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REVIEW

Double- and multi-carbapenemase-producers: the excessively armored bacilli of the current decade

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Abstract Multidrug-resistant (MDR) and extensively drug-resistant (XDR) Gram-negative nosocomial pathogens commonly carry one carbapenemase gene conferring resistance to carbapenems and other beta-lactam antibiotics. However, increasing reports show that double-carbapenemase-producing (DCP) and even multi-carbapenemase-producing (MCP) bacteria are emerging in some parts of the world, diminishing further, in some cases, the already limited treatment options. In the present review, the up-to-date reports of DCP and MCP isolates are summarized and concerns regarding their emergence are discussed.

Introduction

Carbapenems are the most important beta-lactam antibiotics, presenting an exceptionally broad spectrum of activity, while, at the same time, being less vulnerable to beta-lactam-hydrolyzing enzymes, including the extended-spectrum beta-lactamases (ESBLs). Resistance to these agents in Gram-positives is known to be mediated by mutation-derived changes of penicillin-binding proteins (PBPs). Carbapenem resistance in Gram-negative bacteria on the other hand, is due to carbapenemase production, diminished outer membrane permeability, efflux pumps over-expression, or a combination of the aforementioned mechanisms. Enzyme-mediated resistance to carbapenems however, is by far considered the most clinically important because carbapenemases may often: (i) hydrolyze all or almost all beta-lactams, (ii) confer high carbapenem minimum inhibitory concentrations (MICs), (iii) be encoded by genes which are horizontally transferable by mobile genetic elements, such as plasmids and transposons, and (iv) be associated with genes encoding resistance determinants to antimicrobials other than beta-lactams. Carbapenem resistance mediated by transferable carbapenemases was initially detected in the early 1990s and has spread to all continents since then, leading to an ongoing health crisis. Under these circumstances, a novel phenomenon has been observed lately: the worldwide emergence of double- and multi-carbapenemase-producing (DCP and MCP, respectively) Gram-negative nosocomial pathogens, mainly *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*.

Carbapenem-hydrolyzing enzymes

Carbapenemases are enzymes that share the common property of hydrolyzing, at least partially, a carbapenem together with other beta-lactam antibiotics [1]. In this heterogeneous group of beta-lactamases belong Ambler class A enzymes KPC, GES/IBC, IMI/NMC-A, SFC-1, SME, Ambler class B metallo-beta-lactamases (MBLs) IMP, VIM, NDM, GIM, SIM, AIM, FIM, and numerous Ambler class D carbapenemases, most of them showing only weak carbapenemase activity [2–4]. Among these, KPC, VIM, IMP, NDM, and OXA-48 types are the most disseminated worldwide, and their properties have been extensively studied and described [5]. Briefly, KPC hydrolyze all beta-lactams and are partially inhibited in vitro by clavulanic acid, tazobactam, and boronic acid. MBLs contain zinc in their active

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center, inactivate all beta-lactams except aztreonam, are not affected by the beta-lactamase inhibitors, and are in vitro inhibited by not clinically applicable metal chelators, such as EDTA. KPC and MBL encoding genes are often incorporated in mobile genetic structures presenting, thus, high levels of intra- and interspecies dispersion. The $bla_{\text{OXA-48}}$-type genes are always plasmid borne [6], unlike other OXA-type carbapenemase-encoding genes that are commonly located to the chromosome [7].

Klebsiella pneumoniae

In 2010, Greece was characterized as endemic for KPC and VIM carbapenemases [8]. Thus, not surprisingly, this was the first country in which the concomitant presence of KPC and VIM carbapenemases was detected. In late 2009 [9] and early 2010 [10], four cases of *K. pneumoniae* co-harboring KPC-2 and VIM-1 were published. Interestingly, these isolates were from Heraklion, Athens, Trikala, and Thessaloniki, and unrelated to each other (Table 1). Later in 2010, a study performed in Evgenidion Hospital of Athens on 42 carbapenem-resistant *K. pneumoniae* isolated between February and December 2009 revealed 14 KPC-2+VIM-1 producers, showing that double-carbapenemase *K. pneumoniae* were already established in that setting [11]. A slightly different combination was detected the same year in an isolate submitted in 2009 to the Greek National School of Public Health from an Athens hospital. This was found to bear VIM-4 together with KPC-2 [12]. Moreover, a novel VIM variant, VIM-19, was described by Pournaras et al. in a *K. pneumoniae* isolated in 2008 in the General Hospital of Serres, together with KPC-2 and other beta-lactamases [13].

Meanwhile, from another endemic part of the world, India, reports of Enterobacteriaceae carrying two carbapenemases appeared almost simultaneously. In Lucknow, researchers studied retrospectively 64 isolates obtained between 2005 and 2006 from the respiratory samples of patients with ventilator-associated pneumonia. Twelve were found to bear MBLs and, among them, a SIM-1+IMP *K. pneumoniae*, a SIM-1+IMP *Enterobacter aerogenes*, and a SIM-1+VIM *K. pneumoniae* [14]. Moreover, in Chennai, three *K. pneumoniae* and one *Escherichia coli* co-producing NDM-1 and OXA-48 were isolated from the intensive care unit (ICU) of a tertiary care hospital [15].

A more accurate view of the situation in Greece was available in 2011 when the National School of Public Health published a large study including 378 KPC-producing *K. pneumoniae* isolated between January 2009 and April 2010 from 40 Greek hospitals [16]. In that study, 18 KPC-2+VIM-1/-4 were found, accounting for approximately 4.8 % of the study sample. Moreover, in a different study, 256 *K. pneumoniae* isolates recovered from eight hospitals during July 2010 were tested for carbapenem resistance and carbapenemase production [17]. One hundred and thirty-two (51.6 %) were found positive for at least one carbapenemase, whereas 2.8 % carried both bla_{KPC} and bla_{VIM} genes.

Another interesting report was published later that year from Larisa, where a *Citrobacter koseri* harboring KPC-2 was isolated from a patient colonized by a KPC-2+VIM-1-producing *K. pneumoniae* [18]. The authors concluded that bla_{KPC} was most probably transferred from *K. pneumoniae* to *C. koseri*.

The second European country to face the threat of such strains was Germany, where an outbreak of KPC-2+VIM-1 *K. pneumoniae* occurred in a university hospital between July 2010 and January 2011, probably imported by a patient previously hospitalized in Greece [19].

In 2012, double-carbapenemase-producers became steadily present in Greek hospitals, as shown also in a study by Poulou et al. in Serres [20], whereas KPC plus MBL-producing isolates emerged in Asian countries. A *K. pneumoniae* co-harboring $bla_{\text{NDM-1}}$ and $bla_{\text{KPC-2}}$ was reported from Chennai [21], whereas a KPC-2+IMP-4-producer was isolated from a urine sample of a pediatric patient in Wuhan, China [22].

This phenomenon was developed further in the following two years. In 2013, a KPC-3+VIM-2 isolate was characterized from Italy [23], a KPC-2+VIM-24 from Colombia [24], and two NDM-1/5+OXA-181 from two epidemiologically unrelated patients in Singapore [25]. More recently, in 2014, two isolates carrying both $bla_{\text{NDM-1}}$ and $bla_{\text{IMP-4}}$ [26], as well as five isolates harboring $bla_{\text{KPC-2}}$ and $bla_{\text{IMP-4}}$ [27], were reported from China, and the NDM-1+KPC-2 combination was found in Pakistan [28]. A *K. pneumoniae* co-producing NDM-1 and OXA-232 (an OXA-48 variant) was imported to the USA from India [29], and another was found also in a French hospital, where its cross-transmission was documented [30]. Similarly, an NDM-1+OXA-48 *K. pneumoniae* was found in Bern, Switzerland from the surveillance rectal swab of a patient imported from Belgrade, Serbia [31].

Pseudomonas aeruginosa

P. aeruginosa harboring multiple carbapenemase genes are rare and the respective reports are all from different countries of central and south America. Interestingly, a retrospective study conducted in 14 clinical *P. aeruginosa* isolated in Mexico City in 2004 showed that the occurrence of MCP strains remained unknown for many years. The investigators found two VIM-2+VIM-11+GES-5- and four VIM-11+GES-5-producers [32].

In 2012, a fatal case of infection due to extensively drug-resistant (XDR) *P. aeruginosa* isolated in 2009 in Puerto Rico was published. Polymerase chain reaction (PCR) and sequencing analyses showed the simultaneous presence of KPC-2 and IMP-18, together with other beta-lactamases [33]. Another KPC+

Table 1 Reports of multiple carbapenemase-producing isolates

Year of publication	Year of isolation	Combination of carbapenemases	Gene location	Other β-lactamases	Host (no.)	Carbapenem MICs (mg/L)				ST	Origin	Reference
						Im	Mer	Ert	Dor			
2009	2008–2009	KPC-2; VIM-1	pl; pl		*K. pneumoniae* (3)	32 2 32	8 2 64	64 8 >128	NA	NA	Greece	[9]
2010	2009	KPC-2; VIM-1	NA	TEM-1; SHV-1	*K. pneumoniae* (1)	≥256	≥256	≥256	≥256	NA	Greece	[10]
2010	2009	KPC-2; VIM-1	NA		*K. pneumoniae* (14)	8-32	32-64	NA	NA	NA	Greece	[11]
2010	2009	KPC-2; VIM-4	pl; pl	CMY-4	*K. pneumoniae* (1)	16	4	32	NA	383	Greece	[12]
2010	2008	KPC-2; VIM-19	pl; pl	CMY-2; CTX-M-15	*K. pneumoniae* (1)	32	16	64	NA	NA	Greece	[13]
2009	2005–2006	SIM-1; IMP SIM-1; IMP SIM-1; VIM	NA NA NA		*K. pneumoniae* (1) *E. aerogenes* (1) *K. pneumoniae* (1)	NA NA NA	NA NA NA	NA NA NA	NA NA NA	NA NA NA	India	[14]
2010	2009	NDM-1; OXA-48	pl; pl		*K. pneumoniae* (3) *E. coli* (1)	NA	NA	NA	NA	NA	India	[15]
2011	2009–2010	KPC-2; VIM-1/-4	pl; NA		*K. pneumoniae* (18)	1 to≥64	1 to≥64	4 to≥64	N	147 323 383	Greece	[16]
2011	2010	KPC-2; VIM-19 KPC-2; VIM-1 KPC-2; VIM-1	NA	CMY-4 SHV-12	*K. pneumoniae* (1) *K. pneumoniae* (2) *K. pneumoniae* (4)	>32 >32 16–32	>32 >32 3–32	>32 >32 6–24	>32 >32 2–16	NA	Greece	[17]
2011	2011	KPC-2; VIM-1	NA	TEM-1	*K. pneumoniae* (1)	32	16	32	NA	147	Greece	[18]
2011	2010–2011	KPC-2; VIM-1	NA		*K. pneumoniae* (7)	≥32	≥32	NA	NA	NA	Germany	[19]
2012	2009–2011	KPC-2; VIM-1	NA		*K. pneumoniae* (9)	4 to>32	2 to>32	>32	NA	NA	Greece	[20]
2012	2010	NDM-1; KPC-2	pl; pl	TEM-1; CTX-M-15	*K. pneumoniae* (1)	256	128	NA	NA	NA	India	[21]
2012	2010	KPC-2; IMP-4	pl; pl	TEM-1; OKP-B	*K. pneumoniae* (1)	8	32	32	NA	476	China	[22]
2013	2011	KPC-3; VIM-2	pl; chr	TEM-1; SHV-1	*K. pneumoniae* (1)	>8	>8	NA	NA	NA	Italy	[23]
2013	2010	KPC-2; VIM-24	pl; pl		*K. pneumoniae* (1)	2	≤0.5	NA	NA	20	Colombia	[24]
2013	2012	NDM-1; OXA-181 NDM-5; OXA-181	pl; pl pl; pl	CTX-M-15 CTX-M-15	*K. pneumoniae* (1) *K. pneumoniae* (1)	>32 >32	>32 >32	>32 >32	NA NA	29 231	Singapore	[25]
2014	2012	NDM-1; IMP-4 NDM-1; IMP-4	pl; pl pl; pl	TEM-1; SHV-1 TEM-1; SHV-12	*K. pneumoniae* (1) *K. pneumoniae* (1)	>32 >32	>32 >32	NA NA	NA NA	1043 571	China	[26]
2014	2011 2010	KPC-2; IMP-4 KPC-2; IMP-4	pl; pl pl; pl	TEM-1 CTX-M-15	*K. pneumoniae* (4) *K. pneumoniae* (1)	>32 32	>32 >32	>32 >32	NA NA	395 890	China	[27]
2014	2012	NDM-1; KPC-2	NA		*K. pneumoniae* (2)	NA	>512	NA	NA	NA	Pakistan	[28]
2014	2013	NDM-1; OXA-232	NA; pl		*K. pneumoniae* (1)	NA	NA	NA	NA	14	USA	[29]
2014	2014	NDM-1; OXA-232	NA; pl		*K. pneumoniae* (2)	>32	>32	>32	NA	14	France	[30]
2014		NDM-1; OXA-48	pl; pl	CTX-M-15; CMY-16; TEM-1; SHV-1	*K. pneumoniae* (1)	4	≥16	≥8	≥4	101	Switzerland	[31]
2012	2004	VIM-2; VIM-11; GES-5 VIM-2; VIM-11; GES-5 VIM-11; GES-5	chr; chr; pl chr; chr; chr chr; chr/pl	OXA-2	*P. aeruginosa* (1) *P. aeruginosa* (1) *P. aeruginosa* (4)	NA NA NA	NA NA NA	NA NA NA	NA NA NA	NA NA NA	Mexico	[32]
2012	2009	KPC-2; IMP-18	NA	TEM; OXA-1	*P. aeruginosa* (1)	NA	NA	NA	NA	NA	Puerto Rico	[33]

Table 1 (continued)

Year of publication	Year of isolation	Combination of carbapenemases	Gene location	Other β-lactamases	Host (no.)	Carbapenem MICs (mg/L)				ST	Origin	Reference
						Im	Mer	Ert	Dor			
2012	2010	KPC-2; VIM-2	chr; chr+pl		*P. aeruginosa* (1)	>32	>32	NA	NA	111	Colombia	[34]
2014	2004–2005	IMP-18; VIM-2	chr; chr		*P. aeruginosa* (96)	NA	NA	NA	NA	NA	Costa Rica	[35]
2014	1998–2012	KPC-2; SPM-1	NA		*P. aeruginosa* (9)	NA	NA	NA	NA	NA	Brazil	[36]
	2011	KPC-2; SPM-1; VIM-2	NA		*P. aeruginosa* (1)	64	32	NA	NA	NA		
2006	2002	OXA-51; OXA-58	pl; pl		*A. baumannii* (12)	8 to>128	2 to>128	NA	NA	NA	Greece	[37]
2012	2011	OXA-23; OXA-58	NA		*A. baumannii* (1)	NA	NA	NA	NA	106	Greece	[38]
2011	2010	OXA-23; OXA-66	chr; chr	TEM-1	*A. baumannii* (2)	NA	NA	NA	NA	2	Romania	[39]
	2010	OXA-23; OXA-66	chr; chr	TEM-1; PER-1	*A. baumannii* (3)	>32	>32	NA	>32	2		
	2010	OXA-23; OXA-66	chr; chr	TEM-1	*A. baumannii* (2)	NA	NA	NA	NA	2		
	2009–2010	OXA-23; OXA-69	chr; chr		*A. baumannii* (3)	NA	NA	NA	NA	1		
	2009	OXA-23; OXA-69	chr; chr		*A. baumannii* (1)	>32	>32	NA	24	1		
	2010	OXA-58; OXA-64	chr; chr		*A. baumannii* (1)	NA	NA	NA	NA	110		
	2010	OXA-58; OXA-69	chr; chr		*A. baumannii* (1)	NA	NA	NA	NA	1		
2011	2009	OXA-72; OXA-90	NA		*A. baumannii* (33)	32–128	128–256	NA	NA	NA	Croatia	[40]
2006	2004–2005	VIM-1; OXA-58; OXA-66	NA		*A. baumannii* (2)	8–32	4	NA	NA	NA	Greece	[41]
		VIM-1; OXA-66	NA		*A. baumannii* (2)	4 to>32	2–32	NA	NA	NA		
2008	2005–2006	VIM-1; OXA-51; OXA-58	chr; NA		*A. baumannii* (6)	16–32	16–32	NA	NA	NA	Greece	[42]
2008	2005–2007	VIM-1; OXA-58; OXA-66	chr; pl; chr		*A. baumannii* (21)	16–64	8–64	NA	NA	NA	Greece	[43]
		VIM-4; OXA-58; OXA-69	chr; pl; chr		*A. baumannii* (6)	8–16	4–16	NA	NA	NA		
		OXA-58; OXA-69	pl; chr		*A. baumannii* (2)	16–32	8–32	NA	NA	NA		
2012	2010	IMP; VIM	NA		*A. baumannii* (1)	NA	NA	NA	NA	NA	India	[44]
2011	2010	NDM-1; VIM-4; OXA-181	pl; NA; NA	CTX-M-15; TEM-1; OXA-1/-9/-10; CMY	*C. freundii* (1)	>32	>32	>32	NA	NA	India	[45]
2013	NA	NDM-1; OXA-48	pl; pl	CTX-M-15; OXA-2	*E. ludwigii* (1)	32	32	16	NA	NA	India	[46]
2011	2009	NDM-1; OXA-48	NA	CTX-M-15	*E. cloacae* (2)	8	NA	>4	NA	NA	India	[47]
2014	2012	NDM-1; OXA-48	pl; pl	CTX-M-15	*E. coli* (25)	64	64	8	NA	NA	India	[48]
2011	2009	SIM-1; OXA-23	pl; pl		*A. baylyi* (1)	≥32	≥32	NA	NA	NA	China	[49]
2011	2009	KPC-2; IMP-8	pl; pl		*K. oxytoca* (1)	>32	NA	>32	NA	NA	China	[50]
2014	2013	NDM-1; KPC-2	pl; chr	CTX-M-15; TEM-1	*E. cloacae* (1)	16	16	256	NA	NA	Brazil	[51]
2014	2013	NDM-1; KPC-2	pl; pl	CTX-M-15; TEM-1; OXA-1; ACT-7	*E. hormaechei* (1)	≥32	≥32	≥32	NA	NA	Brazil	[52]
2008	NA	VIM-11; IMP-8	chr; chr		*S. marcescens* (1)	NA	NA	NA	NA	NA	Taiwan	[53]
2010	2005–2007	VIM-2; IMP-1	NA		*A.* genomosp. 10 (3)	32	16–32	NA	NA	NA	S. Korea	[54]
		VIM-2; SIM-1	chr; chr		*A.* genomosp. 10 (1)	32	32	NA	NA	NA		
		IMP-1; SIM-1	NA		*A.* genomosp. 10 (1)	64	128	NA	NA	NA		

ST: Sequence type; NA: not available; pl: plasmid; chr: chromosome; Im: imipenem; Mer: meropenem; Ert: ertapenem; Dor: doripenem

MBL-producing *P. aeruginosa* was announced the same year from Cali, Colombia. This isolate was found to be positive for KPC-2 and VIM-2 carbapenemases [34].

The aforementioned sporadic reports were followed by two large studies, with striking results. In a major hospital in San José, Costa Rica, 125 carbapenem-resistant isolates were studied. Among them, 102 were found to be MBL-producers and, surprisingly, 96 (94.1 %) co-harbored $bla_{\text{IMP-18}}$ and $bla_{\text{VIM-2}}$ [35].

In another study from São Paulo, Brazil, 129 carbapenem-resistant clinical isolates recovered over a 12-year period (from 1998 to 2012) were evaluated for the presence of carbapenemase genes. Nine isolates carried both SPM-1 and KPC-2 carbapenemases, while a single isolate recovered in 2011 was found to bear a triple combination of SPM-1, KPC-2, and VIM-2 [36].

Acinetobacter baumannii

Various combinations of OXA-type carbapenemases have been identified in *A. baumannii* isolates in the Balkan Peninsula from 2006 to 2012 [37–40]. More clinically significant however is to be considered the concomitant presence of an MBL with OXA-type-carbapenemases. Many isolates bearing such combinations have been found in Greece. In 2006, two *A. baumannii* bearing VIM-1+OXA-66 and two more bearing VIM-1+OXA-58+OXA-66 were isolated from Thessaloniki and Larisa [41]. Subsequently, in a study from Piraeus published in 2008, six genetically related clinical isolates recovered throughout the period 2005 to 2006 were found to bear OXA-51, OXA-58, and VIM-1, despite the fact that the presence of the MBL was undetectable by imipenem-EDTA synergy tests [42]. In another research work, all imipenem-resistant *A. baumannii* isolates (n=31) recovered consecutively from the clinical specimens of separate patients in the ICU of Serres hospital during the period between April 2005 to March 2007 were assessed for the presence of carbapenemases. Four distinct clones were identified: the first contained $bla_{\text{VIM-1}}$, $bla_{\text{OXA-58}}$ and the intrinsic $bla_{\text{OXA-66}}$ gene; the second contained $bla_{\text{VIM-4}}$, $bla_{\text{OXA-58}}$, and the intrinsic $bla_{\text{OXA-69}}$ gene; the third contained $bla_{\text{OXA-58}}$ and the intrinsic $bla_{\text{OXA-69}}$ gene; and the fourth contained only the intrinsic $bla_{\text{OXA-66}}$ gene [43].

In Chennai, India, 179 non-fermenting clinical isolates of a 1,600-bed university teaching hospital recovered from April to October 2010 were tested by PCR for bla_{IMP} and bla_{VIM}. Among 116 *A. baumannii*, 53 carried the bla_{VIM}, whereas one single isolate harbored both bla_{IMP} and bla_{VIM} [44].

Multiple carbapenemases in other species

Other Gram-negative species co-harboring more than one carbapenemase have been reported sporadically since 2008, mostly from endemic areas. An NDM-1, VIM-4, and OXA-181 *Citrobacter freundii* [45], an NDM-1+OXA-48 *Enterobacter ludwigii* [46], two *Enterobacter cloacae* [47], and 25 *Escherichia coli* [48] were isolated from patients hospitalized in India. A SIM-1+OXA-23 *Acinetobacter baylyi* [49] and a KPC-2+IMP-8 *Klebsiella oxytoca* [50] were found in China. An NDM-1+KPC-2 *Enterobacter cloacae* [51] and an *Enterobacter hormaechei* [52] with the same carbapenemase combination were reported from Brazil. To date, the only DCP (VIM-11+IMP-8) *Serratia marcescens* was detected in Taiwan [53] and all different coupling combinations of VIM-2, IMP-1, and SIM-1 MBLs were found in DCP *Acinetobacter* genomospecies 10 in South Korea [54].

Discussion

The origin of the beta-lactamase-encoding genes is not yet clearly understood, even though their global spread has been well documented [55]. Especially, the dissemination of carbapenemases among Gram-negative nosocomial pathogens is a health problem of major importance. It is probably too soon to predict the impact of the emergence of MCP strains; however, certain reflections may already arise.

Not all carbapenemases, for example, inactivate all beta-lactam antibiotics, leaving some limited treatment options for clinicians. Combined together in a single isolate, their overall hydrolytic spectrum becomes wider and the available antibiotics even fewer. This is clear, for example, for isolates that once harbored an MBL and subsequently acquired a KPC, becoming fully resistant even to aztreonam, which could have remained active without the presence of the second carbapenemase.

Another treatment option for carbapenemase-producing strains is the combined administration of a carbapenem together with an aminoglycoside, a polymyxin, or tigecycline, in case the carbapenem MIC is ≤4 mg/L [56]. This obviously becomes less probable of occurring in the co-presence of two or more carbapenemases, especially when at least a KPC or an MBL are included.

What also needs consideration are the expression levels of carbapenemase-encoding genes in different isolates even of the same species. Diminished expression levels are thought to contribute to silent dissemination within hospital settings because carbapenem MICs remain low and phenotypic tests may result negative. Carbapenem or combined treatment may be successful in these cases, but with the addition of more carbapenemases in its genetic armamentarium, such an isolate may probably increase its carbapenem MICs to much more higher levels.

The majority of the carbapenemase-encoding genes that have been detected in MCP isolates are located in transferable genetic elements and are capable of horizontal gene transfer.

Consequently, the presence, not to mention the evolutionary success, of MCPs within hospitals will lead to the enrichment of the resistance gene pool in a niche where the evolutionary pressure mediated by antibiotics is constant.

The accumulation of carbapenem resistance mechanisms in MBL-producing *P. aeruginosa* under long-term carbapenem use within a Greek hospital has been recently observed [57]. This, combined with the fact that most reports of MCP isolates are from geographic areas where carbapenemases have been largely disseminated, such as the Indian subcontinent, the Balkans, China, and Latin America, could support that the shielding of Gram-negatives against beta-lactam antibiotics will not remain limited to the acquisition of a single carbapenemase-encoding gene, even though this was thought to be "enough bad" some years ago.

Conflict of interest None to declare.

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