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REVIEW ARTICLE

Dissemination of carbapenemases producing Gram negative bacteria in the Middle East

Abed Zahedi bialvaei[1], Hossein Samadi kafil[2*], Hamed Ebrahimzadeh Leylabadlo[3], Mohammad Asgharzadeh[4], Mohammad Aghazadeh[1]

[1]Infectious Disease and Tropical Medicine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
[2]Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
[3]Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
[4]Biotechnology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

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ABSTRACT

The emergence and spread of carbapenemase-producing bacteria, that hydolyze most β-lactams, including carbapenems, are

*Corresponding author: Hossein Samadi Kafil PhD. Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
E-mail: Kafilhs@tbzmed.ac.ir

a major concern of public health system worldwide, particularly in the Middle East area. Since the plasmids harboring resistance genes could be spread across other bacterial populations, detection of carbapenemase-producing organisms has become more problematic. These organisms produce different types of enzymes including the most prevalent types including KPC, VIM, IMP, NDM, and OXA-48. Carbapenemase producers are mostly identified among *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter baumannii.* This study reviewed almost all papers, which conducted in the Middle East. In order to decrease the spread of resistance, the regional cooperation has been emphasized by the Middle East countries. The highest resistance, which is mediated by KPC has been observed in Afghanistan, Saudi Arabia and Jordan followed by NDM in Pakistan and OXA in Turkey and Pakistan. It is important to mention that the spread of these types have been reported sporadically in the other countries of this area. This review described the widespread carbapenemases in the Middle East area, which have been identified in an alarming rate.

Keywords: Carbapenemase, KPC, NDM, OXA, *Acinetobacter baumannii, Enterobacteriaceae, Pseudomonas aeruginosa,* Middle East countries.

INTRODUCTION

After methicillin resistant staphylococcus and extended spectrum beta-lactamases (ESBL), another β-lactamase causing resistance among Gram negative organisms are carbapenemase enzymes, which hydrolysis a group of antibiotics called carbapenems (1). Carbapenems are potent β-lactam antibiotics that is used to treat serious infections in hospital settings. As dipolar compounds, they rapidly enter to the Gram-negative bacterial cell wall (GNB) via outer membrane proteins (OMPs or porins) and target the bacterial penicillin-binding proteins (PBPs) (2).

In comparison to cephalosporins, penicillins or β -lactam/ β -lactamase inhibitor, carbapenems have broad antimicrobial spectrum that includes Gram-positive (e.g., imipenem, doripenem) and Gram-negative bacteria (e.g., meropenem, ertapenem) (3). In the recent few years, the emergence of carbapenem in Gram-negative bacteria either in non-fermenters *(P. aeruginosa and A. baumannii)* or in fermenters *(Enterobacteriaceae)* has been reported worldwide (4).

Transferable carbapenemases (enzymes which inactivate carbapenems together with other β -lactams and can be disseminated via horizontal gene transfer) are a major public health threat, which can increase the rate of mortality and decline the choice of appropriate antibiotic therapy (6). Currently, the spread of carbapenemase producer especially for GNB are the most important clinical problem in antibiotic resistance and it must be strongly controlled and prevented (7). The aim of this study is to provide an extensive review of carbapenemase gene dissemination in the Middle East region.

CARBAPENEMASE

Carbapenemases are a group of enzymes that are able to hydrolyze carbapenems even at low level. Carbapenems includes imipenem, meropenem, ertapenem, cephalosporins, and the broad-spectrum of penicillin (8). Fifteen years after the introduction of carbapenems penicillin became a worldwide health problem (9). Since the first detection of carbapenems in early1990s, the spread of them through all continents increased dramatically (5).

The highly mobile genetic elements of carbapenemase genes contribute to their rapid spread and frequent transfer of multiple other antibiotic resistance genes (10). However, some of them are chromosomally encoded. These mobile genetic elements frequently contain other antibiotic resistance genes, leading to a rapid evolution towards MDR bacteria (11). There are two main molecular families of carbapenemases: serine carbapenemases, which is based on presence of serine in their active site and metallo-carbapenemases, which are a subgroup of metallo- β -lactamases (MBLs) having at least one zinc atom at their active site (12). Difference in structural types has made it more strict for development of phenotypic tests that can identify MBLs, which they inhibited by chelating agents such as ethylene diamine tetra-acetic acid (EDTA) and serine-interactivating compounds such as clavulanic acid or boronic acid derivatives (13).

Based on amino acid homology carbapenemases have been identified in each of the four Ambler molecular classification, however those of class A, B, and D have major epidemiological impact (Table 1). According to the recent reports some of the class C

Table 1: General classification of carbapenemases

Molecolar Class[a]	A	B	D
Functional group[b]	2f	3	2d
Active site	Serine	Zn^{2+}	Serine
Prominent Enzyme	GES, SME, NMC, KPC	IMP, VIM, SPM, GIM, SIM, NDM	OXA
ATM Hydrolysis	+	-	-
EDTA Inhibition	-	+	-
CLA Inhibition	±	-	±
APBA Inhibition	+	-	-
Most Common Bacteria	Enterobacteriaceae (rare reports in *P. aeruginosa*)	*P. aeruginosa* Enterobacteriaceae *Acinetobacter* spp.	*Acinetobacter* spp.

ATM: aztreonam; APBA: 3′-Aminophenylboronic acid; EDTA: ethylene diamine tetra-acetic acid; CLA: clavulanic acid

[a] Ambler classification.

[b] Bush, Jacoby and Medeiros classification.

cephalosporinases are able to hydrolyze imipenem at a measurable rate; however, these enzymes are usually not intended to be important carbapenem-hydrolyzing enzymes, because carbapenems do not represent a major substrate in their hydrolytic profile (14).

Class A

This group contains serine at their active site and are capable of hydrolyzing all β-lactams, such as aztreonam. In this group of carbapenemases, IMI (IMI-1 to IMI-3), Sme (Sme-1 to Sme-3), SFC-1 and NmcA, enzymes are mostly chromosomally encoded, while GES (GES-1 to GES-20) and *K. pneumoniae* carbapenemase (KPC-2 to KPC-13) are plasmid encoded (3). Moreover, all of them have an ability to hydrolyze a wide variety of β-lactam antibiotics, such as penicillins, cephalosporins, aztreonam and carbapenems; however, they are inhibited by tazobactam and clavulanate which placing them in the group 2f functional subgroup of β –lactamases (15). This specific genetic elements can carry resistance to fluoroquinolones and aminoglycosides because the encoding genes for quinolone and aminoglycoside resistance are carried on the same plasmids (10). They are inhibited by tazobactam and clavulanic acid but not sulbactam (16).

These group of carbapenemases are mostly carried and expressed by *K. pneumoniae* isolates, but they can be found in *Escherichia coli, Salmonella enterica, Klebsiella oxytoca, Enterobacter aerogenes, Citrobacter freundii, Proteus mirabilis, Serratia marcescens, Enterobacter cloacae,* as well as in non-fermenting Gram-negative bacilli like *Acinetobacter* spp, *Pseudomonas aeruginosa* and *Pseudomonas putida* (17).

In this group, KPC-types are the most clinically common enzymes. The first KPC producer (KPC-2 in *K. pneumoniae*) was identified in 1996 in the eastern United States (18). Over the few years, KPC producers have been spread around the world and described across the United States (mostly in eastern coast states) and, particularly in Puerto Rico, Greece, Colombia, China, Brazil, Argentina, and Italy (19) and now is widespread in the Middle East region (Fig. 1.). Recently, GES-type carbapenemase Ambler class A has been described in *A. baumannii,* which is responsible for a low level of carbapenem resistance (20).

Class B

Class B carbapenemases are also known as metallo- β -lactamase since they contain two zinc ions in their active site which coordinate and present polarized water ions for the oxyanion attack on the β -lactam ring. Interaction of the β -lactams with zinc ions in the active site of the enzyme is the mechanism of hydrolysis (except subgroup 3b), resulting in the distinctive trait of their inhibition by EDTA, a chelator of Zn^{2+} and other divalent cations (Table 1) (15). Theses enzymes are not inhibited by clavulanic acid

Fig. 1. Geographic distribution of KPC enzymes in the Middle East countries. Gray, no case reported; green, single KPC-producing isolates; yellow, some outbreaks of KPC-producing isolates; red, endemicity of KPC producing isolates

(16). Beside those chromosomally located in environmental bacteria, acquired MBL encoding genes are often located in gene cassettes within integron, being part of a plasmid or chromosome (3).

Class B MBLs are mostly VIM (Verona integron-encoded metallo- β -lactamase) and IMP types, but the recently emerged NDM-type (New Delhi metallo- β -lactamases) is becoming the most threatening carbapenemase (17). In 1991, IMP-1 was first acquired from MBL and reported in *Serratia marcescens* in Japan. Since then, MBLs have been described worldwide (19). There are now more than 30 derivatives of IMP and are still dominant MBLs in Asian continent causing mainly sporadic outbreaks (21). The most commonly found class B carbapenemases are the VIM type, which has been identified in all continents (16). VIM-enzymes (there are now more than 30 derivatives) were firstly described in *P. aeruginosa* isolates, then emerged in *Enterobacteriaceae* as well. These enzymes spread over the whole Europe dramatically and causing many outbreaks in Mediterranean countries such as Greece, Italy, and Turkey (3). In addition, MBL enzymes have spread rapidly, and because of their prolific dissemination and their ability to hydrolyze all β -lactams, with the exception of aztreonam (if no ESBLs and/or AmpCs are co-produced by the isolates), presenting a serious threat (17, 22). Most MBL producers are hospital-acquired and MDR *K. pneumoniae*, but include *Pseudomonas* spp. and *Acinetobacter* spp. as well (17, 19).

New-Delhi MBL (NDM-1), which has more than ten variants is another metallo enzyme that arose from India in 2008 and spread rapidly over Indian subcontinent in the following few years (Fig. 2) and international travel has a significant impact on the spread of NDM-1 (3, 23). Although the diversity of the NDM-1 is low, NDM-1 is the main types among the other types of the NDM. Dissemination often involves the transfer of the $bla_{\text{NDM-1}}$ gene among promiscuous plasmids and clonal outbreaks. Bacteria which contain NDM-1 are typically resistant to almost antibiotics; as a result, reliable detection and surveillance are crucial (24). Scientists claim that $bla_{\text{NDM-1}}$ is widely distributed among *Enterobacteriacae* and has a rapid distribution around the world (25). The bacteria carrying this enzyme are *Klebsiella pneumoniae, Escherichia coli, Citrobacter freundii, Enterobacter cloacae, Providencia* spp. and *Morganella morganii*.

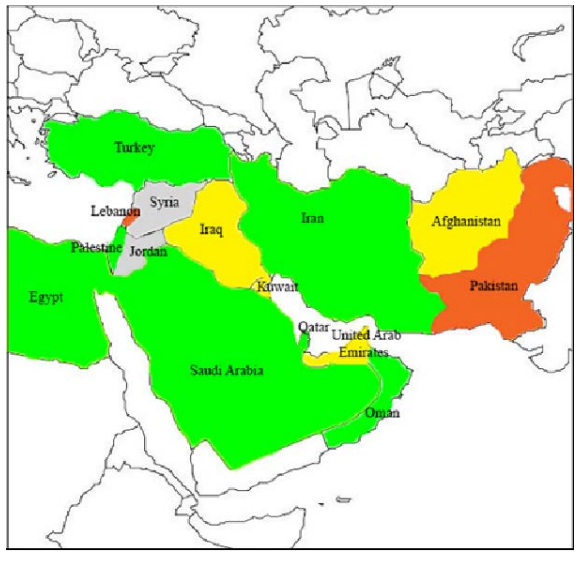

Fig. 2. Geographic distribution of NDM type producers in Middle East countries. Gray, no case reported; green, sporadic NDM producing isolates; yellow, emerging outbreak of NDM-producing isolates; orange, single hospital outbreaks of NDM-producing isolates.

Class D

Class D β-lactamases, which named OXAs for oxacillinases, have more than 440 known variants with 232 of them showing carbapenemase activity (16) and majority of them are encoded by chromosomal genes (26).

Paton et al. described the first OXA β -lactamase with carbapenemase activity in 1993 (27). Since then multiple oxacillinases with a carbapenem-hydrolyzing activity have been reported. The enzyme was purified from a multi drug resistant *A. baumannii* strain that was isolated in 1985 from a patient in Edinburgh, Scotland (15).

Class D carbapenemases, based on sequence homology alone, can be divided into the following clusters: OXA-23 also named ARI-1 (an acronym of *Acinetobacter* resistant to imipenem) (includes OXA-27 and OXA-49); OXA-24/-40 (includes OXA-25, OXA-26) and OXA-58 (21). Some of other OXA-type carbapenemases are widely dispersed in *P. aeruginosa* and in *A. baumannii* (8) but occasionally in *Enterobacteriaceae.*

The most recent and worrying development is the rapid rise in OXA-48, particularly in *K. pneumoniae.* OXA-48-producing *Enterobacteriaceae* (OPE) was first identified in Turkey in 2001, then has been reported from several countries in the Middle East, North Africa and Europe (28). In order to decrease the spread of resistance, the regional cooperation has been emphasized by the Middle East countries (Fig. 3) (29). OXA-181, is a point mutant analog of OXA-48, with similar carbapenemase activity, has been detected in strains that came from India or of Indian origin (19).

The fast spread of *Enterobacteriaceae*-producing the OXA-48 carbapenemase (mostly *E. coli*) is related to the dissemination of a single self-transferable plasmid, which represents another mode of resistance in healthcare-associated Gram-negative bacilli (17).

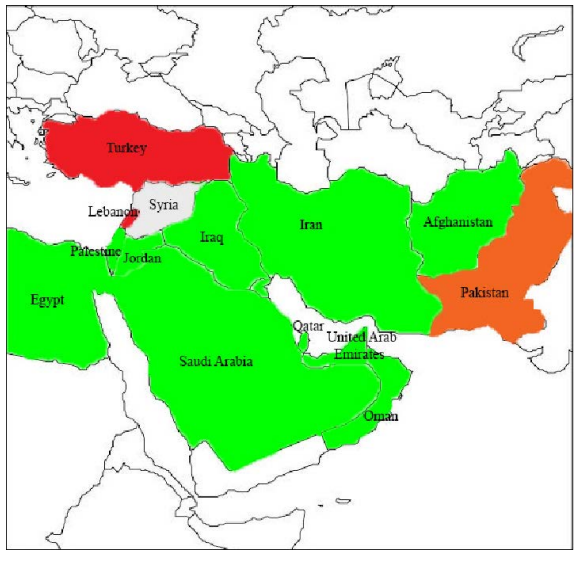

Fig. 3. Geographic distribution of OXA-48 type producers in Middle East countries. Gray, no case reported; green, single OXA-48 producing isolates; orange, several outbreaks of OXA-48-producing isolates; red, nationwide distribution of OXA-48-producing isolates.

Afghanistan and Iraq

Most reports on potentially community-acquired *A. baumannii* from Afghanistan and Iraq have been published during the last 15 years. They acquired infections from survivors of natural disasters, community-acquired pneumonia as well as war (30). In these countries, the military medical facilities has a great evidence of providing rapid and highly advanced care to fight infection, which they have been identified a large number of MDR *A. baumannii* isolates as well (31). The cases of military and nonmilitary personnel of United Kingdom and U.S, which they returned from operations in Afghanistan and Iraq, harbored infections caused by MDR *A. baumannii* but they received an excessive attention from military medical facilities (32). Carbapenem-resistant and OXA-23–producing *A. baumannii* also reported in this region (33). It is notable that the $bla_{\text{OXA-23}}$ gene is one of the most prevalent carbapenemase-encoding genes worldwide, which can be located on the plasmids or chromosome in various genetic structures. According to one the study from Iraq, five isolates recovered from soldiers during the Iraq conflict contained a $bla_{\text{OXA-23}}$ gene that was located on a plasmid (34). Imipenem-resistant isolates also recovered from British and American soldiers repatriated from the Iraq conflict, which have been reported to be associated either with OXA-58- or OXA-23-encoding genes (34). MDR (carbapenem resistant) *A. baumannii* originating from injured Canadian military personnel returning from Afghanistan and Iraq have also been described (35).

Another study demonstrated that there was a dif-

ference in the prevalence of MBL production among each isolated of Gram negative bacteria. For instance, 25.9% of *A. baumannii* were MBL producer by PCR reaction which was higher in comparison to other bacteria in the hospital as this bacteria is more prevalent in the hospital environment and even in soil which comes from the visitors foots to the hospital. However, the main mechanism of carbapenem resistance in *Acinetobacter* spp. is class D $bla_{\text{OXA-23}}$ carbapenemase specifically $bla_{\text{OXA-51}}$, which is intrinsic to the most strains of *A. baumannii* (36).

The first report of NDM-1-producing *P. aeruginosa* in Iraq describes in 2014 (37). In recent study by Alshara et al. the detection of NDM-1-positive *P. aeruginosa* isolates indicates the importance of surveillance for the nosocomial infection and dissemination of NDM-1 in Najaf, Iraq.

In Iraq, little attention has been paid to β -lactamases producing isolates. However, in Najaf city, there is no information regarding the molecular studies of the occurrence of carbapenemases-producing recovered from clinical cases (38). Recent study revealed that most β -lactam resistant *K. pneumoniae* isolates were susceptible to both imipenem and meropenem except four (4.2%) of screened isolates were resistant to both imipenem and meropenem by standard disk diffusion method and in PCR experiments using specific primers for bla_{VIM}, bla_{IMP} and bla_{KPC} genes and the results were negative among all isolates. In February 2011, a strain of *Providencia stuartii* submitted from a military hospital in Afghanistan was positive for $bla_{\text{NDM-1}}$(39).

Egypt

In recent years, Egypt has been considered among the countries that reported high rates of antimicrobial resistance (40). While few studies have determined the resistance rates for carbapenems resistance to carbapenems in clinical *A. baumannii* isolates has been notable in Egypt. In 2008 Soheir Helal claimed, there was a significant increase in the number of Acinetobacter infections in teaching Cairo pediatric hospital compared with 2007 (41). In a study from Al-Agamy et al. the majority of the isolates (70%) were resistant to imipenem (MIC >8 mg/ml) (42). Phenotypic assays indicated that 82% of the carbapenem-resistant *A. baumannii* (CRAB) isolates had carbapenemase activity, which 2.5% of them had metallo- β -lactamase activity and the over-expression of proton gradient- dependent efflux pumps (43). In the same study *A. baumannii* showed the highest imipenem resistance (74%) (43).

Kaase et al. showed the first identification of a bla_{NDM} gene in a clinical isolate arising from Egypt, without obvious link with the Indian subcontinent (44). After the recent identification of NDM producing isolates in Iraq and the Sultanate of Oman, the clinical case suggests that NDM-producing bacteria disseminated in the Middle East countries. The new NDM-2 variant was also first detected in *A. baumannii* from a patient who transferred from Egypt to Germany (44, 45). Recently, NDM-2-positive *A. baumannii* MBL isolate identified from Egypt belonged to the ST103 type (46). MBL VIM, SPM-1, and GIM-1 were also detected previously among *A. baumannii* isolates from Egypt (42). Nevertheless, in the recent study by Al-Agamy, none of the *A. baumannii* isolates harbored bla_{IMP}, bla_{VIM}, bla_{SPM}, bla_{SIM}, bla_{GIM}, or bla_{NDM} MBL-encoding genes (42). According to the study, which was reported carbapenemase-producers in Egypt and conducted by Poirel et al, the OXA-48 and VIM-1 which were involved in carbapenemases were not only observed in Egypt, but also they were noticed in many other countries from the Mediterranean including South Europe and North Africa (47). Furthermore, Al-Hassan et al. claimed that the prevalence of OXA-23, OXA-40, and OXA-58 were 55.88%, 2.9% and 14.7% respectively (48). In recent study by Fouad et al. results indicated that the imipenem resistance is due to the spread of OXA-23-producing clones (43).

Zafer et al. stated that the OXA-10 is the most prevalent ESBL producing *P. aeruginosa* in Egypt. Additionally, there were high levels of resistance to all commercially available antimicrobial agents among *P. aeruginosa* isolated from National Cancer Institute and Kasr El Aini Hospital; with the rate of 39.3% imipenem-resistant isolates, which reflects a threat limiting the treatment options in their hospitals (49). According to the data from Zafer et al. the rates of MBL-producing *P. aeruginosa* isolates from Kasr El Aini Hospital and National Cancer Institute were significant and only a limited number of antimicrobial drugs are active (49). Although the occurrence of an NDM-1-producing *Acinetobacter* in Egypt has been reported in recent study, there are no reports of NDM-1-producing *Enterobacteriaceae* in the literatures (50). However, the NDM-1 producing *K. pneumoniae* isolate identified in a study was shown

to belong to ST11 (51, 52).

The first KPC-producing *K. pneumonia*, which was isolated from patients at a tertiary care hospital in Egypt was reported by Metwally et al. in 2013. Data indicates not only, the increased prevalence of Ertapenem non susceptible *K. pneumoniae* isolates, which partially reflects lowering of clinical breakpoints but also illustrates the spread of carbapenemases, mainly KPC types, in Suez Canal University hospital, Egypt (53).

Pakistan

Due to the few available data for CRAB in Pakistan (54) the molecular epidemiology of *Acinetoacter* isolates is completely unknown and the prevalence of MDRs was reported 100% among *A. baumannii* (55). In recent study by Shah et al. almost all *A. baumannii* isolates were metallo-β-lactamase and carbapenemase producer. Increased frequency of MDR isolates supports the requirement of constant surveillance to determine evolution and prevalence of these enzymes in Pakistan.

Kumarasamy et al in 2010 showed NDM-1 emergence as a novel antibiotic resistance mechanism in UK, India and the Pakistan in 37, 48 and 25 isolates respectively (56). A number of studies have included samples from Pakistan and India to evaluate the prevalence and spread of this enzyme and that's because of its association with Indian sub-continent (57). At the beginning of the 21st century, considering the rapid population exchanges, uncontrolled NDM-1-related resistance may be expected to be identified not only in Bangladesh, India and Pakistan, but also in countries with important population exchanges with the Indian subcontinent (58). In a study which examined by multinational team the emergence and spread of 180 cases of infected patients by NDM-1 producing bacteria, including 143 cases in various sites in Pakistan and India and 37 cases in the United Kingdom, thus suggesting an extensive dissemination (56).

A. baumannii isolate from Pakistan carrying bla_{OXA-23}-like has been reported previously (59). bla_{OXA-23}-like acquiring carbapenemase gene was found in the majority of CRABs from intensive care unit setting, indicating the importance of this gene in carbapenem resistance in Pakistan (60).

As reported by Nahid et al. in a study which is about MBLs producing organisms, PCR amplification confirmed 31 (23.6%) isolates harboring bla_{NDM-1} gene, 33 (25.1%) isolates having bla_{VIM} gene and 2 (1.5%) isolates displaying bla_{IMP} gene (57). The results demonstrated a high level of NDM-1 positive organisms from variety of samples at hospitals, implicating the spread of MBL genes in clinical isolates. In other study, Perry et al. highlighted that bla_{NDM-1} was detected in 64 isolates of seven species of *Enterobacteriaceae* and in three isolates of *A. baumannii* and one of *Aeromonas caviae* (61). In contrast to isolates with the NDM-1 enzyme from infections, the dominant producer species were *E. cloacae* and *E. coli* rather than *K. pneumoniae* (61). This shows that carbapenem resistance varies from region to region and hospital to hospital and this issue is emerging in Pakistan and needs more attention from all countries (62). In a recent study by Fakhuruddin et al. *Enterobacteriaceae* is 49.75% of the total clinical isolates and out of these amounts 12 of them (6.0%) are CRE. Moreover, the frequency of CRE is lower than other countries but it is higher in comparison to the local studies (62). Fakhuruddin mentioned that there are several possible factors: Firstly, carbapenem is not used in this country because of its cost. In this country cephalosporins are the first choice for experimental therapy and there is limited use of carbapenem group. Secondly, the rate of carbapenem resistance in *Pseudomonas* (14%) in Pakistan is lower than other countries. Lastly, limited work has been done on carbapenem resistance in Pakistan regarding *Enterobacteriaceae* (62).

Although other metallo-β-lactamases IMP and VIM have been reported in non-*Enterobacteriaceae*, like *Acinetobacter* species and *Pseudomonas aeruginosa* from this country (63), these were not detected in CRE isolates tested in this country (64).

In conclusion, a considerable prevalence of bla_{NDM-1}, which carrying gram negative pathogens in patients coming to hospitals indicates the request for the countrywide screening of hospitals and community to evaluate the exact prevalence of it (57).

Lebanon

The increasing incidence of carbapenem resistant agents has been described in different countries around the world. Although in the Middle East countries such as Lebanon scattered information is found, the reliable reports are very scarce. During 1999 to 2009, *A. baumannii* strains harboring the *bla-*

$_{OXA-58}$ carbapenemase gene were predominant among carbapenem-resistant bacteria of this species in the hospital flora in different Mediterranean countries including Lebanon (65). Data from Saint George University Hospital in Beirut demonstrate that only 61% of the *A. baumannii* were susceptible to imipenem (66). Between November 2004 and October 2005, an outbreak of MDR *A. baumannii* was observed in the Saint George University Hospital of Beirut, Lebanon (67). It seems likely that the only mechanism for carbapenem resistance in *A. baumannii* isolates was the production of the carbapenem-hydrolyzing oxacillinase OXA-58 causing the outbreak at the Lebanese Hospital (67). The first detection of *A. baumannii*, which carrying the bla_{NDM-1} gene in Lebanon was described by Rafei et al. in 2014 that isolated from Syrian patients wounded during the civil war. All isolates which harbored the bla_{NDM-1} gene were negative for other tested carbapenemases (68). They belonged to the sequence type 85 and formed a single cluster by PFGE. Finally, bla_{OXA-51}-like gene sequencing revealed the presence of the bla_{OXA-94} variant in all of these isolates (68).

The first report from Lebanon on carbapenem resistant *Enterobacteriaceae* isolates imported from Iraq (69). This country, like other countries, is now facing a dangerous threat with the emergence of carbapenem-resistant *Enterobacteriaceae* and the imported NDM-1strains to this country. In 2007, the first metallo-β-lactamase producing in Lebanon was isolated and found to harbor the bla_{IMP-1} and bla_{CTX-M} genes (70). According to the two studies which were reported in 2008 and 2010 (10), OXA-48 (class D) were produced by *E. coli* and *K. pneumoniae* (10, 69). Identification of this novel and powerful resistance determinant outside of Turkey indicates that spread could be more important than expected (71). *E. coli* isolates represented 10% of the OXA-48 clinical producers in 2008–11 and 73% in 2012 in Lebanon (72). In addition, intestinal carriage of OXA-48-producing *E. coli* was observed in the community and was marked by a diversity of strains, suggesting that OXA-48 has become endemic in North Lebanon (72). Beyrouthy et al. showed that the rate of *Enterobacteriaceae* exhibiting a decrease in susceptibility to ertapenem in Nini Hospital, North Lebanon, increased from 0.4% in 2008–10 to 1.6% in 2012. This growth was associated with the emergence of carbapenemase OXA-48, which had been previously reported in Lebanon in 2008–2010 (72).

In 2009, a study from Lebanon revealed that 2.5% of *E. coli* and 7.84% of *K. pneumoniae* were ESBL producers and carbapenem resistant [antimicrobial brochure at the American University of Beirut Medical Center (AUB-MC)] (10) and up to 30% of isolated *E. coli* strains were found to be multi-drug resistant (70). Recently, IMP and VIM have been detected in most GNB isolated from nosocomial infections (73). Although the various countries discussed share regional proximity, it is interesting to note the differences in the recovered carbapenemases. For example, the similarities were noted between OXA enzymes in Turkey and Lebanon. These similarities may be attributed to interactions between different populations and communities in these countries; the exact factors that promote such differences remain to be identified (10).

Iran

Like other countries, several studies have been carried out about drug resistance in Iran as well. Increasing resistance to carbapenems by organisms producing carbapenemase enzymes, particularly *Acinetobacter* and *Pseudomonas* spp. is the main concern in this country. The use of colistin and polymyxin B as a therapeutic agent has been prompted by increasing resistant to antimicrobials including the carbapenems, which it has been used with increasing frequency to treat patients infected with MDR-GNB such as *A. baumannii* in the last several years (74). Carbapenem resistance has been increasingly common issue among *A. baumannii* isolates in Iranian hospitals in recent years (75) with the majority of isolates showing multi-drug resistance (76). Considerably high prevalence (99%) of the isolates was MBL producing which can be a main cause of high carbapenem resistance among *A. baumanni* isolates (77). Recent studies have shown the existence of different MBLs producing clones of *A. baumannii* in Iran (Fig. 4.). The first report about the existence of bla_{SPM-1} and bla_{GES-1} among the clinical strains of *A. baumannii* in Iran carried out by Shahcheraghi et al. Detection of GES-1 among the Iranian strains of *A. baumannii* is another important finding of the recent study (78). Furthermore, in the majority of studies in Iran and other countries VIM-type MBL was the most prevalent gene that reported (22). Peymani et al. found that among MBL-producing *A. baumannii* isolates, 61% and 29% of them carried, respectively (79).

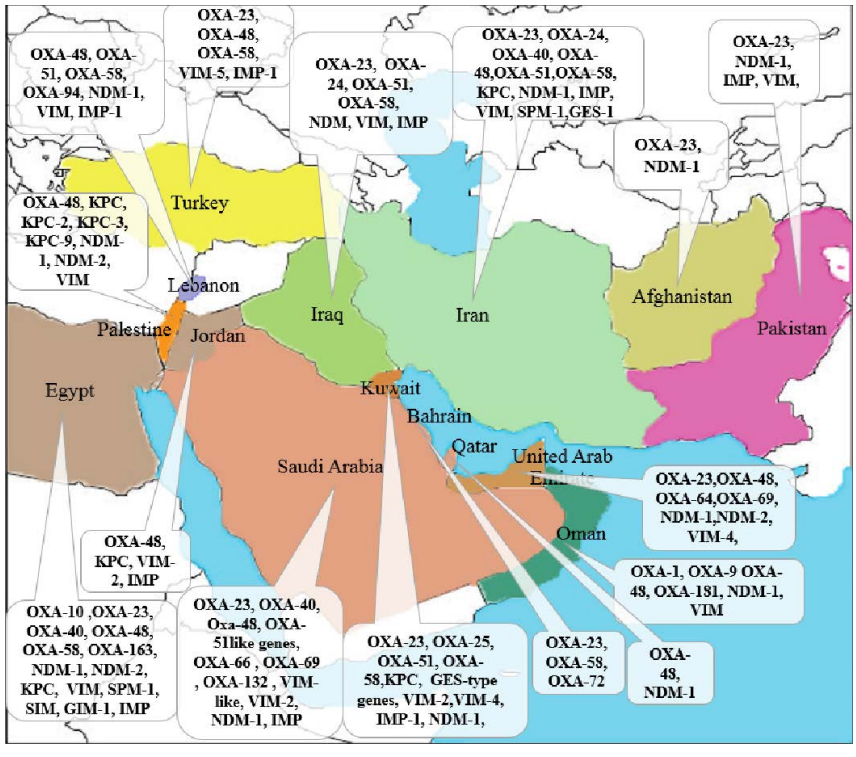

Fig. 4. Geographical distribution of carbapenemase produced by Gram-negative bacilli in the Middle East countries

After the recent identification of the bla_{KPC} and the bla_{NDM-1} genes in a burn unit in Tehran, the identification of the bla_{OXA-48} carbapenemase gene has become more difficult (80, 81). Therefore, the spread of OXA-48 producers may be more widespread than expected like in any countries of the Middle East (82). The first report indicating clonal dissemination of imipenem-resistant *A. baumannii* which was carried out by Peymani et al. correspond to known international clones in Iran. The results of this study revealed that 94% of imipenem-resistant *A.baumannii* isolates belonged to IC II (IC=international clone), suggesting clonal spread and cross-transmission of this organism in different wards of Hospitals, as well as presence of IC I isolates (83). The results obtained in recent study indicated that all isolates carried the bla_{OXA-23}-like gene with a high level of ISAba1 element (83). In the previous paper from Tehran, OXA-23 and OXA-40 were the most prevalent carbapenemases amongst imipenem-resistant isolates; however, the epidemiological background of these isolates was not investigated (76). In 2008, 50% of resistance to meropenem and 49.3% of resis¬tance to imipenem were reported in Iran (76), followed by 52.5% of resistance to imipenem and meropenem in 2009 (84) and 49.26% of resistance to imipenem in 2011 (78). In 2012, 62% of isolates were resistant to imipenem (85). Distribution of OXA gene among *Acinetobacter* isolates, in Tehran in 2008 was as follows: bla_{OXA-23}-like / bla_{OXA-51}-like was detected in 25%, bla_{OXA-24}-like / bla_{OXA-51}-like in 17.9% and bla_{OXA-51}-like / bla_{OXA-58}-like was detected in 9% of the isolates (76). Consequently, the high prevalence of OXA type carbapenemase-encoding genes among the clinical isolates from Iran appears responsible for low susceptibility rates for imipenem (78). According to the data the MDR strains of *A. baumannii* are spreading and carbapenemase resistance is increasingly common in Iran.

Data demonstrated that the majority of *P. aeruginosa* isolates (87.05%) were multi-drug resistant in Iran (86). These findings are also exposed that the prevalence of antibiotic resistance of the *P. aeruginosa* isolates was very high in comparison with the results obtained from other studies conducted in Korea, Greece, Poland, India, Italy and Turkey. Previous studies performed in burn hospitals in various cities of Iran, such as Tehran, Shiraz and Ahwaz demonstrated a high prevalence of resistance to antibiotics in *P. aeruginosa* strains isolated from burn

infections (87-89). There are several reports on the prevalence of bla_{VIM} and bla_{IMP} among carbapenem resistant *P. aeruginosa* strains isolates from burn patients in Iran but the characteristics of other mechanisms of resistance to carbapenems are unknown (87, 90, 91). Other study which has been done in Iran reported that 20 (9%) of 212 *P. aeruginosa* isolate contained bla_{IMP}, whereas 70 (33%) of them harbored the bla_{VIM} (22). In contrast, two recent studies which carried out in Tehran and also in the south of Iran, MBL-producing *P. aeruginosa* isolates were only positive for bla_{VIM} genes (12, 92).

Yazdi et al. isolated 126 *P. aeruginosa* strains from non-burn patients in Iran in 2007. Among 70 imipenem resistant *P. aeruginosa* strains, 8 showed MBLs production in E-test, all carried bla_{VIM}, while none of them were positive for bla_{IMP} gene (93). A paper by Saderi et al. has demonstrated that MBL-producing *P. aeruginosa* is an important cause of imipenem resistance in *P. aeruginosa* strains isolated from burn patients in Tehran, since out of 69 imipenem resistant strains, 65 strains were MBL positive using phenotypic method (94). Therefore, the production of MBLs enzyme and AmpCβ-lactamases are the major emerging mechanism of resistance carbapenem among *P. aeruginosa* isolates in this city (95).

There were limited data on the carbapenemase producing *Enterobacteriaceae* in Iran. High rates of MDR strains in isolates with positive KPC are a major challenge and it could cause an increase in both morbidity and mortality among burn patients (96). In a study which conducted on *K. pneumoniae* clinical isolates from a burn hospitals, imipenem-resistance was observed in 9.1% (5 from 55) isolates, which KPC production was detected in 3 isolate, showing the overall KPC production at 5.45% (unpublished data from Naseh). Azimi et al. claimed that twenty-eight (64%) out of 44 *K. pneumoniae* isolates were resistant to carbapenem according to CLSI breakpoints and 16 (36%) were susceptible. In addition, all isolates were negative for presence of KPC genes on gel electrophoresis (97). The first case of OXA-48-producing *K. pneumoniae* in Iran, was reported by same author, which the bla_{OXA-48} gene was detected in 27/28 isolates and one isolate was positive for the presence of the bla_{VIM-4} gene (98).

Jordan

A study conducted by Dhabaan et al. investigated the antimicrobial susceptibility profile of *A. baumannii* and the contribution of the insertion sequence upstream of ampC β-lactamase on the susceptibility profile of *A. baumannii* clinical isolates collected from a Jordan hospital. A total of 64 consecutive clinical isolates of *A. baumannii* were recovered (between March 2005 and December 2006) at the King Abdullah University Hospital (KAUH) which imipenem and meropenem showed increased resistant rates (70.1 and 71.6%, respectively) (99).

According to the Al-Khatatneh et al. the prevalence of carbapenemases among *E. coli* and *Klebsiella* spp. is due to the infected or colonized patients who are admitted to Jordan university hospital and King Hussein Cancer Center to characterize these isolates at the molecular level. Furthermore, 24 isolates from 800 isolates of *E.coli* and *Klebsiella* spp. were demonstrated to have bla_{KPC}, bla_{VIM} and bla_{IMP} genes (100). Adler et al. reported a Jordanian woman referred to the hospital for oncological care and she was diagnosed with an OXA-48-producing *E. coli* bacteremia, and successfully treated with colistin and ceftazidime (28). The VIM-2-producing strain was isolated from a patient who may have been treated with carbapenems in Jordan (101). Although the carbapenemase gene is not well known, bla_{VIM-2} may be present in Jordan, as it is widespread in Asia and Eastern Europe. On the other hand, VIM-2 may have been disseminated from Jordan to the U.S. as well (101).

Persian Gulf countries

The countries of the Persian Gulf (United Arab Emirates [UAE], Qatar, Kuwait, Bahrain and Oman) represent that the international travel is a prominent problem; migrant workers are substantial proportions of the population from the Indian subcontinent and large numbers of citizens seek medical care in specialized centers in the Europe and United States(102).

United Arab Emirates

Among the Arabian Peninsula countries, the high amount of migration is a significant trade, touristic and health care links with the Indian subcontinent. For instance, a known reservoir of such isolates makes this country to encounter with strains.

Some papers demonstrated that a variety of

NDM-producing isolates, have already been present in the Abu Dhabi Emirate, that representing different species and genetic support (103). Screening of 155 carbapenem non-susceptible *A. baumannii* strains recovered in Abu Dhabi hospitals during 2008 to 2011 identified two bla_{NDM} MBL gene-carrying isolates. They were shown the bla_{NDM-2} gene recently detected in *A. baumannii* in Egypt. These isolates indicate that the bla_{NDM-2} gene have prominent similarities with those associated with bla_{NDM-1} in *A. baumannii* and *Enterobacteriaceae* (104).

Recent data displayed that OXA-23-positive *A. baumannii* strains have spread around the world especially in the UAE (105). Lu et al. mentioned in the UAE, resistance to carbapenems was associated with the OXA-23 production (106). Five CRAB isolates, collected from the UAE in 2006, were investigated to identify the responsible mechanism(s) in carbapenem resistance. Genotyping assays verified that the fifth isolates have the gene on a transferrable plasmid and the four isolates with the bla_{OXA-23} gene were on the chromosome within a Tn2006 composite transposon, which were clonally related (105).

In recent report by Sonnevend et al. among 28 clinically carbapenem which were non-susceptible *Enterobacteriaceae* isolates collected in 2009–2011 in the UAE, three *K. pneumoniae*, two *E. coli*, one *C. freundi* and one *E. cloacae* were identified to produce NDM-1 carbapenemase (103). Moreover, in Abu Dhabi hospitals NDM producing *Enterobacteriaceae* have been found in 9 out of 34 carbapenem non-susceptible isolates, while OXA-48-like was found in 11 isolates. Screening of these isolates have been identified an *E. cloacae* strain containing $bla_{CTX-M-15}$, bla_{CMY-4}, and bla_{VIM-4}. It was isolated from the urine of an Egyptian patient repeatedly hospitalized and treated with broad-spectrum antibiotics, including carbapenems, in the UAE (107).

Kuwait

Hospitals have long served as reservoirs for the transmission of pathogenic bacteria and this has become a problem in Kuwait (108). Recently, infections due to MDR *A. baumannii* strains have become a serious problem in some hospitals in Kuwait, these isolates are the second most frequently isolated pathogens, particularly in the ICUs (109).

Epidemic isolates from wounded U.S. military service members were described that a novel clone which had previously been identified in European countries, by the U.S. military healthcare facility and one hospital in Kuwait. The bla_{OXA-58}-type carbapenemase was identified in two carbapenem resistant isolates, one from Kuwait and one from U.S. soldiers. The bla_{OXA-51}-type gene which is usually present in *A. baumannii* was detected in all isolates around this country (110). The first report of a novel OXA carbapenemase, OXA-58, came from Kuwait (111, 112). Other studies reported that *A. baumannii* carrying OXA-type carbapenemases have emerged from Kuwait, which have been suggested that carbapenemase producers are emerging pathogens in this region (113). Besides, the sequence data were not obtained for the carbapenem-hydrolyzing OXA enzyme from the isolate in Kuwait; nevertheless, the enzyme was phenotypically similar to OXA-25 and OXA-26(111).

Recently, the emergence of GES-type Ambler class A carbapenemases in *A. baumannii* has been demonstrated and identified in this country (114). Bonnin et al. reported a total of 63 bla_{GES} positive isolates were analyzed, one isolate have the bla_{GES-14} gene encoding a carbapenemase activity, whereas the other isolates harbored the bla_{GES-11} ESBL gene (114).

P. aeruginosa and *A. baumannii* producing VIM-2 were also reported from Kuwait (109). In 2012, Al-Sweih et al. emphasized that 40 (42.6%) of 94 isolates, were resistant to either meropenem or imipenem and in some cases to both of them (CRAB). Most CRAB isolates (29 of 40 or 72.5%) carried *bla* genes, which code for metallo-β-lactamase (VIM-2 and IMP-1) enzymes and two isolates was bla_{OXA-23} harboring (109).

Reports of emerging carbapenemases among *Enterobacteriaceae* have been published worldwide such as Kuwait (115). Overall, carbapenem resistance in *Enterobacteriaceae* was extremely rare in Kuwait, but in the last few years especially after 2009, some articles showed resistant isolates to carbapenems (116). New Delhi metallo-β-lactamase (NDM) has been recently detected among members of *Enterobacteriaceae* family in the Middle Eastern countries including Kuwait (113). During 2010 and 2011, two NDM-1-producing *K. pneumoniae* were identified in Kuwait (115). In recent study, Jamal et al. reported that 11 of 14 isolates produced VIM-4 (six *K. pneumoniae*, three *E. coli*, one *E. cloacae*, and one *K. oxytoca*) and three isolates produced the NDM-1 MBL and co-produced the plasmid-encoded AmpC CMY-4 (116). In conclusion, the emergence of car-

bapenem-resistant *Enterobacteriaceae* in Kuwait has significant prevalence like many other countries.

Qatar

Due to carbapenemase producing bacteria in Qatar, data on carbapenem resistance are extremely limited. Between January and June 2002, an outbreak of MDR *A. baumannii* reported by El Shafie et al. which involved 21 ICU patients, caused by carbapenem-resistant *Acinetobacter* occurred in a trauma intensive care unit (TICU) at the Hamad Medical Corporation, Qatar (117). It was reported that carbapenems had the best activity against *A. baumannii*, but in this outbreak, the strain was resistant, due to the production of carbapenemase (117). In other study, Khan et al. observed high resistance rate to carbapenems among the *Acinetobacter* isolates (41.5%), whereas resistance among *P. aeruginosa* was emerging 14.3% (3/21) and *Enterobacter* spp., *E. coli* and *Klebsiella* spp. were all sensitive to carbapenems (118). El Shafie et al. found that 6% of the reported isolates of both *Klebsiella* spp. and *E. coli* were resistant to imipenem but not to meropenem (117).

Bahrain

Studies reported that *A. baumannii* carrying OXA-type carbapenemases have emerged from Bahrain, signifying that carbapenemase producers are emerging pathogens in this region (119). Mugnier et al. have analyzed eight *A. baumannii* strains isolated in the Salmaniya Medical Complex from Bahrain and found that all isolates produced carbapenemase genes. Of eight isolates, two harbored $bla_{\text{OXA-23}}$ and one isolate carried $bla_{\text{OXA-58}}$, while the other five *A. baumannii* isolates produced $bla_{\text{OXA-72}}$ (119). However carbapenems were the most active drug against the ESBL-producing isolates (120).

Oman

Over the past decade carbapenem resistance was not common in Omani hospitals; for example, between 2004 and 2005 all ESBL producers isolated from a hospital in Muscat were found to be susceptible to carbapenems (102). KP3 was isolated from a patient transferred to the Sultanate of Oman from India that was resistant to all β-lactams, including carbapenems (121).

In a study Dortet et al. described the dissemination of carbapenemase producers, especially OXA-48- types and NDM-1, in Sultanate of Oman. The close relationship between the India and Arab Peninsula in terms of patient exchange might be related to emergence of those carbapenemase producers in that country (122). NDM-type-producing isolates from Oman and Qatar were genetically unrelated to all other NDM-type positive strains isolated from this region (123). Piorel et al. showed that two $bla_{\text{NDM-1}}$ carbapenemase genes harboring isolates including 419 and 601, which were recovered from an Omani patient who had not travelled abroad and from a patient who was transferred from India respectively. However, the two isolates were clonally unrelated, and belonged to ST340 (isolate 419) and ST14 (isolate 601) (124). In addition to NDM-1, the ST14 isolate expressed β-lactamases TEM-1, CTX-M-15, SHV-28, OXA-1, OXA-9, and the aminoglycoside resistance methylase ArmA and the ST340 isolate expressed β-lactamases OXA-1, SHV-11 and ArmA as well. In both isolates, the $bla_{\text{NDM-1}}$ gene was located on plasmids with the similar size (170 kb), but in different incompatibility groups (124).

The rates of carbapenem-resistant *Acinetobacter* and *P. aeruginosa* isolates from different sites in Omani hospitals were reportedly less than observed in other GCC (Gulf Cooperation Council) states. For example, isolates from a hospital in Muscat (2007) showed that susceptibility to meropenem was 100% and 85% for *Acinetobacter* and *P. aeruginosa* respectively (102). In this study, we are aware of un-sequenced VIM-related enzymes in *P. aeruginosa* strains from Oman (125).

Saudi Arabia

Limited data is available on the antimicrobial susceptibility of *Acinetobacter* species in Saudi Arabia, and most recently; this information was restricted to the study of the epidemiology of an outbreak (126). On the other hand, studies on carbapenem resistance *Acinetobacter* in Saudi Arabia reported inconsistent results (102). For instant, in a tertiary hospital ICU in Riyadh, IMP susceptibility in *Acinetobacter* declined from 55% in 2004 to 10% in 2009 (127). In contrast, a national study on 228 *Acinetobacter* isolates from 24 hospitals in 2009 found that 94.6% of them were IMP susceptible. This susceptibility rate

is significantly higher than other rates reported in studies from individual hospitals or from other GCC states (128). In Saudi Arabia, carbapenem resistance has high prevalence in *A. baumannii* isolates from hospitals, which these isolates are much more likely to be resistant than susceptible. In addition, a very high percentage of isolates (~95% of isolates) co-harboring a VIM-type MBL whereas the high levels of carriage of the acquired carbapenemases $bla_{\text{OXA-40}}$ and $bla_{\text{OXA-23}}$ (129). In recent study which has been conducted by Alsultan et al. diabetic patients were significantly carried carbapenem-resistant isolates (129). The emergence of multi-drug resistant nosocomial *A. baumannii* has also reported in different hospitals in Saudi Arabia (130). Furthermore, in nine *Acinetobacter* strains isolated from three different sites, a novel OXA-51-like-encoding genes were identified (131). A high OXA-51-like genotypic diversity was revealed by sequence-based typing from inpatients at a tertiary care hospital in Riyadh, Saudi Arabia and showed that all isolates were clustered into four main groups including OXA-66 (62.3 %), followed by OXA-69 (19.1 %), OXA-132 (7.6 %) and other OXA-51-like genes (10.3 %), such as OXA-79, -82, -92, -131 and -197 (132). Moreover, a high prevalence (81.4 %) of OXA- 69 and OXA-66-like genes in *A. baumannii* was identified (132).

The frequency of imipenem resistance among *P. aeruginosa* isolates in Saudi Arabia was 11% in 1998 (133) 9.3% in 1999 (134), 20% in 2004 (133) and 16.3% in 2007 (135). This resitance was increased to 38.57% in 2011 (136). Additionally, high prevalence of imipenem resistant and MBL-producing *P. aeruginosa* isolates in Saudi Arabia was reported by the recent studies which were conducted in this region. Imipenem resistance is increasing and MBL is responsible for 20.57% of the resistance (136). In this country, MBLs have emerged as a main mechanism of carbapenem resistance in *P. aeruginosa* (102). The $bla_{\text{VIM-2}}$ is the dominant MBL gene in MBL-producing isolates in Saudi Arabia (136). In 2007, Al-Agamy et al. in screening of 135 *P. aeruginosa* clinical isolates from Riyadh has found that 16.29% of them have bla_{VIM}-like genes (135). Another study found that 19.4% and 22.6% of 31 metallo-β-lactamase-producing *P. aeruginosa* isolates from Makkah (Mecca) harbored bla_{VIM} and bla_{IMP}, respectively (137).

Although there were only limited phenotypic reports, the emergence of carbapenem-resistant *Enterobacteriaceae* in Saudi Arabia was reported in 2000 (102). Although mechanisms of increased carbapenem MICs were not explored, during 2002 and 2003, studies claimed that 14% of ESBL-producing *E. coli* in the eastern province of Saudi Arabia had increased MICs to meropenem and imipenem (138). Between 2004 and 2009, studies on ICUs in Riyadh showed that out of 285 ESBL-positive isolates, just one single carbapenem-resistant was isolated (127). The first documented outbreak of carbapenem-resistant in Saudi Arabia occurred in Riyadh during 2009 and 2010 and involved 20 patients (102).

In 2013, among *Enterobacteriaceae* isolates, 53% showed resistance to meropenem and 36% to imipenem, which is alarming, because carbapenems have been the drug of choice. As reported by Poirel et al. in 2011, a KPC-producing isolate has also been reported in Riyadh and was found to be tigecycline resistant (139). In the Arabian Peninsula, OXA-48 and NDM have been reported in the United Arab Emirates, Oman and Kuwait (4, 104, 121, 122, 124), but regarding Saudi Arabia little has been published, which is the largest region's and most populous country, with significant international population flows(124). In 2012, Shibl et al. provided the first insight into the widespread occurrence of isolates harboring $bla_{\text{OXA-48}}$ and $bla_{\text{NDM-1}}$ among patients in healthcare facilities in Riyadh, Saudi Arabia (140).

Turkey

In the last two decades, *A. baumannii* has become a significant nosocomial pathogen in Turkey as well as throughout the world and is a leading issue in antibiotic therapy due to its MDR (141). Carbapenemases seem to be the main cause of carbapenem-resistance in *A. baumannii* and thus have to be considered as the main target for development of inhibitors (142). According to the SENTRY Antimicrobial Surveillance Program, a significant increase in carbapenem-resistance among *A. baumannii* isolates (20–60 %) in two Turkish medical centers was detected in the 2000–2006 period (143). Until 2005, carbapenem resistant *A. baumannii* strains had only been isolated sporadically in Turkey (144). At the August 2005, a rapid increase in the isolation of CRAB was observed in the ICU setting (144). In recent years, molecular epidemiology studies have documented multiple outbreaks of MDR clones of *A. baumannii* in Turkish hospitals (145, 146). Moreover, the multiple data of carbapenemases have been described in

this country including OXA-producing *A. baumannii*. From 2006, carbapenem-resistant strains were evaluated for the presence of epidemic clonally and encoding genes. OXA-23-like and OXA-58-like carbapenemase-producing strains were previously identified in Turkey. An ICU-based OXA-23-producing MDR *A. baumannii* outbreak was detected between 2005 and 2006 (147).

In Turkey, carbapenem resistance in *Enterobacteriaceae* isolates also has been reported and most often mediated by OXA-48 type carbapenemases (148). Although the spread of this type is periodically in 2001, the first OXA-48 producer was identified in 2003 from a strain isolated in Istanbul (19,149). This case was resistant to all β-lactams, including carbapenems (149). The hospital outbreaks in the main cities of this country were under controlled (150). Subsequently, dissemination of carbapenem-producing isolates not only reported in Turkey but also in the Middle East, North Africa and Europe as well (151). OXA-48 has been found in a *C. freundii* (152) isolate, *P. rettgeri, E. cloacae*(150) and an *E. coli* isolate as well as several isolates (153, 154). The number of OXA-48-producing isolates in the hospitals of this country from 2 and 6 isolates between 2007 and 2008 respectively, increased to 27 isolates in 2009; conversely, metallo-β-lactamase production rates were stable throughout the 3 years surveyed (155). Another study also demonstrated that although the strains were isolated from the same clinical units, the $bla_{\text{OXA-48}}$ gene dissemination was not by a single clone (156). This means that in Istanbul, multiple OXA-48-producing clones are present. Clinical laboratory detection of OXA-48-producing strains may be difficult, since the $bla_{\text{OXA-48}}$-carrying plasmid confers a low level of resistance to carbapenems by itself (157). As reported by Labarca et al. the first detection of the globally spread of carbapenem-resistance clone ST258 and carbapenemase-2-producing have been occurred in Turkey (158). Although, this issue have been never detected in Turkey, this country has a specific epidemiology where OXA-48 carbapenemase has been widely detected for a decade (159). But there is only one known report of imported NDM-1-producing from an Iraqi patient when admitted at the Turkish hospital (160). The OXA-23 chromosome-encoded oxacillinase was previously described for *Proteus mirabilis* (161).

VIM-enzymes causing outbreaks in many Mediterranean countries, like Turkey (3). VIM-5 is a variant which is closely related to VIM-1 was originally reported in an IMP-resistant isolate from this country (VIM-5 compared with VIM-1, differs by five amino acid substitutions) (162). The presence of VIM-5 enzyme, which was identified in an isolated from a different Turkish area, suggests that the regional spread of this resistance is determinant. Other MBL detected in *Enterobacteriaceae* was IMP-1 in 2003 and in *E. cloacae* in 2003 and 2004 (163).

CONCLUSION

The increasing incidence of carbapenem resistant agents has been described in different countries around the world especially in the Middle East. In recent years, the emergence of carbapenem-resistant GNB in this region is an alarming problem. Carbapenemases represent the strict threat for human health worldwide, and stand as one of the most challenging problems confronting containment of infectious diseases in the following years. The prevalence of carbapenemases is variable across the Middle East countries; a high prevalence of KPC enzymes can be found in Afghanistan, Saudi Arabia and Jordan, but little has been reported in other countries. Moreover, the highest resistance mediated by NDM carbapenemases has reported in Pakistan; however, in other countries have reported sporadically. Additionally, the resistant mediated by OXA carbapenemases in Turkey and Pakistan much has been observed and in other countries have been occasionally. Variety of carbapenemase enzymes depend on the country; may be influenced by historical and cultural relationships and may also be due to wars and moving troops. Cross border transfer of patients, medical tourism, travelers and refugees might also play a significant role. Thus, guidelines and appropriate infection control measures are needed to prevent such infections among patients.

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