mohajeri et al., 2014)
<b>Kurdistan</b>	Gram negative bacil	Community	TEM, CTX-M, SHV	(12.66)	(Ramazanzadeh et al., 2010)
<b>Kurdistan</b>	Gram negative bacil	Community	CTX- M, TEM, SHV	(14.5)	(Ramazanzadeh, 2010)
<b>Kurdistan</b>	<i>P.aeruginosa</i>	Hospital	PER-1, OXA-10	(28)	(Kalantar et al., 2012)
<b>Kurdistan</b>	<i>P.aeruginosa</i>	Hospital	SHV	(17.89)	(Bahmani and Ramazanzadeh 2013)
<b>East Azerbaijan</b>	<i>K. pneumoniae</i>	Hospital	SHV, TEM, CTX-M	(43.7)	(Ghafourian et al., 2011)
<b>East Azerbaijan</b>	<i>A. baumannii</i>	Hospital	PER-1, VEB-1	(70)	(Farajnia et al., 2013)
<b>East Azerbaijan</b>	<i>P.aeruginosa</i>	Hospital	PER-1	(75.86)	(Akhi et al., 2012)
<b>Ardebil</b>	<i>Enterobacteriac eae</i>	Hospital Community	and Not analyzed	(36.75)	(Akbari et al., 2014)
<b>West Azerbaijan</b>	<i>E. coli</i>	Hospital	CTX-M-15	(41.98)	(Parsania and Sohrabpour 2104)
<b>Lorestan</b>	Gram negative bacilli	Hospital	Not analyzed	(23.6)	(Zadegan et al., 2009)

### Southern part of Iran

Southern part of Iran has a warm and dry weather. This region mostly includes provinces around the Persian Gulf and the Gulf of Oman. In Kerman Province, in the burn ward of Shafa Hospital during January 2006 to December 2007, 41 (34%) isolated *P.aeruginosa* were reported to be ESBL producers; however, none of the isolates could produce any MBL enzyme and all ESBL-producing isolate were multidrug resistant (MDR). According to the PCR and multiplex PCR assays, the most prevalent genes among ESBL producers in the recent study were SHV and PER-1; but, no Amp-C gene was detected in any of the isolates (Shakibaie et al., 2008).

Another study in the burn ward of Kerman University showed that the ESBL-producing *P.aeruginosa* was the same as the previous study. However, the frequency of PER-1 gene was very high and molecular results showed that *bla*<sub>VEB-1</sub> in the *P.aeruginosa* strains harbor (643bp) was the most frequent ESBL gene. These data were in line with other results in the Middle East and Iran (Shakibaie et al., 2008). Surveys on the isolation of MDR non-fermenting GNB of the patients from three hospitals in Kerman indicated that all of the isolates were resistant to cefoxitin, and ESBL production was higher in *A. baumannii* than other tested bacterial species; but, the difference was not significant. A study from November 2007 to July 2008 on the patients admitted to hospitals in the Kerman showed that, among *K. pneumoniae* isolates, 44% produced ESBLs and 28% had AmpC (Mansouri et al., 2014). Also, among *E. coli* isolates, 43.7% isolates had ESBLs and 39.3% produced AmpC. Co-existence of ESBLs and AmpC  $\beta$ -lactamases was observed in 39.3% of



isolates. In this study, the prevalence rate of *bla*<sub>CTX-M</sub> gene among ESBLs- and AmpC-producing isolates of *K. pneumoniae* and *E. coli* was 21.3% and 13.3%, respectively (Mansouri et al., 2014).

Khuzestan is another province in the southern part of Iran. In an 11-month study from August 2011 to July 2012, 500 Enterobacteriaceae isolates were collected from Ahvaz and the prevalence rates of CTX-M-1 genes among ESBLs-positive isolates *K. pneumoniae* were found in 26.92% (Khosravi et al., 2013). In Ganjavian Hospital, Dezful, Khuzestan Province, among 128 ESBL-producing Enterobacteriaceae isolates, 73 (57%) were positive for TEM and/or SHV by multiplex PCR. Also, 14 isolates (19%) had both *bla*<sub>TEM</sub> and *bla*<sub>SHV</sub> genes; but, *bla*<sub>CTX-M</sub> was not detected in ESBL-producing strains (Moosavian and Deiham 2012).

Analysis of *P. aeruginosa* isolates from the burn ward of a hospital in Khuzestan showed that 176 (95.13%) isolates were MDR, and the prevalence of ESBL was higher than that of a similar study in Yazd Province (Farshadzadeh et al., 2014). During the study period between 2009 and 2010 in Fars Province, *K. pneumoniae* was collected from Intensive Care Units (ICUs) of Namazi Hospital in Shiraz and high prevalence (60%) of ESBL-producing *K. pneumoniae* were demonstrated. In addition, this study showed a new pattern of *bla*<sub>TEM</sub> distribution, in which *bla*<sub>TEM</sub> was found to be predominant, followed by *bla*<sub>CTX-M</sub> and *bla*<sub>SHV</sub>, respectively (Ghasemi et al., 2013). Several Iranian studies have had a similar pattern of ESBLs distribution, such as in Tehran Province (Nasehi et al., 2010). However, this pattern is different from other countries (e.g., Italy, Egypt and Austria) in which CTX-M is the most prevalent  $\beta$ -lactamases (Ahmed et al., 2009). In another study at Namazi Hospital during a 2 year period, 39 *Serratia* strains were isolated from blood samples; overall, positive ESBL phenotype was identified in 69% (n=27) of the isolates: 70.37% (n=19) for *S. marcescens* and 29.62% (n=8) for *S. liquefaciens* and TEM gene was detected in none of the isolates in this study (Mostatabi et al., 2013). In previous studies from Taiwan and Mexico, it has been reported that *bla*<sub>SHV</sub> and *bla*<sub>CTX-M-3</sub> are identified as the most common ESBL genes in *Serratia* (mostly in *S. marcescens*) (Cheng et al., 2006). A research on patients with diarrhea conducted in Shiraz among 2010 revealed that the prevalence of ESBLs-producer *E. coli* isolates was 12.96% (Ghorbani-Dalini et al., 2015). Antimicrobial resistance testing showed a high resistance to cefexime, trimethoprim-sulfamethoxazole, ampicillin and penicillin. In their study,  $\beta$ -lactamase genes were identified in 96.30% isolates which were identified as 83.33% *bla*<sub>TEM</sub>, 31.48% *bla*<sub>SHV</sub> and 20.37% *bla*<sub>CTX-M</sub>. In addition, this study indicated that the *bla*<sub>TEM</sub> gene for ESBLs-producer *E. coli* isolates was widespread in Iran (Ghorbani-Dalini et al., 2015).

Generally, in the southern part of Iran, classes A and D are more common in various samples from the provinces and AmpC is also present in one study. The prevalence of ESBL was between 11.75% and 69% in both hospitals and communities and, on average, it was 42.2%. In addition, the prevalence of ESBL in the community samples was less than in the hospitals (Table-1).

### Central part of Iran

Central part of Iran consists of area between Alborz Mountains, Zagros Mountains and the scattered mountains of Khorasan in the east. It includes some provinces that are shown in Table-1. Most of the region has a warm and dry weather with the milder climate in the mountain areas. Tehran, the capital city of Iran, is the largest city of the country and also the largest city in Western Asia. Several surveys have been performed in this area. Analysis of *K. pneumoniae* isolates in the central parts showed that the rate of ESBL producers was between 18.1% and 72% among the sample hospitals and communities. The ESBL-producing *K. pneumoniae* in the community's samples was less than that in the hospitals. However, samples from Tehran Hospital were more than other provinces, mostly carrying *bla*<sub>SHV</sub>, *bla*<sub>CTX-M</sub>, and *bla*<sub>TEM</sub> genes predominantly, among which the prevalence of *bla*<sub>SHV</sub> was higher than others (26%-77%). An investigation from Motahari and Shariati hospitals revealed that the rates of drug resistance in burn isolates of *K. pneumoniae* were higher compared to the non-burn strains, while no significant differences were observed in ESBL production between the two groups (Eftekhar and Naseh 2015). In the burn ward of Motahari Hospital, Tehran, in 2011, the first cases of OXA-48-producing *K. pneumoniae* in Iran were reported and *bla*<sub>OXA-48</sub> gene was detected in 96.42% (27/28) of isolates by PCR analysis followed by sequencing (Azimi et al., 2014). Another study in Tehran from October 2011 to May 2012 reported that 83 non-duplicate and non-consecutive *K. pneumoniae bla*<sub>OXA-48</sub> genes were found in two (4.1%) out of the 48 ESBL-producing isolates and 2 isolates harbored both *bla*<sub>OXA-48</sub> and *bla*<sub>CTX-M-15</sub> (Hashemi et al., 2014). Reports of *bla*<sub>OXA-48</sub> have been dramatically increased in recent years worldwide and OXA-48-producing *K. pneumoniae* and other isolates have been reported from various regions such as Turkey, Morocco, Lebanon, Belgium, United Kingdom, Tunisia, Argentina, and India (Cuzon et al., 2011).

A study demonstrates the predominant presence of the gene encoding CTX-M-1 group among ESBLs producing of *Salmonella* spp. that they can transmit to bacteria of this genus or even other genera of enteric bacteria (Rizi et al., 2015). In the recent study, four *Salmonella* spp. (3.6%) showed ESBLs phenotype, which all have *bla*<sub>CTX-1</sub> genes group. ESBL-producing *E. coli* in the central part of Iran has different ranges between hospitals and the community. According to the data, the majority of ESBL-producing isolates were from hospital patients in Tehran. Substantial proportions of *E. coli*

reported from urine samples in the central part of Iran and rate of ESBL-producing *E.coli* between hospitals in this region were 28%-89.8%, which was higher than that of the communities. Also, CTX-M and TEM type ESBLs appear to be predominating among ESBL-producing *E.coli* in the region (Pakzad et al., 2011). A study about *E.coli* isolated from urine samples from patients with urinary tract infection (UTI) referred to two main hospitals in Tehran, during September 2010 to March 2011, showed that 20% of *E. coli* isolates were ESBL-producer and frequency of *bla*<sub>CTX-M</sub>, *bla*<sub>TEM</sub>, and *bla*<sub>SHV</sub> genes was 87%, 82%, and 65%, respectively (Abdi et al., 2014). In a similar study from a Children Medical Center in Tehran between 2012 and 2013, the presence of *bla*<sub>CTX-M</sub> and *bla*<sub>TEM</sub> were detected in 69 (69%) and 74 (74%) of isolates, respectively, while *bla*<sub>SHV</sub> gene was absent (Goudarzi et al., 2013).

Notably, in the other province in the central part of Iran in isolates of *Enterobacteriaceae* from Markazi province, the frequency of CTX-M-1,-2,-8,-9 among the isolates were as 92.2%, 28.5%, 17.5%, and 38.3%, respectively (Safari et al., 2013). This value was different from other studies in other countries. For example, studies in Sudan, Korea, and Thailand have demonstrated that the prevalence of CTX-M-1 was 45.9%, 16.4%, and 14%, respectively (Safari et al., 2013). However, the prevalence of CTX-M-9 in Germany, America, and Canada is in the range of 38.5%-58.5% (Safari et al., 2013). Nevertheless, other studies have shown that the dissemination of CTX-M-8 gene in Iran is higher compared to the rest of the world (Kim et al., 2008). Analysis of non-fermenting GNB in the central part of Iran showed that the lowest ESBL-producing was 8.1% in Isfahan Province and the highest was 83.3% in hospitals of Tehran Province (Kim et al., 2008; Fazeli et al., 2015).

In a study from Tehran, 51 non-duplicate *P. aeruginosa* isolates were randomly selected from a collection of burn isolates of a hospital in 2011 and it was found that 43 isolates (84.3%) carried  $\beta$ -lactamase genes, out of which 31 (60.8%) harbored *bla*<sub>AmpC</sub>, 20 (39.2%) isolates had *bla*<sub>TEM</sub>, and 11 (21.6%) carried *bla*<sub>PER-1</sub> genes (Rafiee et al., 2014). But, in another study, during a 3 month period, from November 2011 to January 2012, 72 clinical isolates of *P. aeruginosa* collected from the samples included blood specimen, urine, wound, tracheal, throat, and other samples from a major pediatric hospital in Tehran reported that none of them had *bla*<sub>PER</sub>, *bla*<sub>BEL</sub>, and all of the isolates had *ampC* gene (Fazeli et al., 2015). This study was the first work among the samples from children in which PER was not detected (Fazeli et al., 2015).

Other provinces in the central part of the country have also reported non-fermenting ESBL-producing GNB. In a study from Beheshti Hospital in Kashan that was conducted during 2010 to 2011, it was reported that, from 86 urine, trachea, and stool samples, 19 (20.9%) *P. aeruginosa* isolates were resistant to all extended-spectrum cephalosporins (Tavajjohi et al., 2011). This study also reported 8.1% ESBL-production among *P. aeruginosa* isolates and the *bla*<sub>GES-2</sub> gene was detected in all ESBL-producing *P. aeruginosa*. GES-2 in the same study was different from other results in the Middle East region and Iran (Tavajjohi et al., 2011). It was reported from Kashan that the prevalence of *bla*<sub>CTX-M</sub> among *Enterobacteriaceae* isolates was at an alarming rate (Hasan Afzali et al., 2015). In the recent study that conducted in 2013, from 100 *Klebsiella spp.* isolates, 41% of isolates had resistance ceftazidime or aztreonam and 35% were ESBLproducers, which 80% of the resistant isolates carried the *bla*<sub>CTX-M</sub> type genes. Moreover, CTX-M-1, CTX-M-2 and CTX-M-9 were identified in 60%, 42% and 34% of these isolates, respectively (Hasan Afzali et al., 2015). In another research from Kashan, 47% of ESBL-producing isolates were identified by DDST confirmatory test and majority (80.5%) of isolates carried *bla*<sub>CTX-M</sub> genes including CTX-M-1 (60%), CTX-M-2 (42.9%), and CTX-M-9 (34.3%) (SHAMS et al., 2015). Also, 77 ESBL-producing *K. pneumoniae* were positive with PMQR genes, which mostly consisted of *aac(6')-Ib-cr* (70.1%) and *qnrB* (46.0%), followed by *qnrS* (5.7%). Among these PMQR positive isolates, 35.1% and 1.3% of isolates carried 2 and 3 different PMQR genes, respectively (Shams et al., 2015). Frequency of *bla*<sub>OXA-10</sub> in ESBL-producing *P. aeruginosa* was 40 (64%) in another study from Isfahan in 2012 (Golshani and Sharifzadeh, 2013). In a study on *P. aeruginosa* clinical isolates, 76 isolates were collected from Milad hospital in Tehran (Akbariqomi et al., 2015). In their study, 76.3% of isolates classified as MDR and The majority of them were found in ESBL producer *P. aeruginosa*. Also, the effective antibiotics against ESBL and non-ESBL were meropenem and amikacin, respectively. In the central region of the country, only in the hospitals of Tehran, ESBL-producing *Acinetobacters* were between 21.4% and 84.2% in three studies. The rate of PER-1, VEB-1, CTX-M-15, TEM, and SHV was 78.03%, 39.5%, 9.3%, 56%, and 63%, respectively (Hakemi et al., 2014; Sharif et al., 2014).

Another study that was conducted in a major pediatric hospital in Tehran showed that 4 out of 55 *Shigella* isolates, including three *S. sonnei* and one *S. flexneri*, had ESBL-positive phenotype (Tajbakhsh et al., 2012). Also one *S. sonnei* isolate had CMY-59 gene. The ESBL-producing *Shigella* isolates in this study were higher than previous studies in other countries (Tajbakhsh et al., 2012). Therefore, the prevalence of ESBL-producing GNB in the central part of Iran was between 2.3% and 89.8% and the average prevalence of ESBL-producing GNB in the central part of Iran was 43.55% in hospitals and community samples. Also, class A and D  $\beta$ -lactamases were the most prevalent in the region (Table 1).



### Eastern part of Iran

This part of Iran has a warm and dry weather and is near Afghanistan and Pakistan borderlines. In this area, ESBL-producing GNB was reported in Khorasan as well as Sistan and Baluchestan Provinces. Analysis of *E. coli* isolates from urine samples of hospitalized patients was collected in 2009 at two hospitals in Mashhad city, which showed that 33.3% were ESBL producers and carrying *bla*<sub>CTX</sub> in 94.6%, *bla*<sub>TEM</sub> in 56.8%, and *bla*<sub>SHV</sub> in 13.5% of the isolates (Moghaddam et al., 2012). In this study, *bla*<sub>CTX-M</sub> was found to be higher than the developed countries and other studies in Iran (Moghaddam et al., 2012). To determine the frequency of *qnr* genes in isolates from Imam Reza hospital in Mashhad, 200 clinical isolate of *E. coli* were investigated (Mood et al., 2015). Results indicated that 43% of isolates were ciprofloxacin-resistant. Also, the phenotypic confirmatory test identified 42.5% isolates as ESBL-producing. Isolates were positive for *bla*<sub>TEM</sub> in 76.47%, *bla*<sub>SHV</sub> in 27%, *qnrA* in 31%, *qnrB* in 17%, and *qnrS* in 7%. In another research that was carried out in 2010, 82 *E. coli* and 78 *K. pneumoniae* were isolated from different clinical samples. In their study, 43.9% of *E. coli* and 56.1% of *K. pneumoniae* were ESBL producer, which in the community was lower than the hospital samples and frequencies of SHV and TEM were 14.4% and 20.6%, respectively (Riyahi et al., 2012). Recently, a survey conducted on Enterobacteriaceae isolates from urine samples on inpatients and outpatients who referred to Qaem and 17-Shahrivar Hospitals in Mashhad city in 2012. It was found that 27 (27%) isolates were ESBL-producing organisms with the highest frequency for *K. pneumoniae* (47.4%) and *E. coli* (17.9%). Also, 26 (26%) Enterobacteriaceae isolates harbored the *bla*<sub>CTX-M</sub> gene. It was the first report of *bla*<sub>CTX-M-15</sub> among *E. coli* isolates in this region. No *bla*<sub>PER</sub> was found among the isolates, which was similar to the work conducted by Shahcheraghi et al. in Tehran (Moghaddam et al., 2014).

To evaluate 180 isolates including 30 *K. pneumoniae* and 150 *P. aeruginosa*, a study was performed on the urine samples of hospitalized patients in a hospital of Zabol city in Sistan and Baluchestan Province (74). In this work, the prevalence of ESBL-producing isolates was 13.3% for *P. aeruginosa* and 66.6% for *K. pneumoniae*. Also, 75% and 65% of *K. pneumoniae* harbored the TEM and CTX-M genes, respectively, and 55% of *P. aeruginosa* isolates harbored the gene TEM; but, none of them demonstrated CTX-M gene. This prevalence of ESBLs-producing organisms was higher than that of other studies (Saeidi et al., 2014). Another study was conducted on non-fermentative GNB isolates during 2012–2013 on 116 *P. aeruginosa* isolates from Zahedan city, 6.89% isolates were ESBL-positive. Among them, 100% had *bla*<sub>TEM</sub>, 13.3% had *bla*<sub>PER-1</sub>, 6.6% had *bla*<sub>VEB-1</sub> and 6.6% had *bla*<sub>SHV</sub>. *bla*<sub>TEM</sub> gene in this study had 100% identity with *bla*<sub>TEM-116</sub> (Bokaeian et al., 2015). In characterization of ESBL and AmpC producers among *E. coli* from three major hospitals in Zahedan, almost half of isolates were resistant to third generation of cephalosporins; of these 62.7% and 5% were ESBL and AmpC producers, respectively. Molecular analysis showed that 49.1% and 5% were positive for *bla*<sub>TEM</sub> and *bla*<sub>CMY2</sub>, respectively (Shayan and Bokaeian, 2015).

Overall, in this part of Iran, the prevalence of ESBL-producing GNB ranged between 6.89% and 66.6%, the average of which was 31.13%. Among ESBL-producing GNB in this region, class A  $\beta$ -lactamase was the most prevalent one (Table 1).

### Western part of Iran

This part of the country with several cities has a cold and rainy weather and is bordered with Turkey and Iraq. The prevalence of ESBL-producing isolates in this region has been also studied and in some provinces and cities. During a 7-month study in 2009, out of 106 isolates of *P. aeruginosa* from two tertiary hospitals in Hamadan, 88.7% of the isolates were MDR and 58.25% were ESBL producer (Alikhani et al., 2014). Also, among 60 ESBL-producing strains, 16 (26.6%), 9 (15%), and 3 (5%) strains had *bla*<sub>PER-1</sub>, *bla*<sub>VEB-1</sub>, *bla*<sub>PER-1</sub>, and *bla*<sub>VEB</sub> related genes, respectively (Alikhani et al., 2014). The rates of *bla*<sub>VEB</sub> and *bla*<sub>PER</sub> ESBLs were the same as other studies in Tehran (SHAHCHERAGHI et al., 2009); however, it was higher than those of Turkey and Korea and lower than Thailand and Italy (Shahcheraghi et al., 2009). In another survey, 100 *A. baumannii* strains were isolated from ICU wards of three educational hospitals in Hamadan (Safari et al., 2015). This study was conducted in 2011 and reported that 7% of isolates were ESBLs producers; this rate was very lower than that of other Iranian studies. Among all the isolates, 58%, and 20% were harboring SHV and CTXM genes, respectively (Safari et al., 2015).

Kurdistan is another province located in the west of the country. Studies have shown that the rate of ESBL-producing strains in communities is lower than hospitals. For example, out of 158 GNB isolated from the outpatients referring to hospital in Sanandaj, 20 (12.66%) isolates were ESBL producer and the majority of community acquired ESBL types belonging to CTX-M and SHV were 10.76% and TEM was 9.49% (Ramazanadeh et al., 2010). In another study from Kurdistan that was conducted on 188 urinary tract infection outpatients in 2008, it was revealed that 27 (14.5%) isolates were ESBL-producing GNB and CTX-M type was the most prevalent one (12.7%). Also, the prevalence of SHV, TEM was 11.7% and 10.1%, respectively (Ramazanadeh et al., 2010). The analysis of *P. aeruginosa* isolates from the patients who were hospitalized in Sanandaj showed that 17.89% of the isolates were ESBL producer and the prevalence of

*bla*<sub>SHV</sub> was 10.57%; this rate was lower than that of other Iranian studies (Bahmani and Ramazanzadeh, 2013). Another work on the burn patients of Tohid Hospital in Kurdistan showed that, out of 100 *P. aeruginosa* isolates, 28% were positive for ESBL production and 48% and 52% had PER-1 and OXA-10 producers, respectively (Kalantar et al., 2012).

East Azerbaijan and West Azerbaijan are other provinces in this part of the country which have the highest prevalence of  $\beta$ -lactamases. The prevalence of ESBLs rate in East Azerbaijan was reported 43.3% in a survey (Ghafourian et al., 2011). In a study that was conducted in 2008, *bla*<sub>SHV</sub>, *bla*<sub>TEM</sub>, and *bla*<sub>CTX-M</sub> were identified as 86.7%, 15.6%, and 15.6%, respectively (Ghafourian et al., 2011). ESBLs-producing *E. coli* at hospitals of West Azerbaijan Province was relatively similar to that of the previous study (41.98%) that carried 23.63% *bla*<sub>CTX-M-15</sub> gene (Parsania and Sohrabpour, 2014). Analysis of ESBL-producing non-fermentative bacteria in East Azerbaijan showed that 70% and 75.68% of the isolates were *A. baumannii* and *P. aeruginosa*, respectively; this rate was the maximum in Iran. Also, analysis of ESBL genes in this bacteria showed that, among 100 *A. baumannii* isolates, 51% were positive for PER-1 and 10% positive for VEB1, whereas none of the isolates were positive for PER2 type gene. In this study, the prevalence of *bla*<sub>PER-1</sub> among 56 *P. aeruginosa* isolates was 27.5% (Farajnia et al., 2013). In a study from the Tabriz region, *K. pneumoniae* isolates had the same ESBL prevalence as *E. coli* isolates (SHAMS et al., 2015). In a same study, the presence of integron class 1 was associated with presence of ciprofloxacin resistance in both organisms and co-presence of class 1 and 2 and the presence of ESBL production. However, nalidixic acid resistance was related significantly with only integron class 1 and to the presence of ESBL production. Class 1 and 2 integrons were found in 73.5% of MDR isolates with 13.2% of them possessing both *intI1* and *intI2* genes (Shams et al., 2015).

The frequency of ESBL-producing GNB is reported in other provinces in this region; however, ESBL genes have not been analyzed. For example, in a study performed in Ilam hospitals during March 2007 to April 2008, among the samples taken from the wards of surgery as well as lesion and infection of the respiratory tract, 25% of *K. oxytoca* were reported to be ESBL-positive (Ghafouryan et al., 2010). In another study from Kermanshah Province, 200 isolates of Uropathogenic *Escherichia coli* (UPEC) were collected among urine samples in the community from February 2012 to February 2013 and 24.5% ( $n = 49$ ) of isolates were found to be positive for ESBL production (Mohajeri et al., 2014). The prevalence of ESBL-producing GNB in the urine samples of hospitalized patients in Imam Khomeini Hospital of Ardabil Province in 2012 showed that, out of 400 *Enterobacteriaceae*, 147 (36.75%) isolates were positive for ESBL (Akbari, Amir Mozaffari et al., 2014). In another study from Shohada-ye Ashayer Hospital in Lorestan Province, from 225 isolates, 53 (23.6%) were positive in terms of ESBL production (Zadegan et al., 2009).

Finally, in the western part of Iran, the prevalence of ESBL-producing GNB ranged from 7% to 75.86% in the samples of communities and hospitals and, on average, it was 34.26%. Also, Class A, D Ambler was the most prevalent one (Table 1).

## Conclusion

Iran, like many other parts of the world, has experienced a significant increase in the number of ESBL-producing GNB in the hospitals and communities. Thus, this review indicates that spread of ESBL-producing GNB is a great problem in healthcare centers. In the community setting, ESBL-producing GNB mostly have a lower prevalence than the hospital. However, it should be considered that the prevalence of ESBL genes varies in different geographical areas. The current rates in some parts of the country are very high, especially in the central part of Iran, such as Tehran Province. So, the highest rate of ESBL-producing *E. coli*, *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa* has been reported in the hospitals of Tehran in the recent years. Other parts of the country also have high prevalence of ESBL-producing GNB in both hospitals and communities. It is clear that ESBL-producing organisms are widely distributed globally; but, this rate is lower in several parts of the world than Iran. Most frequent types of ESBL enzymes in Iran include TEM, CTX-M, SHV, and OXA; but, there are other ESBL enzymes with different frequencies among GNB such as PER, VEB, and GES. In many parts of the world such as European Countries, Latin America, East and West Asia in Gulf Cooperation Council (GCC), and Africa, CTX-M variants become dominant  $\beta$ -lactamases in compare to TEM and SHV enzymes in GNB. In most reports, TEM, CTX-M, and SHV are the predominant and OXA-type ESBLs have been found mainly in *P. aeruginosa* and *A. baumannii* isolates in this region. Therefore, the presence of ESBLs genes is a risk factor for the future use of antimicrobial treatment in Iran. ESBLs distribution and the facilitation of their spread in different regions may be caused by factors such as "mobility" of ESBL genes, strong selective pressure of antibiotic use, purchase antibiotics without prescriptions, lack of observing hand hygiene, use of antibiotics in animals, travel, and different weather conditions. Future research should be focused on the areas in which no reports of ESBL have been made. Also, the areas with less prevalence of ESBL-producing GNBs and ESBL genes must be considered in order to take specific measures and increase supervision in the hospitals and the community in case any changes or increase occur in terms of prevalence.

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## References

1. Abdi, S., Ranjbar, R., Vala, M. H., Jonaidi, N., Bejestany, O. B., and Bejestany, F. B. (2014). Frequency of bla TEM, bla SHV, bla CTX-M, and qnrA Among Escherichia coli Isolated From Urinary Tract Infection. Archives of Clinical Infectious Diseases; 9(1).
2. Ahanjan, M., Kholdi, S., and Rafiei, A. (2014). Antibiotic-resistance Patterns and Frequency of TEM and CTX Type Extended-spectrum  $\beta$ -lactamases in Acinetobacter Clinical Isolates. Journal of Mazandaran University of Medical Sciences; 24(116), 32-40.
3. Ahmed, S. H., Daef, E. A., Badary, M. S., Mahmoud, M. A., and Abd-Elseyed, A. A. (2009). Nosocomial blood stream infection in intensive care units at Assiut University Hospitals (Upper Egypt) with special reference to extended spectrum  $\beta$ -lactamase producing organisms. BMC Research Notes; 2(1), 76.
4. Akbari, M., Amir Mozaffari, N., and Peeri Dogahneh, H. (2014). Prevalence of Extended-Spectrum Beta Lactamase in Entrobacteriaceae Isolated from Urinary Tract Infections in Ardabil, Iran. Journal of Ardabil University of Medical Sciences; 14(3), 285-291.
5. Akbariqomi, M., Ghafourian, S., Taherikalani, M., Mohammadi, S., Pakzad, I., and Sadeghifard, N. (2015). Antibiotic Susceptibility Patterns of Extended Spectrum Beta-Lactamase and Non Extended Spectrum Beta-Lactamase Pseudomonas aeruginosa Clinical Isolates. Recent patents on anti-infective drug discovery; 10(2), 128-133.
6. Akhi, M. T., Khalili, Y., Ghotaslou, R., and Aghazadeh, M. (2012). Prevalence of PER-1-type extended-spectrum beta-lactamases in clinical strains of Pseudomonas aeruginosa isolated from Tabriz, Iran. Iranian journal of basic medical sciences; 15(1), 678.
7. Alikhani, M. Y., Tabar, Z. K., Mihani, F., Kalantar, E., Karami, P., Sadeghi, M., and Farajnia, S. (2014). Antimicrobial resistance patterns and prevalence of blaPER-1 and blaVEB-1 genes among ESBL-producing Pseudomonas aeruginosa isolates in West of Iran. Jundishapur Journal of Microbiology; 7(1).
8. Ananthan, S., and Subha, A. (2005). Cefoxitin resistance mediated by loss of a porin in clinical strains of Klebsiella pneumoniae and Escherichia coli. Indian journal of medical microbiology; 23(1), 20.
9. Ashayeri-Panah, M., Feizabadi, M., and Eftekhari, F. (2014). Correlation of multi-drug resistance, integron and blaESBL gene carriage with genetic fingerprints of extended-spectrum  $\beta$ -lactamase producing Klebsiella pneumoniae. Jundishapur Journal of Microbiology; 7(2).
10. Azimi, L., Nordmann, P., Lari, A. R., and Bonnin, R. A. (2014). First report of OXA-48-producing Klebsiella pneumoniae strains in Iran. GMS Hygiene & Infection Control; 9(1).
11. Bahmani, N. and R. Ramazanadeh (2013). Detection of SHV type extended-spectrum B-lactamase and risk factors in pseudomonas aeruginosa clinical isolates. Pakistan journal of medical sciences; 29(3): 788.
12. Bokaean, M., Zahedani, S. S., Bajgiran, M. S., and Moghaddam, A. A. (2015). Frequency of PER, VEB, SHV, TEM and CTX-M Genes in Resistant Strains of Pseudomonas aeruginosa Producing Extended Spectrum  $\beta$ -Lactamases. Jundishapur journal of microbiology; 8(1).
13. Bradford, P. A. (2001). Extended-spectrum  $\beta$ -lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. Clinical microbiology reviews; 14(4), 933-951.
14. Bush, K., and Mobashery, S. (1998). How  $\beta$ -lactamases have driven pharmaceutical drug discovery. In Resolving the Antibiotic Paradox (pp. 71-98). Springer US.
15. Cheng, K., Chuang, Y., Wu, L., Huang, G., and Yu, W. (2006). Clinical experiences of the infections caused by extended-spectrum beta-lactamase-producing Serratia marcescens at a medical center in Taiwan. Japanese journal of infectious diseases; 59(3), 147.
16. Cuzon, G., Ouanich, J., Gondret, R., Naas, T., and Nordmann, P. (2011). Outbreak of OXA-48-positive carbapenem-resistant Klebsiella pneumoniae isolates in France. Antimicrobial agents and chemotherapy; 55(5), 2420-2423.
17. Dallal, M. S., Sabbaghi, A., Aghamirzaeie, H. M., Lari, A. R., Eshraghian, M. R., Mehrabad, J. F., and Rajabi, Z. (2013). Prevalence of AmpC and SHV  $\beta$ -lactamases in clinical isolates of Escherichia coli from Tehran Hospitals. Jundishapur Journal of Microbiology; 6(2), 176-180.

18. Eftekhari, F., and Naseh, Z. (2015). Extended-spectrum  $\beta$ -lactamase and carbapenemase production among burn and non-burn clinical isolates of *Klebsiella pneumoniae*. Iranian journal of microbiology; 7(3), 144.
19. Eftekhari, F., Rastegar, M., Golalipoor, M., and Mansoursamaei, N. (2012). Detection of Extended Spectrum B-Lactamases in Urinary Isolates of *Klebsiella pneumoniae* in Relation to blaSHV, blaTEM and blaCTX-M gene carriage. Iranian journal of public health; 41(3), 127.
20. Fallah, F., Noori, M., Hashemi, A., Goudarzi, H., Karimi, A., Erfanimesh, S., and Alimehr, S. (2014). Prevalence of blaNDM, blaPER, blaVEB, blaIMP, and blaVIM genes among *Acinetobacter baumannii* isolated from two hospitals of Tehran, Iran. Scientifica; 2014.
21. Farajnia, S., Azhari, F., Alikhani, M. Y., Hosseini, M. K., Peymani, A., and Sohrabi, N. (2013). Prevalence of PER and VEB type extended spectrum betalactamases among multidrug resistant *Acinetobacter baumannii* isolates in North-West of Iran. Iranian journal of basic medical sciences; 16(6), 751-755.
22. Farshadzadeh, Z., Khosravi, A. D., Alavi, S. M., Parhizgari, N., and Hoveizavi, H. (2014). Spread of extended-spectrum  $\beta$ -lactamase genes of bla OXA-10, bla PER-1 and bla CTX-M in *Pseudomonas aeruginosa* strains isolated from burn patients. Burns; 40(8), 1575-1580.
23. Fazeli, H., Sadighian, H., Nasr-Esfahani, B., and Pourmand, M. (2015). Identification of class-1 integron and various  $\beta$ -lactamase classes among clinical isolates of *Pseudomonas aeruginosa* at children's medical center hospital. Journal of Medical Bacteriology; 1(3-4), 25-36.
24. Feizabadi, M. M., Mahamadi-Yeganeh, S., Mirsalehian, A., Mirafshar, S. M., Mahboobi, M., Nili, F., and Yadegarinia, D. (2010). Genetic characterization of ESBL producing strains of *Klebsiella pneumoniae* from Tehran hospitals. The Journal of Infection in Developing Countries; 4(10), 609-615.
25. Ghafourian, S., Sadeghifard, N., bin Sekawi, Z., Neela, V. K., Shamsudin, M. N., Mohebi, R., and Raftari, M. (2010). Antimicrobial pattern and clonal dissemination of extended-spectrum beta-lactamase producing *Klebsiella* Spp isolates. American Journal of Infectious Diseases; 6(4), 110.
26. Ghafourian, S., Sadeghifard, N., Sekawi, Z., Neela, V. K., Shamsudin, M. N., Pakzad, I., and Rahbar, M. (2011). Phenotypic and genotypic assay for detection of extended spectrum B-lactamases production by *Klebsiella pneumoniae* isolates in Emam Reza Hospital in Tabriz, Iran. Journal of Pure and Applied Microbiology; 5(1), 1-10.
27. Ghafouryan, S., Sadeghifard, N., Neela, V., Mariana, N. S., Mohebi, R., Rahbar, M., and Pakzad, I. (2010). Occurrence of *Klebsiella oxytoca* producing extended-spectrum beta-lactamases in different seasons in Ilam Hospitals, Iran. African Journal of Microbiology Research; 4(22), 2381-2387.
28. Ghasemi, Y., Archin, T., Kargar, M., and Mohkam, M. (2013). A simple multiplex PCR for assessing prevalence of extended-spectrum B-lactamases producing *Klebsiella pneumoniae* in Intensive Care Units of a referral hospital in Shiraz, Iran. Asian Pacific Journal of Tropical Medicine; 703-708.
29. Gholipour, A., Soleimani, N., Shokri, D., Mobasherizadeh, S., Kardi, M., and Baradaran, A. (2014). Phenotypic and molecular characterization of extended-Spectrum  $\beta$ -lactamase produced by *Escherichia coli*, and *Klebsiella pneumoniae* isolates in an educational hospital. Jundishapur journal of microbiology; 7(10).
30. Ghorbani-Dalini, S., Kargar, M., Doosti, A., Abbasi, P., and Sarshar, M. (2015). Molecular Epidemiology of ESBL Genes and Multi-Drug Resistance in Diarrheagenic *Escherichia coli* strains Isolated from Adults in Iran. Iranian journal of pharmaceutical research: IJPR; 14(4), 1257.
31. Giamarellou, H. (2005). Multidrug resistance in Gram-negative bacteria that produce extended-spectrum  $\beta$ -lactamases (ESBLs). Clinical Microbiology and infection; 11, 1-16.
32. Golshani, Z., and Sharifzadeh, A. (2013). Prevalence of blaOxa10 Type Beta-lactamase Gene in Carbapenemase Producing *Pseudomonas aeruginosa* Strains Isolated From Patients in Isfahan. Jundishapur Journal of Microbiology; 6(5).
33. Goudarzi, H., Aghamohammad, S., Hashemi, A., Nikmanesh, B., and Noori, M. (2013). Distribution of bla TEM, bla SHV and bla CTX-M genes among *Escherichia coli* isolates causing urinary tract infection in children. Archives of Clinical Infectious Diseases; 8(3).
34. Hakemi Vala, M., Hallajzadeh, M., Hashemi, A., Goudarzi, H., Tarhani, M., Sattarzadeh Tabrizi, M., and Bazmi, F. (2014). Detection of Ambler class A, B and D  $\beta$ -lactamases among *Pseudomonas aeruginosa* and *Acinetobacter baumannii* clinical isolates from burn patients. Ann Burns Fire Disasters; 27(1), 8-13.
35. Hasan Afzali, F. F., Amiri, A., Moniri, R., and Zibaei, M. (2015). Characterization of CTX-M-Type Extend-Spectrum  $\beta$ -Lactamase Producing *Klebsiella* spp. in Kashan, Iran. Jundishapur journal of microbiology; 8(10).
36. Hashemi, A., Fallah, F., Erfanimesh, S., Hamedani, P., Alimehr, S., and Goudarzi, H. (2014). Detection of  $\beta$ -lactamases and outer membrane porins among *Klebsiella pneumoniae* strains isolated in Iran. Scientifica; 2014(6).
37. Hemmati, T. B., Mehdi-pour Moghaddam, M. J., Salehi, Z., and Habibzadeh, S. M. (2015). Prevalence of CTX-M-Type  $\beta$ -Lactamases in Multi-Drug Resistant *Escherichia coli* Isolates from North of Iran, Rasht. Biological Journal of Microorganism; 3(12).



38. Hosseini-Mazinani, S. M., Eftekhari, F., Milani, M., and Ghandili, S. (2007). Characterization of  $\beta$ -Lactamases from Urinary Isolates of *Escherichia coli* in Tehran. *Iranian Biomedical Journal*; 11(2), 95-99.
39. Jin, H., Xu, X. M., Mi, Z. H., Mou, Y., and Liu, P. (2009). Drug-resistant gene based genotyping for *Acinetobacter baumannii* in tracing epidemiological events and for clinical treatment within nosocomial settings. *Chinese Medical Journal (English Edition)*; 122(3), 301.
40. Kalantar, E., Taherzadeh, S., Ghadimi, T., Soheili, F., Salimizand, H., and Hedayatnejad, A. (2012). *Pseudomonas aeruginosa*, an emerging pathogen among burn patients in Kurdistan Province, Iran. *Southeast Asian Journal of Tropical Medicine and Public Health*; 43(3), 712.
41. Kargar, M., Kargar, M., Jahromi, M. Z., Najafi, A., and Ghorbani-Dalini, S. (2014). Molecular detection of ESBLs production and antibiotic resistance patterns in Gram negative bacilli isolated from urinary tract infections. *Indian Journal of Pathology and Microbiology*; 57(2), 244.
42. Khoshvaght, H., Haghi, F., and Zeighami, H. (2014). Extended spectrum betalactamase producing *Enterobacteriaceae* *Escherichia coli* from young children in Iran. *Gastroenterology and Hepatology from bed to bench*; 7(2), 131.
43. Khosravi, A. D., Hoveizavi, H., and Mehdinejad, M. (2013). Prevalence of *Klebsiella pneumoniae* encoding genes for CTX-M-1, TEM-1 and SHV-1 extended-spectrum beta lactamases (ESBL) enzymes in clinical specimens. *Jundishapur Journal of Microbiology*; 6(10).
44. Kim, J. Y., Kim, S. H., Jeon, S. M., Park, M. S., Rhie, H. G., and Lee, B. K. (2008). Resistance to fluoroquinolones by the combination of target site mutations and enhanced expression of genes for efflux pumps in *Shigella flexneri* and *Shigella sonnei* strains isolated in Korea. *Clinical Microbiology and Infection*; 14(8), 760-765.
45. Kliebe, C., Nies, B. A., Meyer, J. F., Tolxdorff-Neutzling, R. M., and Wiedemann, B. (1985). Evolution of plasmid-coded resistance to broad-spectrum cephalosporins. *Antimicrobial Agents and Chemotherapy*; 28(2), 302-307.
46. Lasehi, K., Shahcheraghi, F., Nikbin, V. S., and Nematzadeh, S. (2010). PER, CTX-M, TEM and SHV Beta-lactamases in clinical isolates of *Klebsiella pneumoniae* isolated from Tehran, Iran. *Iranian Journal of Basic Medical Sciences*; 13(3), 111-118.
47. Leylabadlo, H. E., Asgharzadeh, M., and Aghazadeh, M. (2015). Dissemination of carbapenemases producing Gram negative bacteria in the Middle East. *Iranian journal of microbiology*; 7(5), 226.
48. Leylabadlo, H. E., Kafil, H. S., Yousefi, M., Aghazadeh, M., and Asgharzadeh, M. (2016). Persistent infection with metallo-beta-lactamase and extended spectrum  $\beta$ -lactamase producer *Morganella morganii* in a patient with urinary tract infection after kidney transplantation. *Journal of Natural Science, Biology, and Medicine*; 7(2), 179.
49. Little, M. L., Qin, X., Zerr, D. M., and Weissman, S. J. (2012). Molecular diversity in mechanisms of carbapenem resistance in paediatric *Enterobacteriaceae*. *International journal of antimicrobial agents*; 39(1), 52-57.
50. Mansouri, S., Neyestanaki, D. K., Shokoohi, M., Halimi, S., Beigverdi, R., Rezagholezadeh, F., and Hashemi, A. (2014). Characterization of AmpC, CTX-M and MBLs types of  $\beta$ -lactamases in clinical isolates of *Klebsiella pneumoniae* and *Escherichia coli* producing Extended Spectrum  $\beta$ -lactamases in Kerman, Iran. *Jundishapur Journal of Microbiology*; 7(2).
51. Mansouri, S., Razavi, M., Norouzi, F., Gholamhoseinian, N. S. (2012). Prevalence of  $\beta$ -Lactamase Production and Antimicrobial Susceptibility of Multidrug Resistant Clinical Isolates of Non-Fermenting Gram Negative Bacteria From Hospitalized Patients in Kerman/Iran. *Jundishapur J Microbiol*; 5(2), 405-10.
52. Mozhddeh, R., Fatemeh, N., and Sasan, G. N. (2012). Prevalence of  $\beta$ -Lactamase production and antimicrobial susceptibility of multidrug resistant clinical isolates of non-fermenting Gram negative bacteria from hospitalized patients in Kerman/Iran. *Jundishapur Journal of Microbiology*; 2012(2, Spring), 405-410.
53. Moghadas, A. J., Irajian, G., and Beheshti, A. (2009). Prevalence of extended-spectrum beta lactamase positive and multidrug resistance pattern of *Escherichia coli* and *Klebsiella pneumoniae* isolates, Semnan, Iran. *Iranian Journal of Microbiology*; 1(1), 49-53.
54. Moghaddam, M. J. M., Mirbagheri, A. A., Salehi, Z., and Habibzade, S. M. (2015). Prevalence of class 1 integrons and extended spectrum beta lactamases among multi-drug resistant *Escherichia coli* isolates from North of Iran. *Iranian biomedical journal*; 19(4), 233.
55. Moghaddam, M. N., Beidokhti, M. H., Jamehdar, S. A., and Ghahraman, M. (2014). Genetic properties of blaCTX-M and blaPER  $\beta$ -lactamase genes in clinical isolates of *Enterobacteriaceae* by polymerase chain reaction. *Iranian journal of basic medical sciences*; 17(5), 378.
56. Moghaddam, M. N., Forghanifard, M. M., and Moshrefi, S. (2012). Prevalence and Molecular Characterization of Plasmid-mediated Extended-Spectrum  $\beta$ -Lactamase Genes (blaTEM, blaCTX and blaSHV) Among Urinary *Escherichia coli* Clinical Isolates in Mashhad, Iran. *Iranian journal of basic medical sciences*; 15(3), 833-839.
57. Mohajeri, P., Darfarin, G., and Farahani, A. (2014). Genotyping of ESBL producing Uropathogenic *Escherichia coli* in west of Iran. *International journal of microbiology*; 2014.



58. Mood, E. H., Meshkat, Z., Izadi, N., Rezaei, M., Jamehdar, S. A., and Nasab, M. N. (2015). Prevalence of Quinolone Resistance Genes Among Extended-Spectrum B-Lactamase-Producing *Escherichia coli* in Mashhad, Iran. *Jundishapur journal of microbiology*; 8(12).
59. Moosavian, M., and Deiham, B. (2012). Distribution of TEM, SHV and CTX-M Genes among ESBL-producing Enterobacteriaceae isolates in Iran. *African Journal of Microbiology Research*; 6(26), 5433-5439.
60. Mostatabi, N., Farshad, S., and Ranjbar, R. (2013). Molecular evaluations of extended spectrum  $\beta$ -lactamase producing strains of *Serratia* isolated from blood samples of the patients in Namazi Hospital, Shiraz, Southern Iran. *Iranian journal of microbiology*; 5(4), 328.
61. Nagdeo, N. V., Kaore, N. M., and Thombare, V. R. (2012). Phenotypic methods for detection of various  $\beta$ -lactamases in Gram-negative clinical isolates: Need of the hour. *Chronicles of Young Scientists*; 3(4), 292.
62. Nasehi, L., Shahcheraghi, F., Nikbin, V. S., and Nematzadeh, S. (2010). PER, CTX-M, TEM and SHV Beta-lactamases in clinical isolates of *Klebsiella pneumoniae* isolated from Tehran, Iran. *Iranian Journal of Basic Medical Sciences*; 13(3), 111-118.
63. NasrolahiOmran, A., Javid, N., Shakeri, F., Yazdi, M., and Ghaemi, E. A. (2012). Extended spectrum beta lactamase producing *E. coli* isolated from Gorgan, North of Iran. *Medical Laboratory Journal*; 6(1), 51-58.
64. Oliver, A., Coque, T. M., Alonso, D., Valverde, A., Baquero, F., and Cantón, R. (2005). CTX-M-10 linked to a phage-related element is widely disseminated among Enterobacteriaceae in a Spanish hospital. *Antimicrobial agents and chemotherapy*; 49(4), 1567-1571.
65. Pakzad, I., Ghafourian, S., Taherikalani, M., Abtahi, H., Rahbar, M., and Mansory Jamshidi, N. (2011). Qnr prevalence in extended spectrum beta-lactamases (ESBLs) and none-ESBLs producing *Escherichia coli* isolated from urinary tract infections in central of Iran. *Iranian journal of basic medical sciences*; 14(5), 458-464.
66. Parsania, S., and Sohrabpour, M. (2014). Prevalence of CTX-M-15 $\beta$ -lactamase Genes in *Escherichia coli* Strains Using PCR. *Journal of Mazandaran University of Medical Sciences*; 24(116), 58-62.
67. Paterson, D. L., and Bonomo, R. A. (2005). Extended-spectrum  $\beta$ -lactamases: a clinical update. *Clinical microbiology reviews*; 18(4), 657-686.
68. Peerayeh, S. N., Eslami, M., Memariani, M., and Siadat, S. D. (2013). High prevalence of blaCTX-M-1 group extended-spectrum  $\beta$ -lactamase genes in *Escherichia coli* isolates from Tehran. *Jundishapur Journal of Microbiology*; 6(7).
69. Peymani, A., Marandi, M., and Najafipour, R. (2014). Prevalence of OXA-1 type ESBLs among clinical isolates of *Enterobacter cloacae* collected from Qazvin Hospitals, Iran. *Iranian Journal of Public Health*; 43(2), 84.
70. Rafiee, R., Eftekhari, F., and Tabatabaei, S. A. (2014). Prevalence of Extended-Spectrum and Metallo  $\beta$ -Lactamase Production in AmpC  $\beta$ -Lactamase Producing *Pseudomonas aeruginosa* Isolates From Burns. *Jundishapur journal of microbiology*; 7(9), e16436-e16436.
71. Ramazanadeh, R. (2010). Etiologic agents and extended-spectrum beta-lactamase production in urinary tract infections in Sanandaj, Iran. *Eastern Journal of Medicine*; 15(2), 57.
72. Ranjbar, R. E. Z. A., Ahmadnezhad, B. A. H. M. A. N., and Jonaidi, N. E. M. A. T. O. L. L. A. H. (2014). The Prevalence of Beta Lactamase Producing *Escherichia coli* Strains Isolated from the Urine Samples in Valiasr Hospital. *Biomed & Pharmacol J*; 7, 425-431.
73. Rezai, M. S., Salehifar, E., Rafiei, A., Langaee, T., Rafati, M., Shafahi, K., and Eslami, G. (2015). Characterization of multidrug resistant extended-spectrum beta-lactamase-producing *Escherichia coli* among uropathogens of pediatrics in North of Iran. *BioMed research international*; 2015.
74. Riyahi Zaniani, F., Meshkat, Z., Naderi Nasab, M., Khaje-Karamadini, M., Ghazvini, K., Rezaee, A., and Darban Hoseini, M. (2012). The prevalence of TEM and SHV genes among extended-spectrum beta-lactamases producing *Escherichia coli* and *Klebsiella pneumoniae*. *Iranian journal of basic medical sciences*; 15(1), 654-660.
75. Rizi, K. S., Peerayeh, S. N., Bakhshi, B., and Rahbar, M. (2015). Prevalence of the blaCTX-M-1 group and their transferability in resistant clinical isolates of *Salmonella* serogroups from several hospitals of Tehran. *Iranian journal of microbiology*; 7(4), 203.
76. Saeidi, S., Alavi-Naini, R., and Shayan, S. (2014). Antimicrobial susceptibility and distribution of tem and ctx-m genes among esbl-producing *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* causing urinary tract infections. *Zahedan Journal of Research in Medical Sciences*; 16(4), 1-5.
77. Safari, M., Nejad, A. S. M., Bahador, A., Jafari, R., and Alikhani, M. Y. (2015). Prevalence of ESBL and MBL encoding genes in *Acinetobacter baumannii* strains isolated from patients of intensive care units (ICU). *Saudi journal of biological sciences*; 22(4), 424-429.
78. Safari, M., Shojapour, M., Akbari, M., Pourbabae, A., and Abtahi, H. (2013). Dissemination of CTX-M-type beta-lactamase among clinical isolates of Enterobacteriaceae in Markazi province, Iran. *Jundishapur Journal of Microbiology*; 6(8).

79. Shacheraghi, F., Shakibaie, M. R., and Noveiri, H. (2010). Molecular identification of ESBL Genes blaGES-blaVEB-blaCTX-M blaOXA-blaOXA-4, blaOXA-10 and blaPER-in *Pseudomonas aeruginosa* strains isolated from burn patients by PCR, RFLP and sequencing techniques. *Int J Biol life Sci*; 3(6), 138-42.
80. Shahandeh, Z., Sadighian, F., and Rekabpou, K. B. (2015). Phenotypic study of Extended-spectrum beta-lactamase, AmpC and Carbapenemase among *E. coli* clinical isolates in affiliated hospitals of Babol University of Medical Sciences. *International Journal of Health System and Disaster Management*; 3(2), 74.
81. SHAHCHERAGHI, F., Nasiri, S., and Noveiri, H. (2009). Detection of extended-spectrum  $\beta$ -lactamases (ESBLs). *Archives of Clinical Infectious Diseases*; 4(2), 65-70.
82. Shahcheraghi, F., Nikbin, V. S., and Feizabadi, M. M. (2009). Prevalence of ESBLs genes among multidrug-resistant isolates of *Pseudomonas aeruginosa* isolated from patients in Tehran. *Microbial Drug Resistance*; 15(1), 37-39.
83. SHAMS, E., Firoozeh, F., Moniri, R., and Zibaei, M. (2015). Prevalence of plasmid-mediated quinolone resistance genes among extended-spectrum  $\beta$ -Lactamase-producing *Klebsiella pneumoniae* human isolates in Iran. *Journal of pathogens*; 2015.
84. Shams, F., Hasani, A., Rezaee, M. A., Nahaie, M. R., Hasani, A., Haghi, M. H. S. B., and Arbatan, A. E. (2015). Carriage of Class 1 and 2 Integrons in Quinolone, Extended-Spectrum- $\beta$ -Lactamase-Producing and Multi Drug Resistant *E. coli* and *K. pneumoniae*: High Burden of Antibiotic Resistance. *Advanced pharmaceutical bulletin*; 5(3), 335.
85. Sharif, M., Mirnejad, R., and Amirzofari, N. (2014). Molecular identification of TEM and SHV extended spectrum  $\beta$ -lactamase in clinical isolates of *Acinetobacter baumannii* from Tehran hospitals. *J Gen Microb Immun*; 2, 1-9.
86. Shayan, S., and Bokaeian, M. (2015). Detection of ESBL-and AmpC-producing *E. coli* isolates from urinary tract infections. *Advanced biomedical research*, 4.
87. Tafti, A., Zandi, H., Vakli, M., Mousavi, S. M., and Zarei, M. (2014). Frequency of  $\beta$ -lactamase and metallo- $\beta$ -lactamase in *Pseudomonas aeruginosa* strains isolated from burn wounds in Yazd burn hospital during 2011-2012. *KAUMS Journal (FEYZ)* ; 18(2), 167-174.
88. Tajbakhsh, M., Migura, L. G., Rahbar, M., Svendsen, C. A., Mohammadzadeh, M., Zali, M. R., and Hendriksen, R. S. (2012). Antimicrobial-resistant *Shigella* infections from Iran: an overlooked problem?. *Journal of antimicrobial chemotherapy*; 67(5), 1128-1133.
89. Tavajjohi, Z., Moniri, R., and Khorshidi, A. (2011). Detection and characterization of multidrug resistance and extended-spectrum-beta-lactamase-producing (ESBLs) *Pseudomonas aeruginosa* isolates in teaching hospital. *African Journal of Microbiology Research*; 5(20), 3223-3228.
90. Vali, P., Shahcheraghi, F., Seyfipour, M., Zamani, M. A., Allahyar, M. R., and Feizabadi, M. M. (2014). Phenotypic and genetic characterization of carbapenemase and ESBLs producing gram-negative bacteria (GNB) isolated from patients with cystic fibrosis (CF) in Tehran hospitals. *Journal of clinical and diagnostic research: JCDR*; 8(1), 26.
91. Yazdi, M. K. S., Dallal, M. M. S., Mirzaei, H. M. A., Sabbaghi, A., Mehrabadi, J. F., Lari, A. R., and Bakhtiari, R. (2011). Molecular detection of TEM broad spectrum  $\beta$ -lactamase in clinical isolates of *Escherichia coli*. *African Journal of Biotechnology*; 10(46), 9454-9458.
92. Zadegan, H. H., Ramazanzadeh, R., and Hasany, A. (2009). Cross-sectional study of extended spectrum beta-lactamase producing gram-negative bacilli from clinical cases in Khorramabad, Iran. *Iranian Journal of Microbiology*; 1(3), 16-19.
93. Zaniani, F., Meshkat, Z., Naderi Nasab, M., Khaje-Karamadini, M., Ghazvini, K., Rezaee, A., and Darban Hoseini, M. (2012). The prevalence of TEM and SHV genes among extended-spectrum beta-lactamases producing *Escherichia coli* and *Klebsiella pneumoniae*. *Iranian journal of basic medical sciences*; 15(1), 654-660.
94. Zowawi, H. M., Balkhy, H. H., Walsh, T. R., and Paterson, D. L. (2013).  $\beta$ -Lactamase production in key gram-negative pathogen isolates from the Arabian Peninsula. *Clinical microbiology reviews*; 26(3), 361-380.