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Global genotype distribution of human clinical isolates of New Delhi metallo-β-lactamase-producing *Klebsiella pneumoniae*; A systematic review

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ABSTRACT

Background and Aim: The global rise of antimicrobial resistance among bacterial strains is a rapidly growing challenge and is becoming a major public health concern. This study documents the worldwide spread and genotype distribution of human clinical isolates of New Delhi metallo-β-lactamase-producing *Klebsiella pneumoniae* (NPKP).

Methods: Several international databases, including Web of Science, Embase and Medline were searched (2010 - 2019) to identify studies addressing the frequency of NPKP regionally or worldwide.

Results: Of 4779 articles identified, 202 studies fulfilled the eligibility criteria and were included in our analysis. The frequency of NPKP in Asia, Europe, America, Africa and Oceania was 64.6%, 20.1%, 9.0%, 5.6% and 0.4%, respectively. The most prevalent sequence types (STs) among NPKP were ST11, ST290, ST147, ST340, ST15, ST278 and ST14 based on published studies.

Conclusion: The dissemination of bla_{NDM} variants in different STs among NPKP in the various region of world is a serious concern to public health. The prevalence of NPKP should be controlled by comprehensive infection control measures and optimization of antibiotic therapy.

Contents

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1. Introduction

The rise of antibiotic-resistant bacteria is a serious threat to global health [1]. This resistance causes difficulties in proper antibiotic treatment of patients suffering from a variety of infections. Carbapenems are a group of beta-lactam antibiotics used to treat infections caused by extended-spectrum beta-lactamase (ESBL)-producing bacteria [2,3]. According to many reports, resistance to these antibiotics in gram-negative bacteria has become epidemic or even pandemic, and is still growing in magnitude. There are many countries that reported the presence of carbapenem resistant gram-negative bacteria in a variety of clinical settings. India [4], China [5], Pakistan [6], Greece [7], Turkey [8], Peru [9], Mexico [10] and Brazil [11] are among these countries.

Hydrolysis of carbapenems by carbapenemase enzymes is the main mechanisms of resistance [12–14]. There are four groups (i.e., A, B, C, D) of beta-lactamase enzymes according to the Ambler classification system [13,15]. Carbapenemases are present in classes A, B, and D. Carbapenemase-producing bacterial species such as members of the order of Enterobacterales are the most important causes of carbapenem resistant infection worldwide [17]. In 2017, the World Health Organization (WHO) announced a list of international priority pathogens, including antibiotic resistant Enterobacterales [18] including *Escherichia coli (E. coli)* and *Klebsiella pneumoniae* (*K. pneumoniae*) [19–21]. *K. pneumoniae* is a gram-negative opportunistic pathogen that causes many different diseases including nosocomial infections involving urinary tract infections, bacteremia, pneumonia, liver abscess and others [22,23]. Beta-lactam antibiotics such as carbapenems and aminoglycosides are used to control and treat infections caused by this pathogen [24]. However, a significant proportion of *K. pneumoniae* strains from clinical origin have become resistant to these antibiotics by acquiring resistance genes such as the New Delhi metallo-beta-lactamase (NDM) gene (bla_{NDM}) [25]. Currently, 24 NDM variants have been characterized from more than 60 species of 11 bacterial families [26]. Members of the NDM family are among the most common carbapenemases which are usually transmitted through horizontal transfer of plasmids [25,27]. Based on available data the highest frequency of NDM-producing bacteria are reported across the following continents and countries : China and India (Asia) [28,29], Brazil (America) and Algeria (Africa), Bulgaria, Italy, Turkey, Germany, Greece, Romania, Poland, France, Serbia, the UK and Ukraine (Europe) [30,31]. Moreover, numerous studies have shown that different variants of bla_{NDM} including bla_{NDM-1}, bla_{NDM-5} and bla_{NDM-7} are distributed in different sequences types (ST) [32,33]. Multi-locus Sequence Typing (MLST) is a method based on nucleotide sequencing that describes the genetic relationships between bacterial isolates. For this method, usually 5–7 well-conserved, house-keeping genes or loci within the bacterial genome are sequenced and based on its results, allelic variants in conserved genes of bacterial species are identified [34]. By this method, different STs have been reported for various isolates of NDM-producing *K. pneumoniae* (NPKP) worldwide. It is important to be able to identify the most common STs to improved infection control programs on a global scale. The purpose of this study was to evaluate the worldwide spread and genotype distribution of human clinical isolates of NPKP based on published studies..

2. Methods

2.1. Search strategy and selection criteria

In the present study, we reviewed original research articles published in public databases from 2010 to 2019. These databases include Medline (via PubMed), Embase, and Web of Science. '*Klebsiella pneumoniae*' or '*K. pneumoniae* and 'New Delhi metallo-β-lactamase' or 'NDM' or 'bla_{NDM}' were the terms used in our search strategy. Searches were limited to original articles on the epidemiology of bla_{NDM} variants in strains isolated from human specimens. These studies were carried out in different parts of the world. Additionally, we searched the bibliographies of the relevant publications selected to identify further studies in this field.

2.2. Inclusion and exclusion criteria

Only studies on human clinical samples with complete information on the frequency of NPKP were evaluated. These data included the frequency of bla_{NDM}, country of origin and assessment methods used. The information in each study was evaluated on the basis of titles and abstracts first, and at the full text level when the study seemed pertinent to our analysis. Studies that qualified for inclusion are [1] original articles with sufficient information on the frequency of NPKP isolated from humans; [2] studies that used molecular techniques to detect bla_{NDM} and presented data regarding the number of patients enrolled. Exclusion criteria include: [1] studies on non-human cases [2], investigations on NDM-producing bacteria other than *K. pneumoniae*, [3] articles that examined other types of carbapenemases [4], meta-analyses, systematic reviews and review articles [5], abstracts presented in conferences, and [6] duplicate publications of the same

Table 1
Prevalence of New Delhi metallo-β-lactamase (NDM)-producing *Klebsiella pneumoniae* isolated from clinical samples in different continents.

Continent	NDM type [n (%)]	Total N[a]
Asia	NDM-1(1370, 87), NDM-4(15, 0.9), NDM-5(163, 10.3),NDM-6(13, 0.8), NDM-7(8, 0.5), NDM-9(2, 0.1), NDM-10(1, 0.06), NDM-19(1, 0.06)	1573
Europe	NDM-1(489, 99), NDM-5(2, 0.4)	491
America	NDM-1(216, 97.7), NDM-5(2, 0.9), NDM-7(3, 1.3)	221
Africa	NDM-1(127, 92.7), NDM-2(1, 0.7), NDM-5(6, 4.3), NDM-7(3, 2.2)	137
Oceania	NDM-1(10, 100)	10
All continents	NDM-1(2212, 90.9), NDM-2(1,0.04), NDM-4(15, 0.6), NDM-5(173, 71), NDM-6(13, 0.5), NDM-7(14, 0.5), NDM-9(2, 0.08), NDM-10(1, 0.04), NDM-19(1, 0.04)	2432

investigation. Two authors separately reviewed inclusion and exclusion criteria and selected the most appropriate articles.

2.3. Data extraction and definitions

The following items were extracted from each of the studies that met the inclusion criteria: the first author's last name, time of study, year of publication, country, numbers of *K. pneumoniae* and NPKP isolates; type of bla_{NDM} variants in *K. pneumoniae* isolates; ST of isolates; source of samples and bla_{NDM} detection techniques (publications using genotypic identification methods). In order to render data extraction highly accurate, this was done by two independent individuals and confirmed by a third researcher. In order to reach a comprehensive view and solve discrepancies, the reviewers participated in a final joint discussion (Table1).

3. Results

3.1. Characteristics of included studies

After an initial review of electronic resources and databases, a total of 5586 articles were collected. Of these, 807 were duplicate articles occurring in multiple databases and were deleted. Eventually 4779 unique articles remained. Based on the evaluation of titles and abstracts, 4503 articles were excluded. Of 276 remained articles, 74 were excluded after full text reading. The reasons for this removal are given in Fig. 1. Finally, there were 202 articles that met the inclusion criteria of this study and were selected for final observational and statistical analyses. Of these 202 studies, 110 reports involved the Asian continent, 55 were European, 19 American, 16 African, and the 2 fin. l studies covered Oceania. In several studies, NPKP frequency has been reported in multiple countries. In the supplementary file (Table S1), the main features of the 202 selected articles are summarized. Based on the information in this table, most of the articles reviewed in this study were from China (39 articles) and India (21 articles), respectively. We found that no studies on NPKP were published before 2010. Most of the researches included in current analysis were published between 2016 and 2019 (more than 50%). Based on published studies, the frequency of NPKP in different continents, including bla_{NDM-1}, bla_{NDM-2}, bla_{NDM-4}, bla_{NDM-5}, bla_{NDM-6}, bla_{NDM-7}, bla_{NDM-9}, bla_{NDM-10}, and bla_{NDM-19} variants are illustrated in Table 2 and Fig. 2.

As shown in Fig. 3, the 4 most common variants of bla_{NDM} in *K. pneumoniae* strains isolated from human samples were bla_{NDM-1}, bla_{NDM-5}, bla_{NDM-4} and bla_{NDM-7}. Two studies reported bla_{NDM-9}. bla_{NDM-2}, bla_{NDM-10} and bla_{NDM-19} were each reported in one study. There were no studies on the frequency of bla_{NDM-3}, bla_{NDM-8} and bla_{NDM-11} to bla_{NDM-18} among the evaluated studies, suggesting that these gene variants were rarely reported and may represent occasional mutants. Table 3 shows the distribution of STs of clinical NPKP in different parts of the world. The most common samples which were assessed in the included studies were blood with 25 studies, rectal swabs [24], urines [13], sputa [8], stools [2], perianal swabs [1] and gastric fluids [1] (Table S1). Typing of NPKP strains in most of eligible studies was performed by PCR and sequencing as well as MLST and pulsed-field gel electrophoresis (PFGE) (Table S1).

3.2. bla$_{NDM}$ variants among K. pneumoniae strains isolated from human clinical samples from different continents based on published studies

The frequency of NPKP in different continents is shown in Table S1. Tables 4,5 and S2 and Fig. 4 show the distribution of the number of reported NPKP isolates across continents. Except for bla_{NDM-2}, all bla_{NDM} variants we have mentioned have been reported in Asia. The highest frequency of NPKP among Asian countries was encountered in China (44.1%; 695/1573), India (15.2%; 239/1573), Saudi Arabia (9.6%; 152/1573) and Iran (7.8%; 123/1573%). The results of studies published in Asian countries show that the highest frequency among the bla_{NDM} variants in this

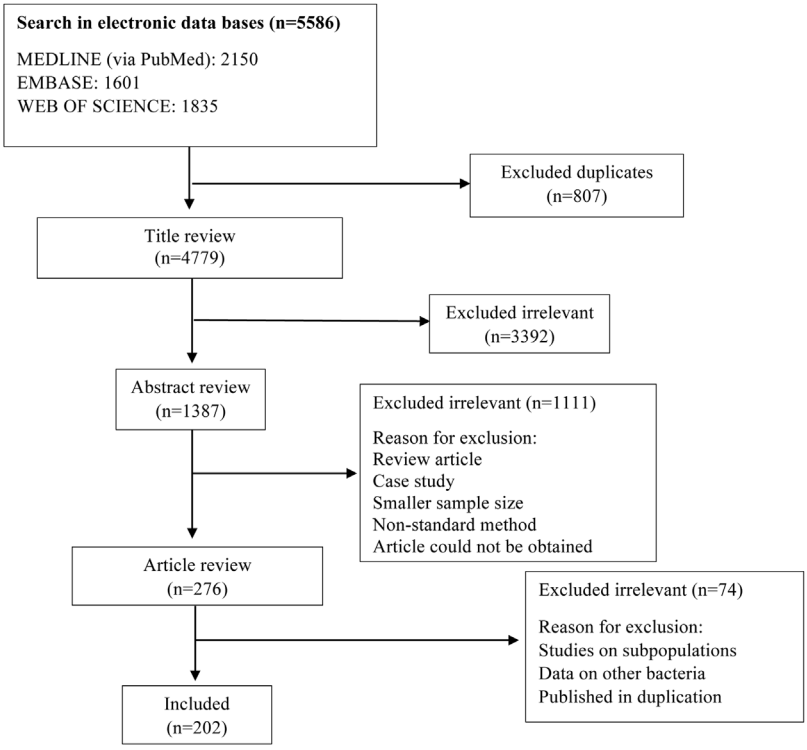

Fig. 1. Flow chart of study selection for inclusion in the systematic review.

Table 2
Distribution of sequence types (STs) among various New Delhi metallo-β-lactamase (NDM) variants in different continents.

Continent	NDM-1 (N) NDM-5 (N) NDM-7 (N)
Asia	ST1 (2), ST5 (1), ST6 (1), ST11 (27) ST1 (1) ST147 (1) ST76 (1) ST13 (2), ST14 (10), ST15 (20) ST258 (1) ST17 (14), ST20 (23), ST25 (6) ST307 (1) ST29 (1), ST36 (1), ST37 (15) ST340 (1) ST38 (1), ST45 (1), ST48 (1) ST290 (67) ST54 (1), ST76 (12), ST86 (1) ST101 (2), ST105 (1), ST147 (14) ST152 (12), ST188 (1), ST199 (1) ST218 (1), ST231 (1), ST234 (2) ST237 (1), ST273 (6), ST278 (23) ST290 (2), ST307 (4), ST334 (2) ST340 (7), ST348 (1), ST367 (1) ST392 (2), ST395 (1), ST397 (1) ST372 (1), ST412 (1), ST414 (3) ST433 (1), ST437 (2), ST483 (1) ST551 (1), ST500 (1), ST700 (1) ST826 (1), ST846(1), ST888(1) ST1035 (1), ST1045 (1), ST1198 (1) ST1318 (3), ST1383 (1), ST1412 (4) ST1473 (1), ST1476 (1), ST1641 (1) ST1636 (1), ST1699 (1), ST1764 (7) ST2735 (9), ST2736 (2)
Europe	ST11 (161), ST14 (7), ST15 (6) ST16 (3), ST45 (1), ST147 (2) ST258 (2), ST301 (1), ST307 (1) ST340 (21)
America	ST22 (3), ST37 (1), ST76 (1) ST278 (2) ST147 (2), ST340 (1) ST1067 (1), ST1773 (1) ST1588 (1), ST3371 (1) ST3372 (1)
Africa	ST11 (2), ST15 (1) ST273 (2) ST101 (14), ST147 (42) ST307 (1) ST307 (3), ST323 (1) ST414 (2) ST2016 (1), ST2017 (3) ST1031 (1) ST3485 (1), ST3486 (1) ST3487 (1), ST3488 (1) ST3490 (1), ST3491 (1)
Oceania	ST11 (1), ST14 (3), ST15 (2) ST256(2), ST340 (2)

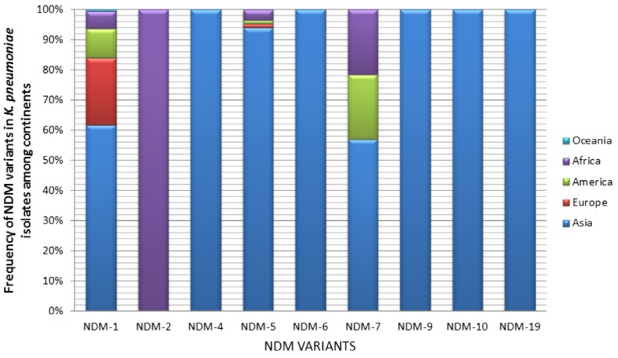

Fig. 2. Frequency of NDM-producing *K. pneumoniae* in different continents based on published studies.

continent are observed for bla_{NDM-1}, bla_{NDM-5}, bla_{NDM-4}, and bla_{NDM-7} at 90.1 % (2212/2432), 7.1% (173/2432), 0.6% (15/2432) and 0.5% (14/2432), respectively. Studies show the presence and frequency of bla_{NDM-1} in all countries of Asia that are mentioned in Table 4. bla_{NDM-19} is reported only in China and bla_{NDM-10} only in India (Table 3). As shown in Table 5, the common variants in Europe are bla_{NDM-1} and bla_{NDM-5}. The most reported bla_{NDM} variants in European countries were in Turkey (18.9%; 93/491), Greece (15.8%; 78/491), Bulgaria (13.2%; 65/491), Estonia (10.3%; 51/491) and the Russia (6.9%; 34/491) (Table 4). According to Table S2, bla_{NDM-1},

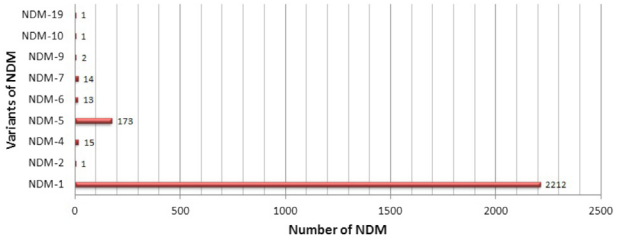

Fig. 3. The number of NDM variants in *K. pneumoniae* strains isolated from human clinical samples around the world based on published studies.

bla_{NDM-5} and bla_{NDM-7} are the most common variants on the American continent. bla_{NDM-1} has been observed in the United States of America (USA) (70.1%; 155/221), Mexico (21.7%; 48/221), Canada (3.1%; 7/221), Brazil (2.2%; 5/221) and Chile (0.4; 1/221). As shown in the Table S2, bla_{NDM-5} (0.9%; 2/221) is only detected in the United States and also, bla_{NDM-7} is only reported in two countries (USA and Canada) of the American continent. Studies from the African continent show that bla_{NDM-1} has been reported in all countries except for Gabon, related data are mentioned in Table S2. As mentioned in this Table, bla_{NDM-2}, bla_{NDM-5} and bla_{NDM-7} have been observed only in Egypt (0.7%; 1/137), Angola (4.3%; 6/137) and Gabon (2.1%; 3/137), respectively. In Oceania, bla_{NDM-1} was reported in both Australia (90.0%; 9/10) and New Zealand (10.0%; 1/10) (Table S2). Fig. 5 shows the serial trend in NPKP emergence. As shown in this figure, the frequency of NPKP has been increasing from 2009 to 2012, though in 2013 there was a downward trend. The frequency of NPKP was highest in 2014-2016. This abundance has been declining since 2017 until now.

3.3. Most prevalent sequence types among NPKP strains found on different continents based on published studies

The studies show that for NPKP isolated from clinical specimens in different countries, 86 unique STs have been reported (Table S3). The number of STs reported in Asia, Europe, the Americas, Africa, and Oceania were 43, 10, 11, 17, and 5, respectively. Obviously, these figures do depend on the number of strains analyzed. ST11 (191 isolates), ST290 (69 isolates), ST147 (61 isolates), ST340 (32 isolates), ST15 (29 isolates), ST278 (25 isolates), ST14 (20 isolates) were the most commonly reported STs among NPKP (Table S3). STs11 and ST15, ST147 and ST340 have been reported on all continents except America, Oceania and Africa, respectively. Still these can be considered globally occurring clones. ST290 was reported only in Asia. ST278 was detected in Asia and America. ST14 has been reported in studies on the continents of Asia, Europe and Oceania. The frequency of STs reported in different countries is illustrated in Table S3. Various studies have shown different results regarding the diversification of STs. Accordingly, China showed the most diverse range of STs with 48 types. ST11, ST147, ST15, ST340 and STs14 and 307 have been observed in the highest number of countries. Also, 69 of the 86 (80.2%) STs were only reported in one country. Figs. 6 and 7 illustrate the frequency of different STs detected among NPKP isolated from clinical samples from different continents and countries. Fig. 8 presents the frequency of STs carrying variants of bla_{NDM} in *K. pneumonia* isolates around the world. Also, the most common STs in each country are shown in Fig. 9.

4. Discussion

To the best of our knowledge, this is the first report on the global frequency of NPKP from human clinical samples. We also detail the occurrence of NPKP STs in different geographical locations.

Table 3
Distribution of New Delhi metallo-β-lactamase (NDM)-producing *Klebsiella pneumoniae* isolated from clinical samples in different countries of Asia.

Country	NDM type [n (%)]	Total N[a]
China	NDM-1(524, 75.3), NDM-5(157, 22.5), NDM-6(10, 1.4), NDM-7(2, 0.2), NDM-9(1, 0.1), NDM-19(1, 0.1)	695
India	NDM-1(222, 92.8), NDM-4(12, 5.0), NDM-5(4, 1.6), NDM-10(1, 0.4)	239
Saudi Arabia	NDM-1(152, 100)	152
Iran	NDM-1(115, 93.4), NDM-6(3, 2.4), NDM-7(5, 4)	123
Singapore	NDM-1(65, 98.4), NDM-7(1, 1.5)	66
Korea	NDM-1(63, 100)	63
Thailand	NDM-1(58, 93.5), NDM-4(2, 3.2), NDM-5(1, 1.6), NDM-9(1, 1.6)	62
Pakistan	NDM-1(33, 100)	33
Malaysia	NDM-1(25, 100)	25
Japan	NDM-1(20, 100)	20
Israel	NDM-1(19, 100)	19
Yemen	NDM-1(16, 100)	16
Kuwait	NDM-1(14, 100)	14
Myanmar	NDM-1(9, 90), NDM-4(1, 10)	10
Oman	NDM-1(7, 100)	7
Taiwan	NDM-1(7, 100)	7
Bangladesh	NDM-1(9, 100)	9
Arab Emirates	NDM-1(8, 88.8), NDM-5(1, 11.1)	9
Iraq	NDM-1(3, 100)	3
Phlippines	NDM-1(1, 100)	1
Total	NDM-1(1370, 87), NDM-4(15, 0.9), NDM-5(163, 10,3), NDM-6(13, 0.8), NDM-7(8, 0.5), NDM-9(2, 0.1), NDM-10(1, 0.06), NDM-19(1, 0.06)	1573

Table 4
Distribution of New Delhi metallo-β-lactamase (NDM)-producing *Klebsiella pneumoniae* isolated from clinical samples in different countries of Europe.

Country	NDM type [n (%)]	Total N[a]
Turkey	NDM-1(93, 100)	93
Greece	NDM-1(78, 100)	78
Bulgaria	NDM-1(65, 100)	65
Estonia	NDM-1(51, 100)	51
Russia	NDM-1(34, 100)	34
UK	NDM-1(26, 100)	26
France	NDM-1(22, 95.6), NDM-5(1, 4.4)	23
Italy	NDM-1(22, 100)	22
Poland	NDM-1(22, 100)	22
Sweden	NDM-1(21, 100)	21
Germany	NDM-1(20, 100)	20
Norway	NDM-1(11, 100)	11
Ireland	NDM-1(9, 100)	9
Croatia	NDM-1(9, 100)	9
England	NDM-1(2, 100)	2
Spain	NDM-1(1, 50), NDM-5(1, 50)	2
Netherland	NDM-1(1, 100)	1
Serbia	NDM-1(1, 100)	1
Finland	NDM-1(1, 100)	1
Total	NDM-1(489, 99), NDM-5(2, 0.4)	491

Investigations show that we are experiencing an increase in the frequency of bla_{NDM} among *K. pneumoniae* strains isolated from clinical samples since 2009 until now. This review evaluates 2432 NPKP strains from 53 countries between 2010 and 2019. The studies show that most of the NPKP are from the Asian continent with a focus on China, India, and Saudi Arabia with 44.1% and 15.2% prevalence for China and India. The frequency of bla_{NDM} among *K. pneumoniae* strains in Europe was found to be at 20.1%. In the Americas, the percentage of NPKP was 9.0%. This is 5.6% in Africa, with the highest frequency in South Africa. In Oceania, the frequency was 0.4%. The most common variants of bla_{NDM} are bla_{NDM-1}, bla_{NDM-5}, bla_{NDM-4} and bla_{NDM-7}. bla_{NDM-1} - the most common variant of bla_{NDM}- has been reported in all countries of 5 continents except Gabon (mentioned in Tables 4,5 and S2). Of the 4 common bla_{NDM} variants listed above, only bla_{NDM-1} has been reported in Oceania. The highest frequency of bla_{NDM-1} in Oceania has been observed in Australia. The results show that bla_{NDM-4}, bla_{NDM-6}, bla_{NDM-9}, bla_{NDM-10} and bla_{NDM-19} have been reported only in Asia. The results of current study were in accordance with findings obtained by Khan et al. in 2017 [35]. In their study, Asia serves as the main reservoir of NDM producers with about 58%

Table 5
Distribution of New Delhi metallo-β-lactamase (NDM)-producing *Klebsiella pneumoniae* isolated from clinical samples in different countries of America, Africa and Oceania.

Country	NDM type [n (%)]	Total N[a]
America		
USA	NDM-1(155, 98), NDM-5(2, 1.2), NDM-7(1, 0.6)	158
Mexico	NDM-1(48, 100)	48
Canada	NDM-1(7, 77), NDM-7(2, 22)	9
Brazil	NDM-1(5, 100)	5
Chile	NDM-1(1, 100)	1
Total	NDM-1(216, 97.7), NDM-5(2, 0.9), NDM-7 (3, 1.3)	221
Africa		
South Africa	NDM-1(39, 100)	39
Tunisia	NDM-1(27, 100)	27
Uganda	NDM-1(24, 100)	24
Egypt	NDM-1(21, 95), NDM-2(1, 4.5)	22
Angola	NDM-1(9, 60), NDM-5(6, 40)	15
Morocco	NDM-1(7, 100)	7
Gabon	NDM-7(3, 100)	3
Total	NDM-1(127, 92.7), NDM-2(1, 0.7), NDM-5(6, 4.3), NDM-7(3, 2.2)	137
Oceania		
Australia	NDM-1(9, 100)	9
Newzelland	NDM-1(1, 100)	1
Total	NDM-1(10, 80)	10

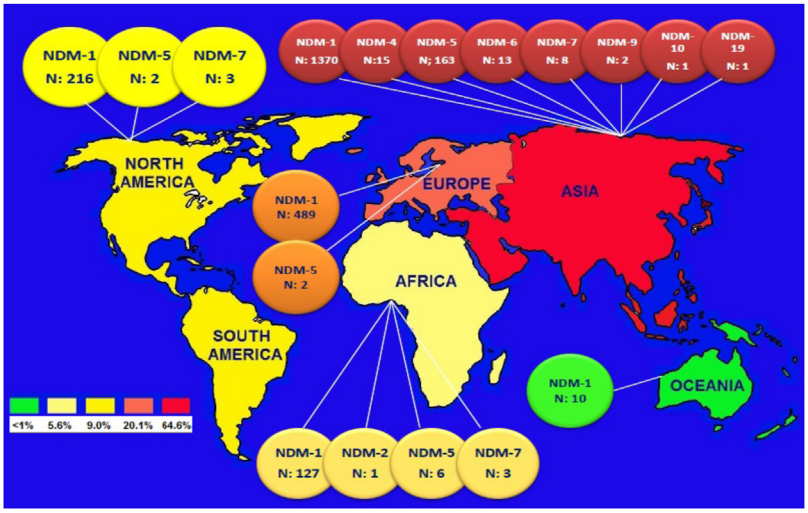

Fig. 4. Distribution of NDM variants reported in *K. penumoniae* strains isolated from human clinical samples among different continents based on published studies.

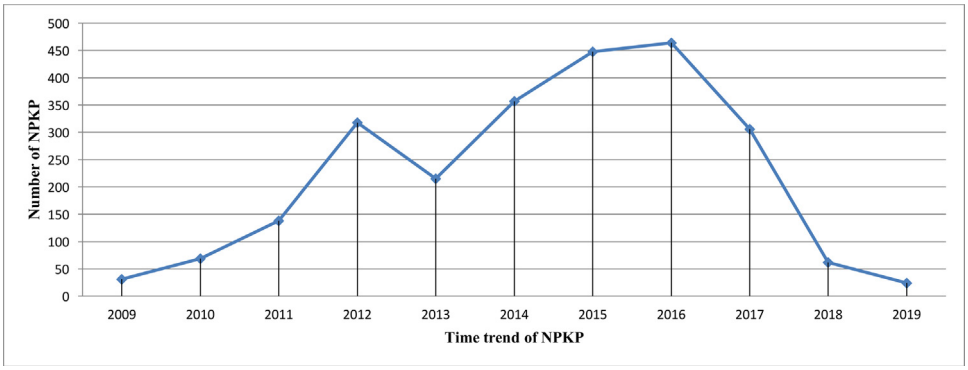

Fig. 5. Time trend of the frequency of the various NDM variants of the carrying strains from 2009-2019.

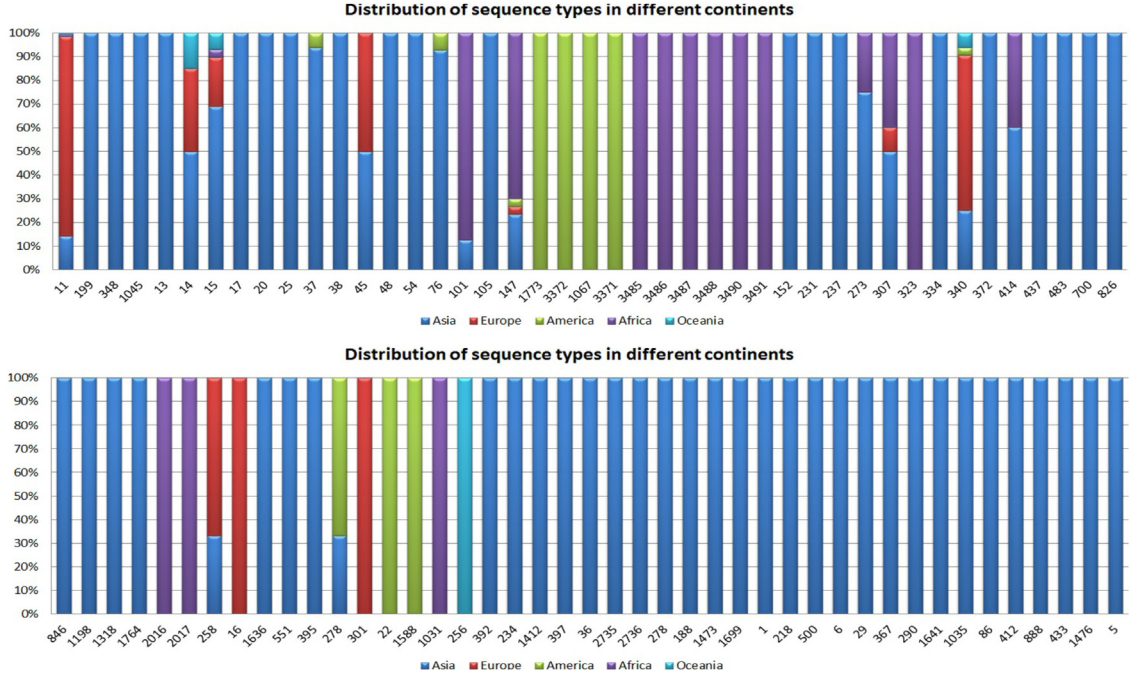

Fig. 6. Distribution of STs of NDM-producing *K. penumoniae* strains isolated from human clinical samples among different continents based on published studies.

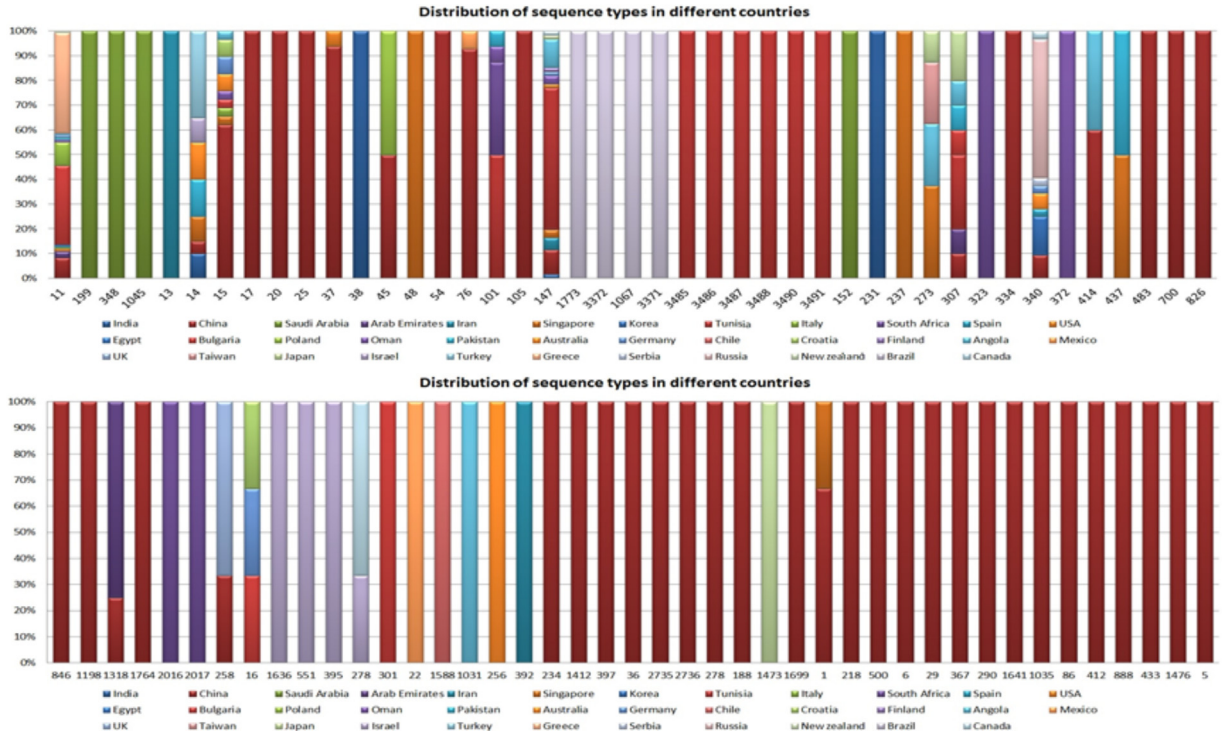

Fig. 7. Distribution of STs of NDM-producing *K. penumoniae* strains isolated from human clinical samples among different countries based on published studies.

abundance of $bla_{\text{NDM-1}}$ frequently in China and India. Also, the frequency of bla_{NDM} in Europe was around 16.8%, with the highest dissemination of the $bla_{\text{NDM-1}}$ variant in Romania, Bulgaria, Poland, Italy, France, Germany, Turkey, Serbia, Greece, London, Croatia, Ukraine, Ireland and Azerbaijan. In this continent NDM-4 was reported in Italy, while NDM-5 and NDM-7 were only reported in two countries (Denmark and France). Khan et al. showed that the frequency of $bla_{\text{NDM-1}}$ in America was around 10.8%. The highest volume of $bla_{\text{NDM-1}}$ was reported in Brazil (as the main reservoir) while Mexico city, Georgia, Colorado, Paraguay, California, Florida, Illinois, Jamaica, Pennsylvania, Argentina, Ecuador and Uruguay were considered as areas with the lowest frequency of $bla_{\text{NDM-1}}$. The frequency of $bla_{\text{NDM-1}}$ was 10.8% in Africa with a high distribution level in Algeria, whereas KwaZulu-Natal, Greater Johannesburg Area, Madagascar, Tunisia, Egypt and Libya showed lower frequencies of $bla_{\text{NDM-1}}$ producers. NDM-5 was identified in Algeria. We investigated the frequency of STs of NPKP in strains from human clinical specimens worldwide. NPKP are found among

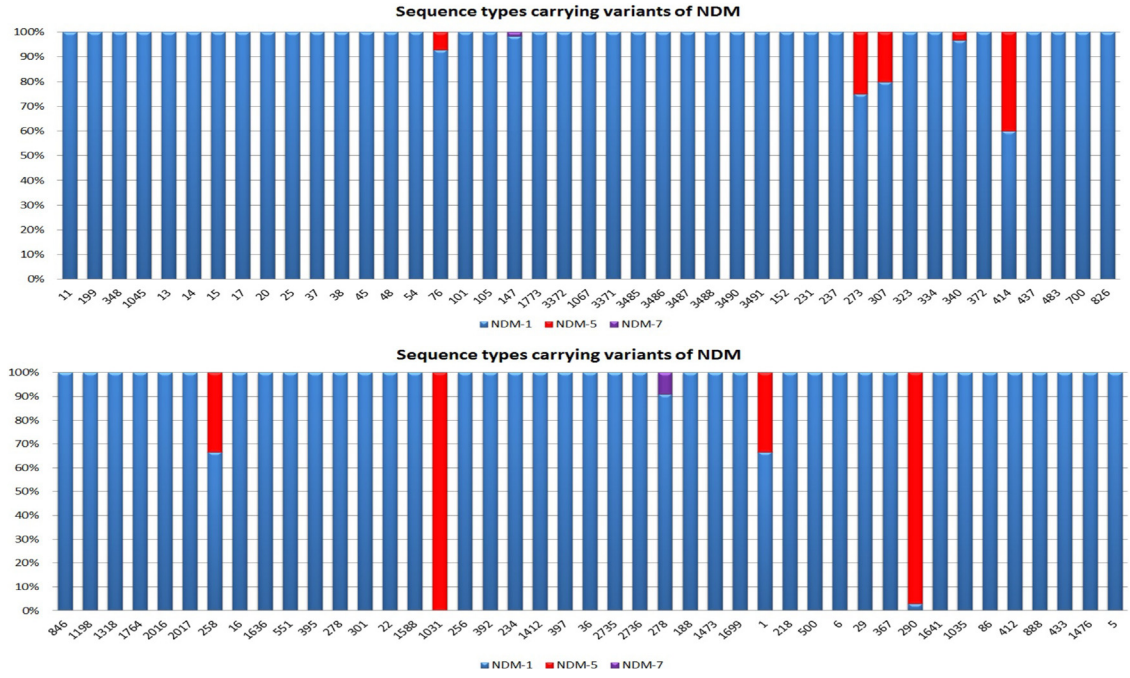

Fig. 8. Frequency of STs of NDM-producing *K. penumoniae* strains carrying variants of NDM around the world based on published studies.

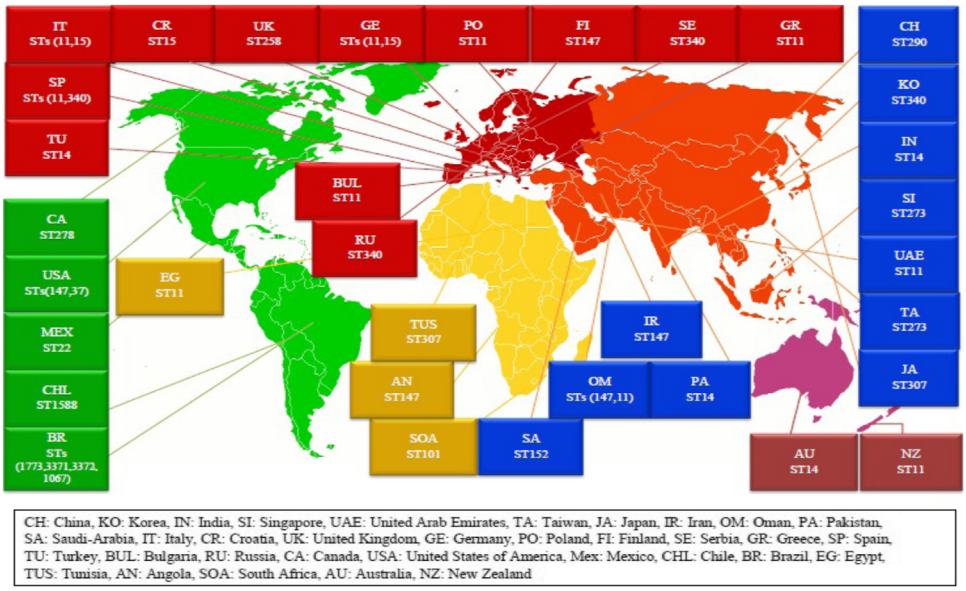

Fig. 9. The most prevalent of STs of NDM-producing *K. penumoniae* strains in different countries based on published studies.

different STs. According to the results of our study Asia, Europe, Africa, Oceania and America reported the highest number of STs respectively. Also, most of the reported STs were associated with bla_{NDM-1} and bla_{NDM-5}. Most of the STs reported in Asia, Europe, America, Africa and Oceania were ST290, ST11, ST22, ST147 and ST14, respectively. ST11 has also been reported as a common type in many studies [36–38]. It is important to note that ST11 is the dominant ST of carbapenem-resistant *K. pneumoniae* in China which is frequently related to bla_{KPC-2} rather than bla_{NDM} [39]. Our results also indicate that ST11 is the most common ST among NPKP from clinical samples. ST14 has been often reported as one of the most common type of NPKP in many studies [40,41]. In the current review, ST14 was reported in Asia (India, China, Singapore, Israel and Pakistan), Europe (Turkey) and Oceania (Australia). The carbapenem-resistant *K. pneumoniae* ST258, which has worldwide distribution, carries most of the bla_{KPC-2} or bla_{KPC-3} [42,43]. ST258 was found in China and the UK carrying bla_{NDM-5} and bla_{NDM-1} respectively. In general, STs 11, 290, 147, 340, 15 and 278 were among the most abundant types of STs among NPKP isolated from human clinical specimens worldwide. Almost 80% of all types of STs were found just in one country. It is noteworthy that not all articles that met the inclusion criteria listed STs in NPKP isolated from human clinical specimens so the frequency of STs between continents and different countries may vary. In addition, migration or other forms of travelling between regions may be an important cause in the spread of certain STs. We show that the most frequent bla_{NDM} genes associated with the reported STs were bla_{NDM-1}, bla_{NDM-5} and bla_{NDM-7} on all continents. Also, bla_{NDM-1} is the only bla_{NDM} variant which associated with all the common STs mentioned above. NPKP strains are spreading around the world [44]. Despite numerous efforts, this remains a major challenge to the international community and a threat to public health. There is currently no consensus treatment for NDM-positive infections in the clinic. Still many agents are being evaluated with different mechanisms of action. According to different reports, polymyxins have recently been used as primary drugs in the treatment of infections caused by bla_{NDM}-positive strains [45]. However, there are limitations to the use of polymyxins, including toxicities, the absence of optimal dosage schemes, and the presence of heterogeneous resistance [46]. Aztreonam-avibactam is a promising alternative option [47,48]. Effective infection control along with the development of antimicrobial agents is important for success in the fight against NDM. Therefore, increasing awareness of infection control and adherence to infection control protocols in health care is essential. Among the factors that significantly increase the strains of NPKP strains are: overuse of antibiotics, failure to implement preventive health measures, inadequate staff training and lack of hospital infection control programs. There are limitations to our study. First, since there is insufficient information from many countries, we have not been able to assess the frequency of NPKP on a truly global scale. Second, as some countries do not systematically monitor for the occurrence of resistant bacteria such as *K. pneumoniae*, the number of reported NPKP isolated from clinical specimens may not be fully accurate. Further, failure to comply with the guidelines on the isolation and identification of bacteria resistant to antimicrobial agents can lead to wrong results. Finally, despite the importance of the impact of NDM on mortality, studies on this issue are rare and the necessity of such investigates is clear.

5. Conclusion

It can be concluded that due to the relatively high frequency of NPKP strains, especially the most common clonal groups, the attention of various groups involved in clinical care is important. Many infection control measures against carbapenem-resistant Gram-negative bacteria may be based on relatively poor quality studies (e.g. using inappropriate diagnostic methods or low sample size) and designing more appropriate studies are needed to define more effective preventative and therapeutic actions. Finally, although many guidelines agree that resistance to carbapenemases should be considered as a general principle in terms of infection control, bla_{NDM} and bla_{KPC}-positive strains have significant differences (in terms of virulence or resistance to multi drugs). Finally, it is imperative that the international health community must cooperate to overcome this threat to public health.

Author Contributions

Designed the study; MD. Performed the search strategy; BH and MG, Extracted the data; MS, NBS, SY, AH and DDS, Analyzed the data; MD, Wrote the manuscript; MD and AVB, Revised the manuscript; MD.

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Ethical Approval

Not required

Competing Interests

None

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jgar.2020.10.016.

References

[1] Roca I, Akova M, Baquero F, Carlet J, Cavaleri M, Coenen S, et al. The global threat of antimicrobial resistance. science for intervention. 2015;6:22–9.
[2] Lee N-Y, Lee N-Y, Huang W-H, Tsui K-C, Hsueh P-R, W-CJAa Ko, et al. Carbapenem therapy for bacteremia due to extended-spectrum-β-lactamase-producing Escherichia coli or Klebsiella pneumoniae. implications of ertapenem susceptibility. 2012;56(6):2888–93.
[3] Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Machuca I, AJCmr Pascual. Treatment of infections caused by extended-spectrum-beta-lactamase-, AmpC-, and carbapenemase-producing. Enterobacteriaceae. 2018;31(2):e00079–17.
[4] Eshetie S, Unakal C, Gelaw A, Ayelign B, Endris M, Moges F. Multidrug resistant and carbapenemase producing Enterobacteriaceae among patients with urinary tract infection at referral Hospital, Northwest Ethiopia. Antimicrobial resistance and infection control 2015;4(1):12.
[5] Hoang CQ, Nguyen HD, Vu HQ, Nguyen AT, Pham BT, Tran TL, et al. Emergence of New Delhi Metallo-Beta-Lactamase (NDM) and Klebsiella pneumoniae Carbapenemase (KPC) Production by Escherichia coli and Klebsiella pneumoniae in Southern Vietnam and Appropriate Methods of Detection: A Cross-Sectional Study. BioMed research international 2019;2019:.
[6] Day K, Salman M, Kazi B, Sidjabat H, Silvey A, Lanyon C, et al. Prevalence of NDM-1 carbapenemase in patients with diarrhoea in Pakistan and evaluation of two chromogenic culture media. Journal of applied microbiology 2013;114 (6):1810–6.
[7] Maltezou H, Giakkoupi P, Maragos A, Bolikas M, Raftopoulos V, Papahatzaki H, et al. Outbreak of infections due to KPC-2-producing Klebsiella pneumoniae in a hospital in Crete (Greece). Journal of Infection. 2009;58(3):213–9.
[8] Karabay O, Altindis M, Koroglu M, Karatuna O, Aydemir ÖA, Erdem AF. The carbapenem-resistant Enterobacteriaceae threat is growing: NDM-1 epidemic at a training hospital in Turkey. Annals of clinical microbiology and antimicrobials 2016;15(1):6.
[9] Tamariz J, Llanos C, Seas C, Montenegro P, Lagos J, Fernandes MR, et al. Draft genome sequence of the first New Delhi metallo-β-lactamase (NDM-1)-producing Escherichia coli strain isolated in Peru. Genome Announc. 2018;6 (13) e00199-18.
[10] Torres-González P, Bobadilla-del Valle M, Tovar-Calderón E, Leal-Vega F, Hernández-Cruz A, Martínez-Gamboa A, et al. Outbreak caused by Enterobacteriaceae harboring NDM-1 metallo-β-lactamase carried in an IncFII plasmid in a tertiary care hospital in Mexico City. Antimicrobial agents and chemotherapy 2015;59(11):7080–3.
[11] Gonçalves IR, Ferreira M, Araujo B, Campos P, Royer S, Batistão D, et al. Outbreaks of colistin-resistant and colistin-susceptible KPC-producing Klebsiella pneumoniae in a Brazilian intensive care unit. Journal of Hospital Infection. 2016;94(4):322–9.
[12] Walsh TR, Toleman MA, Poirel L, Nordmann P. Metallo-β-lactamases: the quiet before the storm? Clinical microbiology reviews 2005;18(2):306–25.
[13] Queenan AM, Bush K. Carbapenemases: the versatile β-lactamases. Clinical microbiology reviews 2007;20(3):440–58.
[14] Cornaglia G, Giamarellou H, Rossolini GM. Metallo-β-lactamases: a last frontier for β-lactams? The Lancet infectious diseases 2011;11(5):381–93.
[15] Hall BG, Barlow M. Revised Ambler classification of β-lactamases. Journal of Antimicrobial Chemotherapy. 2005;55(6):1050–1.
[17] Sheu C-C, Chang Y-T, Lin S-Y, Chen Y-H, Hsueh P-R. Infections caused by carbapenem-resistant Enterobacteriaceae: an update on therapeutic options. Frontiers in microbiology 2019;10.
[18] Asokan GV, Ramadhan T, Ahmed E, Sanad H. WHO Global Priority Pathogens List: A Bibliometric Analysis of Medline-PubMed for Knowledge Mobilization to Infection Prevention and Control Practices in Bahrain. Oman medical journal 2019;34(3):184.
[19] Dadashi M, Yaslianifard S, Hajikhani B, Kabir K, Owlia P, Goudarzi M, et al. Frequency Distribution, Genotypes and the most Prevalent Sequence Types of New Delhi Metallo-beta-lactamase-Producing Escherichia coli among. Clinical Isolates around the World; A Review. 2019.
[20] Dadashi M, Fallah F, Hashemi A, Hajikhani B, Owlia P, Bostanghadiri N, et al. Prevalence of blaNDM− 1-producing Klebsiella pneumoniae in Asia. A systematic review and meta-analysis 2017;19(2):58–65.
[21] Dadashi M, Hashemi A, Eslami G, Fallah F, Goudarzi H, Erfanimanesh S, et al. Evaluation of antibacterial effects of Zataria multiflora Boiss extracts against ESBL-producing. Klebsiella pneumoniae strains. 2016;6(3):336.
[22] Hasani A, Purmohammad A, Rezaee MA, Hasani A, Dadashi M. Integron-Mediated Multidrug and Quinolone Resistance in Extended-Spectrum β-Lactamase-Producing Escherichia coli and Klebsiella pneumoniae. Archives of Pediatric Infectious Diseases. 2017;5(2).
[23] Paczosa MK, Mecsas J. Klebsiella pneumoniae: going on the offense with a strong defense. Microbiol Mol Biol Rev. 2016;80(3):629–61.
[24] Hajjej Z, Gharsallah H, Naija H, Boutiba I, Labbene I, Ferjani M. Successful treatment of a Carbapenem-resistant Klebsiella pneumoniae carrying blaOXA-48, blaVIM-2, blaCMY-2 and blaSHV-with high dose combination of imipenem and amikacin. IDCases. 2016;4:10–2.
[25] Rolain J, Parola P, Cornaglia G. New Delhi metallo-beta-lactamase (NDM-1): towards a new pandemia? Clinical Microbiology and Infection. 2010;16 (12):1699–701.
[26] Hammoudi Halat D, Ayoub Moubareck C. The Current Burden of Carbapenemases: Review of Significant Properties and Dissemination among Gram-Negative Bacteria. Antibiotics (Basel). 2020;9(4).
[27] Cui X, Zhang H, Du H. Carbapenemases in Enterobacteriaceae: detection and antimicrobial therapy. Frontiers in microbiology 2019;10:1823.
[28] Ahmad N, Ali SM, Khan AU. Detection of New Delhi metallo-β-lactamase variants NDM-4, NDM-5, and NDM-7 in Enterobacter aerogenes isolated from a neonatal intensive care unit of a North India Hospital: a first report. Microbial Drug Resistance. 2018;24(2):161–5.
[29] Li X, Fu Y, Shen M, Huang D, Du X, Hu Q, et al. Dissemination of bla NDM-5 gene via an IncX3-type plasmid among non-clonal Escherichia coli in China. Antimicrobial Resistance & Infection Control. 2018;7(1):59.
[30] van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence. 2017;8(4):460–9.
[31] Albiger B, Glasner C, Struelens MJ, Grundmann H, Monnet DL, Eckmanns T. Carbapenemase-producing Enterobacteriaceae in Europe: assessment by national experts from 38 countries, May 2015. 2015.
[32] Iregui A, Ha K, Meleney K, Landman D, Quale J. Carbapenemases in New York City: the continued decline of KPC-producing Klebsiella pneumoniae, but a new threat emerges. Journal of Antimicrobial Chemotherapy. 2018;73 (11):2997–3000.
[33] Shen P, Yi M, Fu Y, Ruan Z, Du X, Yu Y, et al. Detection of an Escherichia coli sequence type 167 strain with two tandem copies of blaNDM-1 in the chromosome. Journal of clinical microbiology 2017;55(1):199–205.
[34] Diancourt L, Passet V, Verhoef J, Grimont PA, SJJocm Brisse. Multilocus sequence typing of Klebsiella pneumoniae. nosocomial isolates. 2005;43 (8):4178–82.
[35] Khan AU, Maryam L, Zarrilli R. Structure, genetics and worldwide spread of New Delhi metallo-β-lactamase (NDM): a threat to public health. BMC microbiology 2017;17(1):101.
[36] Yu F, Hu L, Zhong Q, Hang Y, Liu Y, Hu X, et al. Dissemination of Klebsiella pneumoniae ST11 isolates with carbapenem resistance in integrated and emergency intensive care units in a Chinese tertiary hospital. Journal of medical microbiology 2019;68(6):882–9.
[37] Chen C-M, Guo M-K, Ke S-C, Li C-R, Y.-P.-P, Li C.-R.-R, et al. Emergence and nosocomial spread of ST11 carbapenem-resistant Klebsiella pneumoniae co-producing OXA-48 and KPC-2 in a regional hospital in Taiwan. Journal of medical microbiology 2018;67(7):957–64.
[38] Jiang Y, Wei Z, Wang Y, Hua X, Feng Y, Yu Y. Tracking a hospital outbreak of KPC-producing ST11 Klebsiella pneumoniae with whole genome sequencing. Clinical Microbiology and Infection. 2015;21(11):1001–7.
[39] Fu P, Tang Y, Li G, Yu L, Wang Y, Jiang X. Pandemic spread of blaKPC-2 among Klebsiella pneumoniae ST11 in China is associated with horizontal transfer mediated by IncFII-like plasmids. International journal of antimicrobial agents 2019;54(2):117–24.
[40] Giske CG, Fröding I, Hasan CM, Turlej-Rogacka A, Toleman M, Livermore D, et al. Diverse sequence types of Klebsiella pneumoniae contribute to the dissemination of blaNDM-1 in India, Sweden, and the United Kingdom. Antimicrobial agents and chemotherapy 2012;56(5):2735–8.
[41] Navon-Venezia S, Kondratyeva K, Carattoli A. Klebsiella pneumoniae: a major worldwide source and shuttle for antibiotic resistance. FEMS microbiology reviews 2017;41(3):252–75.
[42] Fortini D, Villa L, Feudi C, Pires J, Bonura C, Mammina C, et al. Double copies of blaKPC-3:: Tn4401a on an IncX3 plasmid in Klebsiella pneumoniae successful clone ST512 from Italy. Antimicrobial agents and chemotherapy 2016;60 (1):646–9.

[43] Mavroidi A, Katsiari M, Likousi S, Palla E, Roussou Z, Nikolaou C, et al. Characterization of ST258 colistin-resistant, bla KPC-producing Klebsiella pneumoniae in a Greek Hospital. Microbial drug resistance 2016;22 (5):392–8.
[44] Huang X, Cheng X, Sun P, Tang C, Ni F, Liu G. Characteristics of NDM-1-producing Klebsiella pneumoniae ST234 and ST1412 isolates spread in a neonatal unit. BMC microbiology 2018;18(1):1–6.
[45] Wei W-J, Yang H-F, Ye Y, Li J-B. New Delhi metallo-β-lactamase-mediated carbapenem resistance: origin, diagnosis, treatment and public health concern. Chinese medical journal 2015;128(14):1969.
[46] Poirel L, Jayol A, Nordmann P. Polymyxins: antibacterial activity, susceptibility testing, and resistance mechanisms encoded by plasmids or chromosomes. Clinical microbiology reviews 2017;30(2):557–96.
[47] Shields R. Aztreonam Combination Therapy: A Long-Awaited Answer to Metallo-β-Lactamase-Producing Gram-Negatives? Clinical Infectious Diseases.
[48] Emeraud C, Escaut L, Boucly A, Fortineau N, Bonnin RA, Naas T, et al. Aztreonam plus clavulanate, tazobactam, or avibactam for treatment of infections caused by metallo-β-lactamase-producing Gram-negative bacteria. Antimicrobial agents and chemotherapy 2019;63(5) e00010-19.