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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-

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Table 1. Carbapenem-resistant *Pseudomonas aeruginosa* report by country

Continent	Country[a]	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					[73]
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]

[a]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 pathogen 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-lactamases (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-

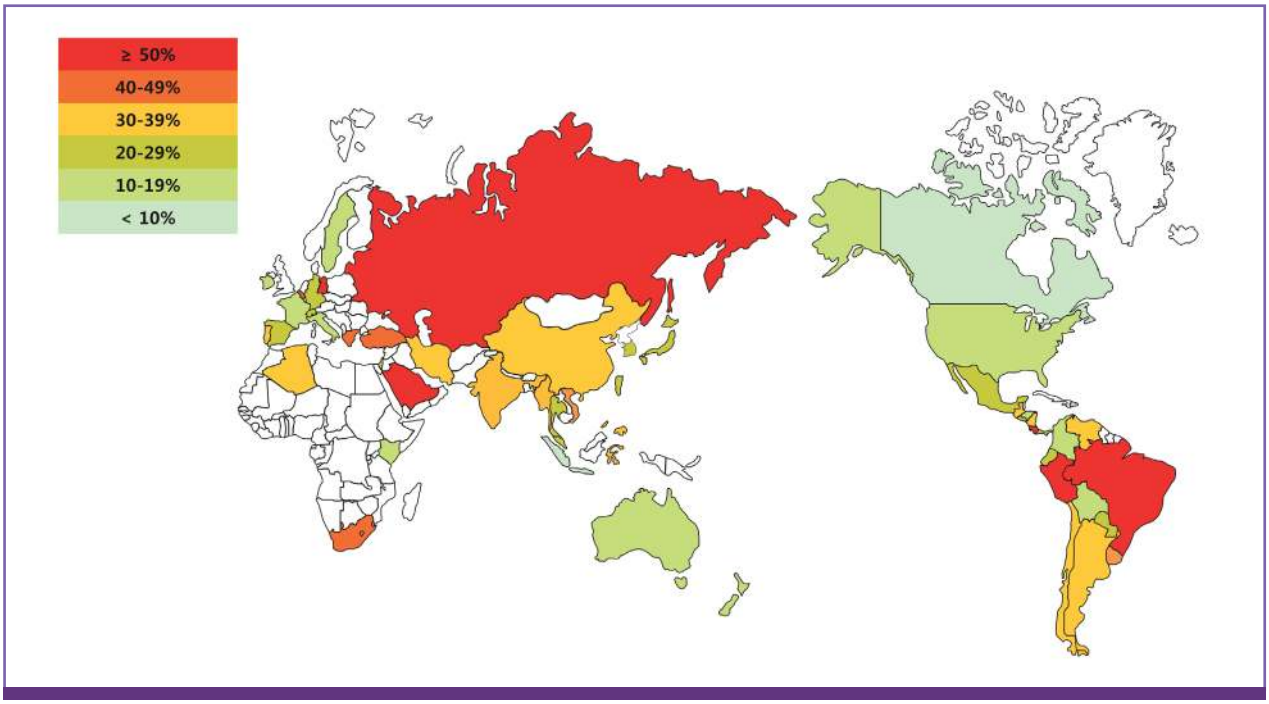

Figure 1. Geographical distribution of carbapenem-resistant *Pseudomonas aeruginosa*. Most isolates were collected from 2009 to 2011 with the following exceptions: Chile (2005), Kenya (2006 to 2007), and South Africa (2006). The white colored areas indicate that there was no available published data for that region.

Table 2. Imipenemase-type metallo-ß-lactamases found in *Pseudomonas aeruginosa*

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	C1I	[38, 87]
		South Korea	C1I	[63]
		Brazil	Unknown	[23]
		China	Unknown	[88]
		Turkey	C1I	[89]
		Singapore	Unknown	[90]
		Thailand	C1I	[91]
		Iran	C1I	[92]
IMP-2	NR	Japan	C1I	[93]
IMP-4	NR	Malaysia	Unknown	[94]
		Australia	C1I	[95]
		China	C1I	[96]
IMP-5	NR	Portugal	C1I	[97]
IMP-6	235, 244, 591, 744, 745, 1,015, 1,162	South Korea	C1I	[98]
		China	Unknown	[99]
IMP-7	235, 357, 744, 745	Canada	C1I	[100]
		Malaysia	Unknown	[101]
		Slovakia	Unknown	[102]
		Japan	C1I	[103]
		Singapore	Unknown	[90]
		Czech Republic	C1I	[104]
		Denmark	Unknown	[105]
IMP-8	308	Germany	C1I	[43]
IMP-9	NR	China	C1I	[106]
		Malaysia	C1I	[107]
IMP-10	NR	Japan	C1I	[108]
		China	C1I	[109]
IMP-11	NR	Japan	Unknown	AB074437
IMP-13	111, 308, 621	Austria	C1I	[110]
		Italy	C1I	[111]
		France	C1I	[112]
		Belgium	C1I	[113]
IMP-14	260	Thailand	C1I	[114]
IMP-15	606, 654, 1,446	Mexico	C1I	[115]
		Spain	C1I	[116]
		Germany	Unknown	[76]
IMP-16	NR	Brazil	C1I	[117]
IMP-18	NR	USA	Unknown	[118]
		Mexico	C1I	[119]
		Puerto Rico	C1I	[120]
IMP-19	235	Japan	Unknown	AB184876
		Italy	C1I	[121]
IMP-20	NR	Japan	C1I	AB196988
IMP-21	NR	Japan	C1I	AB204557

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		China	C1I	EU352796
IMP-26	235, 654	Malaysia	C1I	[123]
		Singapore	Unknown	[31]
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.

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 carbepenem-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 Zn^{2+}, 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

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]

Table 3. Continued

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	C1I	[134]
		Argentina	Unknown	[152]
		Italy	Unknown	AY635904
		Malaysia	C1I	[136]
VIM-13	235	Spain	C1I	[153]
VIM-14	260	Spain	Unknown	EF055455
		Italy	C1I	[154]
VIM-15	NR	Bulgaria	C1I	[155]
VIM-16	NR	Germany	C1I	[155]
VIM-17	NR	Greece	C1I	[156]
VIM-18	NR	India	C1I	[134]
VIM-20	NR	Spain	Unknown	[157]
VIM-28	NR	Egypt	C1I	[158]
VIM-30	NR	France	C1I	JN129451
VIM-36	111	Belgium	Unknown	[76]
VIM-37	NR	Poland	Unknown	[76]
VIM-38	NR	Turkey	C1I	[159]
VIM-43	NR	USA	Unknown	KP096412

VIM, Verona-integron-encoded metallo-ß-lactamase; MBL, metallo-β-lactamase; C1I, Class 1 integron; NR, not reported.

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 MLBs, 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 bla_{IMP-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

Table 4. Other metallo-ß-lactamases found in *Pseudomonas aeruginosa*

MBL enzymes	Frequently identified sequence type	Country of isolation	Reported gene location	Reference(s) or GenBank accession No.
NDM-1	235	Serbia	Chromosome	[20]
		France	Chromosome	[54, 55]
		India	Plasmid	[56]
		Italy	Chromosome	[57]
		Egypt	Unknown	[58]
		Slovakia	Unknown	[59]
SPM-1	NR	Brazil	IS*CR4*	[160]
		Switzerland	IS*CR4*	[48]
GIM-1	NR	Germany	Class 1 Integron, Plasmid	[51, 52]
FIM-1	235	Italy	Chromosome	[60]

MBL, metallo-β-lactamase; NDM, New Delhi metallo-ß-lactamase; SPM, Sao Paulo metallo-ß-lactamase; NR, not reported; IS*CR4*, insertion sequence common region 4; GIM, Germany imipenemase; FIM, Florence imipenemase.

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_{SPM-1} 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_{SPM-1} gene is either chromosomal or plasmid-encoded. In addition, it is associated with the insertion sequence common region 4 (IS*CR4*) 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_{GIM-1} 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. Anaylsis of the kinetic parameters showed that FIM-1 has a broad substrate specificity, especially with penicillins and carbapenems. The bla_{FIM-1} gene was chromosomally located and was associated with IS*CR19*-like elements that were likely involved in its capture and mobilization; its origin remains unknown [60].

Metallo-β-lactamase-producing *P. aeruginosa* in Korea

VIM-2 was first described in *P. aeruginosa* isolated from the blood culture of a woman treated with imipenem in Marseilles, France, in 1996 [62]. The first reported MBL in Korea was a VIM-2-producing *P. aeruginosa* isolated in 2002 [19]. Since then, many MBL enzymes including VIM-2 have been detected in *P. aeruginosa*, *Acinetobacter* spp., and *Enterobacteriaceae* isolates. The prevalence of dominant MBL types has changed with time. In 2003, more than 10% of imipenem-resistant *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 *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 *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 *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 *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 *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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