Epidemiology and Characteristics of Metallo-β-Lactamase-Producing *Pseudomonas aeruginosa*

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Metallo-β-lactamase-producing *Pseudomonas aeruginosa* (MPPA) is an important nosocomial pathogen that shows resistance to all β-lactam antibiotics except monobactams. There are various types of metallo-β-lactamases (MBLs) in carbapenem-resistant *P. aeruginosa* including Imipenemase (IMP), Verona integron-encoded metallo-β-lactamase (VIM), Sao Paulo metallo-β-lactamase (SPM), Germany imipenemase (GIM), New Delhi metallo-β-lactamase (NDM), Florence imipenemase (FIM). Each MBL gene is located on specific genetic elements including integrons, transposons, plasmids, or on the chromosome, in which they carry genes encoding determinants of resistance to carbapenems and other antibiotics, conferring multidrug resistance to *P. aeruginosa*. In addition, these genetic elements are transferable to other Gram-negative species, increasing the antimicrobial resistance rate and complicating the treatment of infected patients. Therefore, it is essential to understand the epidemiology, resistance mechanism, and molecular characteristics of MPPA for infection control and prevention of a possible global health crisis. Here, we highlight the characteristics of MPPA.

**Key Words:** Metallo-β-lactamase; *Pseudomonas aeruginosa*; Carbapenem; Epidemiology; Multidrug resistance

**Introduction**

The continuous emergence, worldwide spread, and increasing prevalence of bacteria resistant to multiple antimicrobial agents are becoming major threats to public health [1-5]. Multidrug and pandrug resistant (MDR or PDR) bacterial infec-
| Continent   | Country       | Collection period (year) | Resistance rate (%) | Reference or GenBank accession No. |
|-------------|---------------|--------------------------|---------------------|-----------------------------------|
|             |               |                          | Carbapenem | Imipenem | Meropenem | Doripenem | Ertapenem |                                                  |
| East Asia   | China         | 2003-2011                | 43.4       | 40.9     |           |           |           | [70]                                              |
|             | Japan         | 2013                     | 28.5       | 22.8     | 12.5      |           |           | [71]                                              |
|             | Korea         | 2011                     | 22         |          |           |           |           | [61]                                              |
|             | Taiwan        | 2003-2011                | 16         | 19       |           |           |           | [72]                                              |
| Southeast Asia | Philippines | 2010                     | 31.1       |          |           |           |           | [73]                                              |
|             | Singapore     | 2010                     | 23.3       |          |           |           |           | [73]                                              |
|             | Thailand      | 2010                     | 28.7       |          |           |           |           | [73]                                              |
|             | Vietnam       | 2010                     | 46.7       |          |           |           |           | [73]                                              |
| South Asia  | India         | 2011                     | 32         |          |           |           |           | [74]                                              |
|             | Iran          | 2011-2012                | 31.8       | 13.5     | 74.4      |           |           | [75]                                              |
| North Asia  | Russia        | 2008-2010                | 75.3       |          |           |           |           | [37]                                              |
| Southwest Asia | Israel | 2009-2011                | 24.7       |          |           |           |           | [76]                                              |
|             | Saudi Arabia  | 2009-2010                | 56         | 34       |           |           |           | [77]                                              |
|             | Turkey        | 2009-2011                | 49.2       |          |           |           |           | [76]                                              |
| West Europe | Belgium       | 2009-2011                | 41.1       |          |           |           |           | [76]                                              |
|             | France        | 2009-2011                | 18.2       |          |           |           |           | [76]                                              |
|             | Germany       | 2009-2011                | 24.4       |          |           |           |           | [76]                                              |
|             | Greece        | 2011                     | 50.0       |          |           |           |           | [78]                                              |
|             | Ireland       | 2009-2011                | 13.8       |          |           |           |           | [76]                                              |
|             | Italy         | 2009-2011                | 19.9       |          |           |           |           | [76]                                              |
|             | Portugal      | 2009-2011                | 35.6       |          |           |           |           | [76]                                              |
|             | Spain         | 2009-2011                | 21.0       |          |           |           |           | [76]                                              |
|             | Switzerland   | 2009-2011                | 21.7       |          |           |           |           | [76]                                              |
| North Europe| Poland        | 2009-2011                | 70.7       |          |           |           |           | [76]                                              |
|             | Sweden        | 2009-2011                | 10.9       |          |           |           |           | [76]                                              |
| Oceania     | Australia     | 2011                     | 16         |          |           |           |           | [74]                                              |
|             | New Zealand   | 2010                     | 10.3       |          |           |           |           | [74]                                              |
| North Africa| Algeria       | 2009-2012                | 39.3       |          |           |           |           | [79]                                              |
| East Africa | Kenya         | 2006-2007                | 13.7       |          |           |           |           | [80]                                              |
| South Africa| South Africa  | 2006                     | 45         | 42       |           |           |           | [81]                                              |
| North America| Canada     | 2009-2010                | 3.3        |          |           |           |           | [82]                                              |
|             | Mexico        | 2005-2010                | 22         |          |           |           |           | [83]                                              |
|             | US            | 2012-2013                | 20         |          |           |           |           | [84]                                              |
| Central America | Costa Rica | Unavailable              | 63.1       |          |           |           |           | [85]                                              |
|             | Dominica Republic | 2010                  | 8          | 8        |           |           |           | [86]                                              |
|             | El Salvador   | 2010                     | 25         | 24       |           |           |           | [86]                                              |
|             | Guatemala     | 2010                     | 36         | 34       |           |           |           | [86]                                              |
|             | Honduras      | 2010                     | 20         |          |           |           |           | [86]                                              |
|             | Nicaragua     | 2010                     | 32         | 40       |           |           |           | [86]                                              |
|             | Panama        | 2010                     | 34         | 23       |           |           |           | [86]                                              |
| South America| Argentina     | 2010                     | 33         | 37       |           |           |           | [86]                                              |
|             | Bolivia       | 2010                     | 20         | 14       |           |           |           | [86]                                              |
|             | Brazil        | 2005                     | 37-57      | 36-52    |           |           |           | [86]                                              |
|             | Chile         | 2005                     | 32-40      | 30-33    |           |           |           | [86]                                              |
|             | Columbia      | 2010                     | 17         | 19       |           |           |           | [86]                                              |
|             | Ecuador       | 2010                     | 21         | 27       |           |           |           | [86]                                              |
|             | Paraguay      | 2010                     | 30         | 30       |           |           |           | [86]                                              |
|             | Peru          | 2010                     | 66         | 57       |           |           |           | [86]                                              |
|             | Uruguay       | 2010                     | 35         | 43       |           |           |           | [86]                                              |
|             | Venezuela     | 2010                     | 33         |          |           |           |           | [86]                                              |

*Countries are listed in alphabetical order.*
tions are closely associated with high mortality, prolonged hospitalization, multiple morbidities, and increased cost due to the limited antimicrobial therapeutic options for infected patients [6, 7]. Pseudomonas aeruginosa is one of the primary opportunistic pathogens that causes a variety of nosocomial infections including sepsis, pneumonia, urinary tract infection, and soft-tissue infection [8]. This species is frequently isolated from immunocompromised patients who underwent organ transplantation, invasive procedure, immunosuppressive therapy, or intensive care [9-11].

P. aeruginosa is one of the most important bacteria with documented resistance to multiple antimicrobial classes including β-lactams, carbapenems, aminoglycosides, fluoroquinolones, and polymyxins [12, 13]. Due to its intrinsic and acquired antimicrobial resistance, only limited classes of antibiotics are effective for the treatment of P. aeruginosa infections. Among these antibiotics, carbapenems have been regarded as the most potent β-lactams against MDR Gram-negative bacilli including P. aeruginosa due to their high affinity with penicillin-binding proteins, stability against extended-spectrum β-lactamas (ESBLs), and permeability of bacterial outer membranes [14]. Resistance to carbapenems is particularly challenging in clinical settings because they are the mainstays for treatment of multidrug resistance P. aeruginosa. There are few remaining antibiotic options for this strain, and multidrug resistance is much more common for patients infected with carbapenem-resistant P. aeruginosa [6, 15, 16].

Among the various antimicrobial resistance mechanisms, the production of carbapenemase is one of the most important mechanisms by which P. aeruginosa acquires carbapenem resistance. Many carbapenemases have been identified in P. aeruginosa, including (1) KPC and GES variants of Ambler class A, (2) IMP-, VIM-, SPM-, GIM-, NDM-, and FIM-type metallo-β-lactamases (MBLs) of Ambler class B, and (3) OXA variant enzymes of Ambler class D [17-25].

Here, we overview the epidemiology and molecular characteristics of metallo-β-lactamase-producing P. aeruginosa (MPPA).

Epidemiology of carbapenem-resistant P. aeruginosa

The global epidemiology of carbapenem-resistant P. aeruginosa (CRPA) was analyzed based on a careful and thorough literature search of http://www.ncbi.nlm.nih.gov/pubmed with the combination of key words including the name of each nation, carbapenem, P. aeruginosa, MBL, epidemiology, prevalence, Gram-negative, national survey, and resistance. Countries were grouped by continent in order to show international differences in CRPA prevalence related to geographi-
| IMP variant | Frequently identified sequence types | Country of isolation | Reported gene location | Reference(s) or GenBank accession No. |
|-------------|------------------------------------|----------------------|------------------------|-------------------------------------|
| IMP-1       | 175, 186, 235, 244, 277, 308, 360, 357, 593, 645, 964, 1,015, 1,070, 1,162 | Japan, South Korea, Brazil, China, Turkey, Singapore, Thailand, Iran | CII | [38, 87] |
| IMP-2       | NR                                 | Japan                | CII                    | [93] |
| IMP-4       | NR                                 | Malaysia, Australia, China | CII | [94, 95, 96] |
| IMP-5       | NR                                 | Portugal             | CII                    | [97] |
| IMP-6       | 235, 244, 591, 744, 745, 1,015, 1,162 | South Korea, China | CII, Unknown | [98, 99] |
| IMP-7       | 235, 357, 744, 745                  | Canada, Malaysia, Slovakia, Japan, Singapore, Czech Republic, Denmark | CII, Unknown | [100, 101, 102, 103, 90, 104, 105] |
| IMP-8       | 308                                | Germany              | CII                    | [43] |
| IMP-9       | NR                                 | China, Malaysia, China | CII, CII | [106, 107] |
| IMP-10      | NR                                 | Japan, China         | CII, CII | [108, 109] |
| IMP-11      | NR                                 | Japan, Unknown       | Unknown, AB074437    |                                 |
| IMP-13      | 111, 308, 621                       | Austria, Italy, France, Belgium | CII | [110, 111, 112, 113] |
| IMP-14      | 260                                | Thailand             | CII                    | [114] |
| IMP-15      | 606, 654, 1,446                     | Mexico, Spain, Germany | CII, CII | [115, 116, 76] |
| IMP-16      | NR                                 | Brazil                | CII                    | [117] |
| IMP-18      | NR                                 | USA, Mexico, Puerto Rico | CII, CII | [118, 119, 120] |
| IMP-19      | 235                                | Japan, Italy         | Unknown, AB184876    |                                 |
| IMP-20      | NR                                 | Japan                | CII                    | AB196988 |
| IMP-21      | NR                                 | Japan                | CII                    | AB204557 |
cal distance. We found published reports from a total of 50 countries regarding country of isolation and collection period of clinical isolates, as well as the ratio of CRPA to all P. aeruginosa (Table 1).

In most countries, the reported CRPA ratio ranged from 10 to 50%. The carbapenem resistance rates in Canada (carbapenem 3.3%) and the Dominican Republic (imipenem and meropenem, both 8%) were the lowest of all countries, with ratios lower than 10%. On the other hand, ratios in Brazil, Peru, Costa Rica, Russia, Greece, Poland, Iran, and Saudi Arabia were higher than 50% in all drugs of the carbapenem class (imipenem, meropenem, doripenem, ertapenem) ranging from 50% to 75.3% (Fig. 1). As shown in Figure 1, Russia, Southwest Asia, and South America were the predominant areas with antimicrobial resistance rates high enough to cause concern for public health to microbiologists and infection specialists.

The geographical distribution and ratio of CRPA differed from country to country; many CRPA strains have been identified and their prevalence is increasing gradually. The worldwide emergence of carbapenem-resistant strains with similar mobile genetic elements indicates the dissemination of genes encoding carbapenemases through horizontal gene transfer [26]. The increase in CRPA ratio is known to be driven by both carbapenem use and the application of medical devices, which prompt the selection of resistant organisms [27]. Both factors are related to patient characteristics and clinical practice policies and/or antibiotic prescription patterns of health care facilities in each country.

Resistance mechanisms to carbapenem can be categorized into (1) deficiency of the outer membrane porin OprD, (2) bacterial production of carbapenemases, or (3) overexpression of efflux pump [28-32]. Carbapenem resistance in P. aeruginosa is most often associated with OprD deficiency and less frequently with the release of carbapenemase by the pathogen [33-35].

Carbapenemases from each β-lactamase Ambler class have been identified in P. aeruginosa. Of these, Ambler class B β-lactamases are the most clinically significant carbapenemases and are called metallo-β-lactamase (MBL) because a metal ion, such as Zn²⁺, is essential for their activity, which can be inhibited by metal ion chelators.

**Types of metallo-β-lactamases in P. aeruginosa**

MBLs efficiently hydrolyze carbapenems and other β-lactams (except monobactams) and are not inhibited by the clinically available β-lactamase inhibitors including clavulanic

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**Table 2. Continued**

| IMP variant | Frequently identified sequence types | Country of isolation | Reported gene location | Reference(s) or GenBank accession No. |
|-------------|-------------------------------------|----------------------|------------------------|--------------------------------------|
| IMP-22      | 175, 620                            | Austria              | C1I                    | [110]                                |
|             |                                     | Italy                | C1I                    | [122]                                |
| IMP-25      | 235, 654                            | Malaysia             | C1I                    | EU352796                             |
| IMP-26      | 235, 654                            | Singapore            | Unknown                | [123]                                |
| IMP-29      | 235                                 | France               | C1I                    | [124]                                |
| IMP-30      | NR                                  | Russia               | Unknown                | [125]                                |
| IMP-31      | 235                                 | Germany              | Unknown                | [126]                                |
| IMP-33      | NR                                  | Italy                | C1I                    | [127]                                |
| IMP-35      | 622                                 | Germany              | C1I                    | [128]                                |
| IMP-37      | 111, 308, 621                       | France               | Unknown                | JX131372                             |
| IMP-40      | NR                                  | Japan                | Unknown                | AB753457                             |
| IMP-41      | NR                                  | Japan                | Unknown                | AB753458                             |
| IMP-43      | 235, 357                            | Japan                | C1I                    | [129]                                |
| IMP-44      | 357                                 | Japan                | C1I                    | [129]                                |
| IMP-45      | 308                                 | China                | C1I                    | [130]                                |
| IMP-48      | NR                                  | USA                  | Unknown                | KM087857                             |

IMP, imipenemase; C1I, Class 1 integron; NR, not reported.
Table 3. Verona integron-encoded metallo-ß-lactamases found in *Pseudomonas aeruginosa*

| VIM type MBL | Frequently identified sequence type | Country of isolation | Reported gene location | Reference(s) or GenBank accession No. |
|--------------|-----------------------------------|----------------------|------------------------|-------------------------------------|
| VIM-1        | 17, 111, 227, 228, 235             | Italy                | C1I                    | [39]                                |
|              |                                    | France               | C1I                    | [131]                               |
|              |                                    | Greece               | C1I                    | [132]                               |
|              |                                    | Germany              | Unknown                | [76]                                |
|              |                                    | Italy                | C1I                    | [121]                               |
| VIM-2        | 17, 111, 155, 175, 179, 229, 233, 235, 244, 309, 364, 639, 640, 654, 773, 811, 973, 1,020, 1,074, 1,699, 1,700 | Tunisia             | C1I                    | [133]                               |
|              |                                    | Thailand             | Unknown                | [114]                               |
|              |                                    | Austria              | C1I                    | [110]                               |
|              |                                    | Mexico               | C1I                    | [115]                               |
|              |                                    | India                | Unknown                | [134]                               |
|              |                                    | Kenya                | Unknown                | [80]                                |
|              |                                    | Hungary              | C1I                    | [135]                               |
|              |                                    | Malaysia             | C1I                    | [136]                               |
|              |                                    | South Korea          | C1I                    | [19]                                |
|              |                                    | Japan                | C1I                    | [137]                               |
|              |                                    | France               | C1I                    | [138]                               |
|              |                                    | Greece               | C1I                    | [139]                               |
|              |                                    | Italy                | C1I                    | [140]                               |
|              |                                    | Portugal             | C1I                    | [141]                               |
|              |                                    | Spain                | Unknown                | [142]                               |
|              |                                    | Croatia              | C1I                    | [143]                               |
|              |                                    | Poland               | C1I                    | [144]                               |
|              |                                    | Chile                | C1I                    | [44]                                |
|              |                                    | Venezuela            | C1I                    | [44]                                |
|              |                                    | Argentina            | Unknown                | [44]                                |
|              |                                    | USA                  | C1I                    | [44]                                |
|              |                                    | Belgium              | Unknown                | [76]                                |
|              |                                    | Germany              | Unknown                | [76]                                |
|              |                                    | Turkey               | Unknown                | [76]                                |
|              |                                    | Egypt                | C1I                    | [145]                               |
| VIM-3        | 298                                | Taiwan               | Unknown                | [146]                               |
| VIM-4        | 111, 229, 230, 235, 313             | Greece              | C1I                    | [44]                                |
|              |                                    | Sweden               | Unknown                | [44]                                |
|              |                                    | Poland               | C1I                    | [44]                                |
|              |                                    | Hungary              | C1I                    | [135, 147]                          |
|              |                                    | France               | Unknown                | [76]                                |
| VIM-5        | 85, 534                            | India                | Unknown                | [134]                               |
|              |                                    | Turkey               | C1I                    | [44]                                |
| VIM-6        | 85, 746                            | India                | C1I                    | [134]                               |
|              |                                    | Indonesia            | C1I                    | [148]                               |
|              |                                    | South Korea          | C1I                    | [148]                               |
|              |                                    | Philippines          | C1I                    | [148]                               |
| VIM-7        | NR                                 | USA                  | C1I                    | [149]                               |
| VIM-8        | NR                                 | Columbia             | Unknown                | [150]                               |
acid or tazobactam. Except for the SPM-type enzymes, most MBL genes reside within various compositions of integron gene cassettes that are encoded on genes linked to mobile elements, which is a condition that facilitates their spread among different bacterial species and genera through horizontal gene transfer [36, 37]. The most notable of the acquired MBLs, the IMP- and VIM-type enzymes, were first detected in the early 1990s [38, 39]. Thereafter, many additional types of acquired MBLs have been reported, including the SPM-, GIM-, SIM-, KHM-, NDM-, AIM-, DIM-, SMB-, TMB-, and FIM-type enzymes [40, 41]. Since the discovery of IMP-1, which was the first MBL identified in *P. aeruginosa*, IMP-, VIM-, SPM-, GIM-, NDM- and FIM-type variants in *P. aeruginosa* have been reported steadily.

**Imipenemase (IMP)**

In 1988, transferable IMP-1 was first isolated from *P. aeruginosa* in Japan [38] and was found in a class 1 integron located on a conjugational plasmid. Thereafter, it was identified in many other species suggesting horizontal gene transfer of *blaIMP-1* between unrelated Gram-negative species, and also showed predominance of specific IMP type-producing isolates demonstrating clonal expansion [15]. Currently 33 of the 51 known IMP variants have been identified from *P. aeruginosa*, including the recent detection of IMP-8-producing strains in Germany [42, 43] (Table 2). IMP-like enzymes are divided into several subgroups, and the percentage amino acid identity within these subgroups ranges from 90% to 99% showing very similar hydrolytic activities among them [44].

**Verona integron-encoded metallo-β-lactamase (VIM)**

VIM enzymes share the same hydrolytic spectrum the IMP-type enzymes, with less than 40% amino acid identity [45]. VIM-1 was identified first in *P. aeruginosa* in 1999, and after that, has also been reported in other Gram-negative species from several countries [39]. Currently, VIM-2 is the most widespread MBL in *P. aeruginosa* and has been the source of multiple outbreaks [44]. Twenty-four of the 46 VIM variants, including VIM-43 found in the USA (GenBank accession

| VIM type MBL | Frequently identified sequence type | Country of isolation | Reported gene location | Reference(s) or GenBank accession No. |
|--------------|------------------------------------|----------------------|------------------------|--------------------------------------|
| VIM-9        | NR                                 | UK                   | Unknown                | AY524988                             |
| VIM-10       | NR                                 | UK                   | Unknown                | [151]                                |
| VIM-11       | NR                                 | India                | CII                    | [134]                                |
| VIM-13       | 235                                | Spain                | CII                    | [153]                                |
| VIM-14       | 260                                | Spain                | Unknown                | EF055455                             |
| VIM-15       | NR                                 | Bulgaria             | CII                    | [155]                                |
| VIM-16       | NR                                 | Germany              | CII                    | [155]                                |
| VIM-17       | NR                                 | Greece               | CII                    | [156]                                |
| VIM-18       | NR                                 | India                | CII                    | [134]                                |
| VIM-20       | NR                                 | Spain                | Unknown                | [157]                                |
| VIM-28       | NR                                 | Egypt                | CII                    | [158]                                |
| VIM-30       | NR                                 | France               | CII                    | JN129451                             |
| VIM-36       | 111                                | Belgium              | Unknown                | [76]                                 |
| VIM-37       | NR                                 | Poland               | Unknown                | [76]                                 |
| VIM-38       | NR                                 | Turkey               | CII                    | [159]                                |
| VIM-43       | NR                                 | USA                  | Unknown                | KP096412                             |

VIM, Verona-integron-encoded metallo-ß-lactamase; MBL, metallo-ß-lactamase; C1I, Class 1 integron; NR, not reported.
number KP096412), have been identified in *P. aeruginosa* (Table 3).

**Sao Paulo metallo-β-lactamase (SPM)**

SPM-1 was first isolated in Brazil in 1997 from a *P. aeruginosa* clinical isolate that was resistant to all available antibiotics except colistin [46] (Table 4). SPM is quite different from VIM and IMP, presenting the highest amino acid identity to IMP-1 (35.5%), and represents a new subfamily of MBLs. Dissemination of MDR *P. aeruginosa* producing SPM-1 was demonstrated in distinct regions of Brazil; however, these strains have not yet spread to other countries, with only one exception of a single isolate identified in a Swiss patient who had previously been hospitalized in Brazil [47, 48]. The *bla_{spm1}* gene has been reported in *Pseudomonas* and *Acinetobacter* spp. isolated from various hospitals in Brazil, and its product is a major contributor to the high level carbapenem resistance observed in South America. Currently, the ratio of carbapenem resistance in South America is among the highest in the world [49]. The *bla_{spm1}* gene is either chromosomal or plasmid-encoded. In addition, it is associated with the insertion sequence common region 4 (ISCR4) at the origin of its acquisition and expression and is likely transposed through a rolling-circle replication mechanism [50].

**Germany imipenemase (GIM)**

In 2002, GIM-1 was identified in *P. aeruginosa* isolates from Germany (Table 4). Molecular analysis revealed that the amino acid sequence identity of GIM-1 with other clinically significant MBL genes, including IMP and VIM variants, was less than 45%, indicating that GIM-1 is a new phylogenetic subclass of MBLs. Initially, this enzyme was not predicted to be mobile because the 22-kb plasmid carrying In77 is nonconjugative and has a restricted host range [51]; however, GIM-1 has also been found in *Enterobacter cloacae*, *Pseudomonas putida*, *Serratia marcescens*, *Escherichia coli*, *Klebsiella oxytoca*, and *Citrobacter freundii* [52]. Molecular analysis of class 1 integron arrays showed that most *bla_{gim1}* gene cassettes shared identical elements (*aacA4*, *aadA1*, and *bla_{OXA-2})*, which demonstrates horizontal gene transfer of a large block of genetic information [52]. To date, there have been no reports of GIM-1-producing strains outside of Germany.

**New Delhi metallo-β-lactamase (NDM)**

NDM-1 was first isolated in *Klebsiella pneumoniae* and *Escherichia coli* recovered from a patient who was previously admitted to a hospital in New Delhi, India, in 2009 [53]. Since then, additional six NDM variants (NDM-2 to NDM-7) have been identified in *P. aeruginosa*, *Acinetobacter baumannii*, and *E. coli*. NDM-1-producing *P. aeruginosa* strains were first reported in 2011, with two isolates recovered from Serbia [20] (Table 4). In 2012, NDM-1-producing *P. aeruginosa* sequence type 235 (ST235) strain was isolated in France from a patient previously hospitalized in Serbia [54, 55]. Since then, NDM-1-positive *P. aeruginosa* isolates have been recovered throughout the world including India, Italy, Egypt, and Slovakia [56-59].
Florence imipenemase (FIM-1)

In 2012, a novel FIM-1 MBL was isolated from a MDR P. aeruginosa in Florence (Italy) that showed highest similarity (40% amino acid identity) with NDM-type enzymes [60] (Table 4). This isolate belonged to the ST235 epidemic clonal lineage. Analysis of the kinetic parameters showed that FIM-1 has a broad substrate specificity, especially with penicillins and carbapenems. The bla\text{\textit{Vim}}, gene was chromosomally located and was associated with \textit{ISCR19}-like elements that were likely involved in its capture and mobilization; its origin remains unknown [60].

Metallo-\(\beta\)-lactamase-producing \textit{P. aeruginosa} in Korea

VIM-2 was first described in \textit{P. aeruginosa} isolated from the blood culture of a woman treated with imipenem in Marseille, France, in 1996 [62]. The first reported MBL in Korea was a VIM-2-producing \textit{P. aeruginosa} isolated in 2002 [19]. Since then, many MBL enzymes including VIM-2 have been detected in \textit{P. aeruginosa}, \textit{Acinetobacter} spp., and \textit{Enterobacteriaceae} isolates. The prevalence of dominant MBL types has changed with time. In 2003, more than 10% of imipenem-resistant \textit{P. aeruginosa} produced VIM-2 type MBL, but the ratio of VIM-2 carriage decreased to 7.7% according to a study in 2005, which was followed by IMP-1 at 2.4% and IMP-6 at 0.7% [63-65]. In 2011, the ratio of imipenem-resistant \textit{P. aeruginosa} was 22% among 15,032 clinical isolates in Korea, and IMP-6 became the dominant MBL enzyme in Korea, representing 7.8% of all \textit{P. aeruginosa} clinical isolates, followed by VIM-2 at 0.3% [66]. This trend in MPPA was also found in 2015; although the prevalence of MPPA in \textit{P. aeruginosa} clinical isolates slightly decreased from 8.0% (31/386) to 6.4% (21/329), IMP-6 was still the most frequently detected MBL type in \textit{P. aeruginosa} in Korea, followed by VIM-2 at 1.2% (4/329), which is different from the worldwide prevalence of VIM-2 [66-68]. IMP-6 was first identified in Japan in 1996 in plasmid pKU501 from \textit{Serratia marcescens} KU383. It showed very similar amino acid identity with IMP-1 MBL, differing by only one Ser196Gly amino acid substitution, resulting in augmented hydrolytic activity for meropenem [69].

Molecular analysis demonstrated that ST235 is the most dominant MPPA in Korea [67]. Association of ST235-like strains with MBL genes has been reported in several European countries, with VIM-1-producers in Italy; VIM-4-producers in Greece, Sweden, Hungary and Belgium; VIM-13-producers in Spain; and IMP-29-producers in France [42]. This clone might therefore possess some specific traits enhancing its clonal dissemination. The combination of prevalent sequence types and specific MBL enzymes might suggest the keys to understand the proliferation of resistant strains and mechanisms of gene transfer. Given that MPPA ST235 was the only strain detected in Korea five years ago, it is also worthy to note that MPPA ST309 and ST463 have emerged along with the prevalent MPPA ST235 strain because this clonal diversity might be a sign of alarm for additional dissemination of MPPA in Korea.

Conclusion

The emergence and dissemination of MPPA is a global concern threatening not only immunocompromised patients, but also healthy members of the community. MPPA is an important bacteria due to the antimicrobial resistance characteristics as well as its pathogenicity. It contains multiple antimicrobial resistance genes and has the potential to transfer these to other strains, which is a major clinical problem because of limited treatment options for patients infected with MPPA. There are many obstacles to overcome regarding bacterial resistance. These can be broadly categorized into issues of emergence, spread, and clonal expansion with diversity. These factors are related to each other and are very difficult to control. Several factors are already well known to cause the proliferation of resistant strains, which include natural genetic diversification caused by mutation, horizontal gene transfer among other species, an increase of international travel and patient transfer between countries raising the possibility for further dissemination of resistant strains, and greater antibiotic selective pressure especially in immunocompromised patients who received aggressive and invasive treatment. Further studies on epidemiology, antimicrobial resistance mechanisms, proper antibiotic stewardship, and rapid diagnostic methods for detection of MPPA are recommended in order to develop strategies that contain the dissemination and limit the transmission of MPPA.

Conflicts of Interest

No conflicts of interest.

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