Review Article

Global spread of New Delhi metallo-beta-lactamase-1(NDM-1)

Fatemeh Fallah[1], Arezou Taherpour[2], Mojdeh Hakemi Vala[3], Ali Hashemi[3]*

Abstract

Global spread of blaNDM-1 genes among multidrug resistant bacterial pathogens is a threat for human that affects all patients throughout the world. Therefore, 2011 was named as Antibacterial Resistance year. Carbapenems are last–line antibiotics for treatment of nosocomial infections. Resistance to this group of antibiotics is because of producing metallo-β-lactamase especially NDM-1. Different sorts of plasmids in different sizes carry blaNDM-1 gene. In addition to NDM-1, plasmids have the other resistance genes like extended spectrum β-lactamase (ESBL), cephalosporinases, carbapenemases, macrolides as well as rifampin and fluoroquinolones resistance genes. These plasmids can be transferred from bacteria to bacteria, from man to man and even country to country. There is still no vaccine to prevent from infections produced by bacteria which have carbapenemases. So, it is necessary to inspect phenotyping and genotyping NDM-1 resistant pattern worldwide.

Introducti

Antibacterial-resistant pathogens are serious threat for worldwide hospitalized patients. Rapid expanding multi-drug resistant bacteria is a major public health problem (1-3). Alteration of normal flora caused by antibacterial therapies results in fungi and other opportunistic microorganisms to grow and invade host tissues (4). Therefore, the year 2011 was named "Antibacterial Resistant year" by world health organization (WHO). WHO recommendations to governments are focused on prevention and control such antimicrobial resistance patterns, logical use of antibiotics and control of infections (5,6). The increasing pattern of multi-drug resistant (MDR) bacteria has limited therapeutic options especially for nosocomial isolates of Klebsiella pneumonia (7, 8). It has been especially very difficult to treat neonatal infections because of MDR organisms (9) and many neonatal deaths occur due to MDR bacteria in developing countries (10).

1-Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences Tehran, Iran.
2 -Department of Microbiology, Kurdistan University of Medical Sciences,
3- Department of Microbiology, Faculty of Medicine, Shahid Beheshti University, of Medical Sciences Tehran, Iran.
Email:Hashemi1388@yahoo.com
Email:ali.hashemi@sbmu.ac.ir
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β-lactamases are major defensive mechanisms in gram negative bacteria against antibiotics (11). According to Bush-Jacoby classification, β-lactamases are divided into four groups (12). (Table 1)
cephalosporins (by TEM, SHV and CTX-M enzymes), quinolones (by qnrAB, qnrB1 and qnrB2 types), aminoglycosides (by 16s rRNA methylase genes), trimethoprim/sulfamethoxazole and piperacillin /tazobactam (15, 16). In addition, drugs such as carbapenems are used for severe infections caused by bacteria, particularly Pseudomonas aeruginosa and Acinetobacter species (17). The carbapenemases are classified based on their amino acid sequence homology: Important clinical enzymes are; KPC (Ambler class A), IMP and VIM types (class B) and OXA- 48 (class D), which are found in Entrobacteriaceae especially K.pneumonia which is a source of hospital epidemics (14, 18, 19, 29). Carbapenem resistance in bacteria is due to production of carbapenemases and other mechanisms such as changing outer membrane permeability, ESBL, over expression of Amp C and porin loss that can be combined with cephalosporinases (9, 11, 21). In more carbapenem resistant isolates of Acinetobacter baumannii, over expression of OXA β-lactamases such as OXA-40, OXA-58, OXA-23, OXA-143- related and OXA-51-like enzymes are causes of antibiotics resistance (2, 22). Carbapenems are the last-line antibiotics against hospital infections (10, 11, 14, 23-25). In addition, at least nine MBL types have been recognized demonstrated in figure 1 (13).

Bush-Jacoby group (2009)	Bush-Jacoby-Medeiros group (1995)	Molecular class (subclass)	Distinctive substrate(s)	Inhibited by		Defining characteristic(s)	Representative enzyme(s)
				CA or TZB[a]	EDTA		
1	1	C	Cephalosporins	No	No	Greater hydrolysis of cephalosporins than benzylpenicillin; hydrolyzes cephamycins	*E. coli* AmpC, P99, ACT-1, CMY-2, FOX-1, MIR-1
1e	NI[b]	C	Cephalosporins	No	No	Increased hydrolysis of ceftazidime and often other oxyimino-β-lactams	GC1, CMY-37
2a	2a	A	Penicillins	Yes	No	Greater hydrolysis of benzylpenicillin than cephalosporins	PC1
2b	2b	A	Penicillins, early cephalosporins	Yes	No	Similar hydrolysis of benzylpenicillin and cephalosporins	TEM-1, TEM-2, SHV-1
2be	2be	A	Extended-spectrum cephalosporins, monobactams	Yes	No	Increased hydrolysis of oxyimino-β-lactams (cefotaxime, ceftazidime, ceftriaxone, cefepime, aztreonam)	TEM-3, SHV-2, CTX-M-15, PER-1, VEB-1
2br	2br	A	Penicillins	No	No	Resistance to clavulanic acid, sulbactam, and tazobactam	TEM-30, SHV-10
2ber	NI	A	Extended-spectrum cephalosporins, monobactams	No	No	Increased hydrolysis of oxyimino-β-lactams combined with resistance to clavulanic acid, sulbactam, and tazobactam	TEM-50
2c	2c	A	Carbenicillin	Yes	No	Increased hydrolysis of carbenicillin	PSE-1, CARB-3
2ce	NI	A	Carbenicillin, cefepime	Yes	No	Increased hydrolysis of carbenicillin, cefepime, and cefpirome	RTG-4
2d	2d	D	Cloxacillin	Variable	No	Increased hydrolysis of cloxacillin or oxacillin	OXA-1, OXA-10
2de	NI	D	Extended-spectrum cephalosporins	Variable	No	Hydrolyzes cloxacillin or oxacillin and oxyimino-β-lactams	OXA-11, OXA-15
2df	NI	D	Carbapenems	Variable	No	Hydrolyzes cloxacillin or oxacillin and carbapenems	OXA-23, OXA-48
2e	2e	A	Extended-spectrum cephalosporins	Yes	No	Hydrolyzes cephalosporins. Inhibited by clavulanic acid but not aztreonam	CepA
2f	2f	A	Carbapenems	Variable	No	Increased hydrolysis of carbapenems, oxyimino-β-lactams, cephamycins	KPC-2, IMI-1, SME-1
3a	3	B (B1)	Carbapenems	No	Yes	Broad-spectrum hydrolysis including carbapenems but not monobactams	IMP-1, VIM-1, CcrA, IND-1
		B (B3)					L1, CAU-1, GOB-1, FEZ-1
3b	3	B (B2)	Carbapenems	No	Yes	Preferential hydrolysis of carbapenems	CphA, Sfh-1
NI	4	Unknown					

[a] CA, clavulanic acid; TZB, tazobactam.
[b] NI, not included.

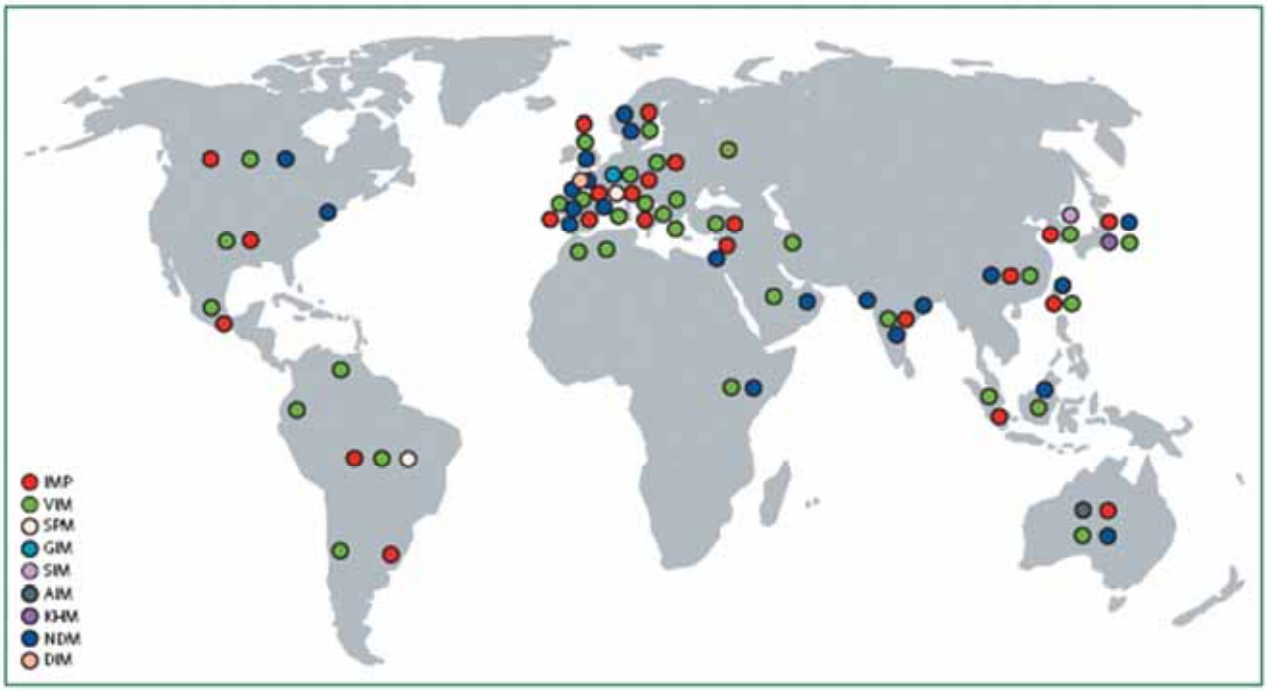

Figure 1: *Worldwide dissemination of different types of metallo-β-lactamases

***Reprinted from Cornaglia G, Giamarellou H, Rossolini GM. Metallo-β-lactamases: a last frontier for β-lactams?. Lancet Infect Dis. 2011 May; 11(5):381-93.**

Figure 2: Dissemination of different types of metallo-β-lactamases in Iran (26, 27).

The IMP-type enzymes (imipenemase), first discovered in Japan during the early 1980s, have since been reported worldwide in bacteria particularly, Enterobacteriaceae and in Gram-negative non-fermenters such as P.aeruginosa and Acinetobacter species (13). More than 33 different IMP allotypes have been described (Table 2).
The different IMP types often have a defined area in the globe, however, some of which (e.g. IMP-1, IMP-4, and IMP-7) were discovered in different areas which shows their potential for intercontinental dissemination (14).
The VIM-type β-lactamase (Verona integron-encoded metallo-β-lactamases) was first described in a multidrug-resistant P.aeruginosa strain in Italy during 1990s (28) and have since been reported worldwide (Figure 1). More than 33 different VIM allotypes are described (Table 3).

Table 2:*IMP-type ß-lactamases

Enzyme	Nucleotide	Reference
IMP-1	S71932	AAC 38:71-78, 1994
IMP-2	AJ243491	AAC 44:1229-1235, 2000
IMP-3	AB010417	AAC 44:2023-2027, 2000
IMP-4	AF244145	AAC 45:710-714, 2001
IMP-5	AF290912	FEMS Microbiol. Lett. 215: 33-39, 2002
IMP-6	AB040994	AAC 45:1343-1348, 2001
IMP-7	AF318077	AAC 46:255-258, 2002
IMP-8	AF322577	AAC 45: 2368-2371, 2001
IMP-9	AY033653	AAC 50:355-358, 2006
IMP-10	AB074433	AAC 46:2014-2016, 2002
IMP-11	AB074436	
IMP-12	AJ420864	AAC 47:1522-1528, 2003
IMP-13	AJ550807	JAC 52:583, 2003
IMP-14	AY553332	
IMP-15	AY553333	AAC 52:2289-2290, 2008
IMP-16	AJ584652	AAC 48:4693, 2004
IMP-17	Assigned	
IMP-18	AY780674	AAC 50:2272-2273, 2006
IMP-19	EF118171	AAC 51:4486-4488, 2007
IMP-20	AB196988	
IMP-21	AB204557	
IMP-22	DQ361087	JAC 63:901-908, 2009
IMP-23	Assigned	
IMP-24	EF192154	Int J Antimicrob Agents 32: 475-480, 2008
IMP-25	EU541448	
IMP-26	GU045307	J. Clin. Microbiol. 48:2563-4, 2010
IMP-27	JF894248	
IMP-28	Assigned	
IMP-29	HQ438058	
IMP-30	DQ522237	
IMP-31	Assigned	
IMP-32	Assigned	
IMP-33	JN848782	

Table 2: More than 33 different IMP allotypes have been described *(Reprinted from www.lahey.org/studies/).

Table3: *VIM-type β-lactamases

Enzyme	Nucleotide	Reference
VIM-1	Y18050	AAC 43: 1584, 1999
VIM-2	AF191564	AAC 44: 891, 2000
VIM-3	AF300454	AAC 45: 2224, 2001
VIM-4	AY135661	AAC 46: 4026, 2002
VIM-5	AY144612	JAC 54:282, 2004
VIM-6	AY165025	AAC 48:2334, 2004
VIM-7	AJ536835	AAC48:329, 2004
VIM-8	AY524987	JCM 42:5094-5101, 2004
VIM-9	AY524988	
VIM-10	AY524989	
VIM-11	AY605049	AAC 49:474-5, 2005.
VIM-12	DQ143913	AAC 49:5153-5156, 2005
VIM-13	DQ365886	AAC 52:3589-3596, 2008
VIM-14	AY635904	
VIM-15	EU419745	AAC 52:2977-2979, 2008
VIM-16	EU419746	AAC 52:2977-2979, 2008
VIM-17	EU118148	AAC 53:1325-1330, 2009
VIM-18	AM778091	AAC 53:1225-1227, 2009
VIM-19	FJ822963	AAC 54:471-476, 2010
VIM-20	Assigned	
VIM-21	Assigned	
VIM-22	Assigned	
VIM-23	GQ242167	
VIM-24	HM855205	AAC 55:2428-2430, 2011
VIM-25	HM750249	
VIM-26	FR748153	
VIM-27	HQ858608	AAC 55:3570-3572, 2011
VIM-28	JF900599	
VIM-29	Assigned	
VIM-30	JN129451	
VIM-31	Assigned	
VIM-32	Assigned	
VIM-33	Assigned	

Table 3: More than 33 different VIM allotypes have been described. * (Reprinted from www.lahey.org/studies/).

These enzymes are causes of resistance to antibiotics such as cephalosporins, penicillins and carbapenems. The others that acquired MBLs (SPM-1, SIM-1, GIM-1, AIM-1, and DIM-1) have a lower rate of spread (Figure 1) and a lower clinical impact than NDM-1(13). It is necessary to identify MBL gram negative bacteria for prompt infection control (29).

What is NDM-1?

Recently NDM-1 has been emerged as a global threat because bacteria which possess this enzyme are resistant to almost all β-lactam antibiotics (2, 9, 14, 22, 30, 31, 32, 33and 34) aminoglycosides, fluoroquinolones and other classes of antimicrobial agents (35), except aztreonam, tigecycline and colistin (9, 36-38). However, pathogens could be resistant to the last three antibiotics (22, 35-43) and also to fosfomycin (41, 44). In 2009, NDM-1 was first identified in a Swedish patient who had traveled to India and was hospitalized in New Delhi during December 2007. He acquired urinary tract infection (UTI) due to carbapenem resistant Klebsiella pneumonia (32, 39, 40, 42, 45). Apart from that, there are NDM enzymes in Enterobacteriaceae (2, 5, 20, 25, 30, 46-49), non-fermentative bacteria, Vibrionaceae (50), S.aureus, S.pneumonia (51, 52), Acinetobacter (22, 53, 54) and Pseudomonas (55). NDM-1 producers of Enterobacteriaceae cause wide range of infections such as UTI, septicemia, pulmonary infections, diarrhea, peritonitis, device-associated and soft-tissue infections (38, 56). Structure of NDM-1 is similar to B1-MBL (22, 46). The bacteria with NDM-1 gene are known as superbugs and public health must pay more attention to them (43, 48). The centers for disease control and prevention (CDC) have guidelines to control isolates with NDM-1 (2). Most infections with NDM-1 producers have been reported in adults, but blaNDM-1 in two isolates of K. pneumonia was reported from a neonatal intensive care unit (NICU) in India as well (10). In 2010, blaNDM-1 and blaNDM-2 genes were found in A.baumannii (22, 53), and in 2011 blaNDM-5 was found in E. coli (57). More than six different NDM allotypes are known (Table 4).

Table 4:*NDM-type β-lactamases

Enzyme	Nucleotide	Reference
NDM-1	FN396876	AAC 53:5046-5054, 2009
NDM-2	JF703135	JAC 66:1260-1262, 2011
NDM-3	Assigned	
NDM-4	Assigned	
NDM-5	JN104597	
NDM-6	JN967644	

Table 4: More than 6 different NDM allotypes are known.
* (Reprinted from www.lahey.org/studies/).

NDM-1 gene is carried on plasmid or chromosome (48). The rapid emergence of NDM-1 has been related to movable plasmids, which can move among different strains, that can subsequently spread throughout the world (2, 58, 59).

Plasmids with NDM-1 gene can be transmitted to other bacteria, even to the human gram negative intestinal flora. There are about 10 - 100 trillion bacteria as human normal flora that can cause many problems in human. It has been estimated that 100 million Indians carry NDM-1 positive bacteria as normal gut flora. (60). Mobile plasmids with NDM-1 gene are Incl/M, FII, A/C and two no-typed plasmids (2, 22, 46, 49, 58, 61). These plasmids can move to other bacterial strains and spread drug resistance in the world (1, 22, 36, 58, 59). The complete sequence of the plasmid PNDM-1-Dok01 with NDM-1 gene was determined in 2011 (62). The bla-alpha (NDM-1) gene encodes a 27.5 KDa protein which consisted of 289 amino acids (37). The blaNDM-1 gene is carried on different plasmids and can harbor a large number of resistance genes including carbapenemase genes (OXA 4-8, OXA 181, VIM), plasmid- associated cephalosporinase genes (CMY-16, CMY-58), ESBL genes (CTX-M-15,SHV-12), Aminoglycoside resistance genes (16s rRNA methylase), Class A genes (KPC), Macrolide resistance genes (esterase), rifampin resistance gene, qnr genes (qnrAB, qnr B1, qnr B2) and sulfamethoxazole resistance genes. The above-mentioned plasmids (with blaNDM-1) do as multidrug resistance pools and cause pan-drug resistance (14, 41, 44, 45, 47, 60, 63, 66) and therefore, the NDM-1 name must be changed to Plasmid- encoding carbapenem- resistant metallo-β-lactamase (PCM) (67). These plasmids can be transferred from bacteria to bacteria, from man to man and even country to country. Patients with carbapenem-mediated plasmid producer bacteria have travelled to Pakistan, India and have been hospitalized in these countries. It is seemed that these bacteria were sourced from an Asian local source (32). An article in Lancet infectious disease Journal (2010) showed NDM-1 cases had been isolated from India, Pakistan and the UK by molecular, epidemiological and biological studies (42). About 70 cases have been identified in the UK, 150 in India and Pakistan, 4 in Australia, 20 in Austria, 2 in Belgium, 4 in Canada, 3 in China, 1 in Germany, 1 in Hong Kong, 1 in Singapore, 1 in Sweden and additional 1, 3, 2,7 and 1 case(s) in Taiwan, America, France, Kenya and Italy, respectively (38). Also, NDM-1 has been identified in Oman (38, 45), Japan (33), the Netherlands (68) and Norway (45). Recently, CDC suggested NDM-1 as a transmissible agent especially in patients who have been hospitalized in India and Pakistan (32, 42). A screening system is needed to prevent dissemination of NDM-1 by passengers from India and Pakistan (42). Poor hygiene and sanitation, unhealthy water and selling antibiotics without prescription lead to dissemination of NDM-1 (38) as there are NDM-1 bacteria detected in acquired infections from hospitals and community (44, 46).

How can NDM-1 producer bacteria be identified?

Some pathogens with NDM-1 and Klebsiella pneumoniae carbapenemase (KPC) may not be recognized by common laboratory tests; consequently, unaffected antibiotics are prescribed in wrong ways that causes to emerge and spread more resistant bacteria (60, 69). Figure 3 shows pattern of drug resistance in K.pneumonia with NDM-1 enzyme (44).

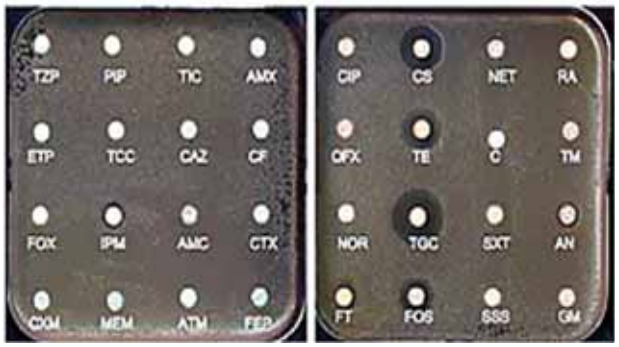

Figure3. *Disk diffusion antibacterial drug susceptibility testing of (Klebsiella pneumoniae) New Delhi metallo-β-lactamase-1 (NDM-1), producing K.pneumoniae clinical isolates. TZP, piperacillin/tazobactam; PIP, piperacillin; TIC, ticarcillin; AMX, amoxicillin; ETP, ertapenem; TCC, ticarcillin/clavulanic acid; CAZ, ceftazidime; CF, cefalotin; FOX, cefoxitin; IMP,imipenem; AMC, amoxicillin/clavulanic acid; CTX, cefotaxime; CXM,cefuroxime; MEM, meropenem; ATM, aztreonam; FEP, cefepime;CIP, ciprofloxacin; CS, colistin; NET, netilmicin; RA, rifampin; OFX,ofloxacin; TE, tetracycline; C, chloramphenicol; TM, tobramycin;NOR, norfloxacin; TGC, tigecycline; SXT, sulfamethoxazole/trimethoprim; AN, amikacin; FT, nitrofurantoin; FOS, fosfomycin;SSS, sulfamethoxazole; GM gentamicin.
*Reprinted from Nordmann P, Naas T, Poirel L. Global spread of Carbapenemase-producing Enterobacteriaceae. Emerg Infect Dis. 2011 Oct; 17(10):1791-8.

Table 5 shows carbapenem MICs for Enterobacteriaceae with MBL (44). NDM-1 producers are resistant to ACHN-40 (a generation of Aminoglycosides) with MIC≥64 µg/ml (19). E-test strips are recommended to identify MBL producer bacteria based on inhibition of MBLs by EDTA.

Table 5. MIC range of Metallo-β-lactamase for Enterobacteriaceae

	MIC, mg/L		
Carbapenemase	Imipenem	Meropenem	Ertapenem
Metallo β-lactamases†	0.5→64	0.25→64	0.5→64

†including New Delhi metallo-β-lactamase-1.

These strips have two parts: imipenem and imipenem-EDTA. The E-test MBL is reliable for detection of resistance, except in Enterobacter cloacae and K.pneumonia (19, 36, 64, 65) that can be substitutes by two imipenem disks (10µg); one disk is placed 25 mm apart the other disk on Muller-Hinton agar. If imipenem-EDTA disk inhibition zone is more than 4 mm and inhibition zone of imipenem disk is not seen, strain is considered as MBL positive (such as NDM-1). The Hodge-test has low specificity, therefore, is not recommended for identification of MBL (36). The modified Hodge-test has been confirmed to detect carbapenemases (47, 70). Except class D of carbapenemases, meropenem-associated inhibitor is very specific and sensitive to detect carbapenemases (71). The Microarray is a very precise method to detect multi-drug β-lactamase positive Enterobacteriaceae (18).

In addition, Real-Time PCR is a useful technique too. Advantages of this method are: its high specificity and sensitivity, rapid detection of NDM-1 producers in less than 2 hours (25, 32, 34, 49), ability to detect KPC, OXA, VIM and IMP (4, 34, 72). The other technique, loop-mediated isothermal amplification (LAMP) was used to detect NDM-1 producers in 2011 (51). To screen carbapenemases such as NDM and KPC, Rapid Multiplex PCR (less than 4 hours) is reliable (54). Pulsed-Field Gel Electrophoresis (PFGE) and Multi-Locus Sequence Typing (MLST) are two techniques to determine the identity and genotype of β-lactamase-related plasmid genes like NDM (9, 19, 20, 22, 39-41, 47). Against other carbapenemase genes, the blaNDM-1 is associated with nonclonally related isolates and species. Its extent is more in E.coli and K.pneumoniae and lesser in other enterobacterial species (44).

As remarkable results, importance of these enzymes such as NDM-1 and KPC are comparable with HIV, tuberculosis and malaria (43). To date, there is no vaccine to prevent infections which are produced by bacteria which have carbapenemases (44). So, it is necessary to inspect phenotyping and genotyping NDM-1 resistant pattern worldwide.

Acknowledgments
This review is presented to researchers who work on drug-resistant bacteria.

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