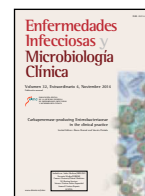




Enfermedades Infecciosas y Microbiología Clínica

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Epidemiology of infections caused by carbapenemase-producing Enterobacteriaceae: Reservoirs and transmission mechanisms

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ABSTRACT

Keywords:

Carbapenemases
Successful clones
Cross-border clones

The dissemination of carbapenemase-producing Enterobacteriaceae has occurred very quickly and has crossed borders rapidly between countries and continents. In some areas, it has exceeded the holding capacity of health systems, reaching epidemic proportions. This form of dissemination has not been the same for all enzymes, with KPC, NDM and OXA-48 genes having a greater ability to spread. These enzymes have primarily been spread clonally in the case of KPC-producing *Klebsiella pneumoniae* from the initial epicenter located in New York, with a very small number of strains causing outbreaks. For NDM and OXA-48, these resistance determinants have been vehiculated by clones with a high transmission capacity; however, simultaneous horizontal transmission is also playing an important role. The most important identified reservoirs are colonized or infected individuals from endemic areas or centers with outbreaks, but the contaminated goods from these endemic areas also play a part. An international effort is needed to control the spread of these multiresistant pathogens.

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Epidemiología de las infecciones causadas por enterobacterias productoras de carbapenemasas: reservorios y mecanismos de transmisión

RESUMEN

Palabras clave:

Carbapenemasas
Clones competentes
Clones transfronterizos

La diseminación de enterobacterias productoras de carbapenemasas ha sucedido muy deprisa y ha cruzado rápidamente los límites entre países y continentes. En algunas áreas ha excedido la capacidad de manejo de los sistemas sanitarios, alcanzando proporciones epidémicas. Esta forma de diseminación no ha sido la misma para todas las enzimas, siendo los genes KPC, NDM y OXA-48 los que tienen una mayor capacidad de diseminación. Estas enzimas se han extendido principalmente de forma clónica en el caso de la *Klebsiella pneumoniae* productora de KPC desde el epicentro inicial localizado en Nueva York, con un número muy pequeño de cepas causantes del brote. En el caso de NDM y OXA-48, estos determinantes de resistencia han sido vehiculizados por clones con una alta capacidad de transmisión; no obstante, la transmisión horizontal simultánea está jugando también un papel importante. Los reservorios identificados más importantes son los individuos colonizados o infectados procedentes de las áreas o centros epidémicos con brotes, pero los productos contaminados procedentes de estas áreas también juegan un papel. Se necesita un esfuerzo internacional para controlar la diseminación de estos patógenos multirresistentes.

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Introduction

The emergence of Enterobacteriaceae producing carbapenemases represents a challenge for health systems worldwide. This emergence has occurred within a very short timeframe: over only the last 5 or 6

years in most cases. At present, the epidemiology of carbapenemase producers appears to be different from their multiresistant extended-spectrum beta-lactamase (ESBL)-producer predecessors. The primary difference lies in their marked clonal spread, particularly in the case of producers of KPC enzymes, but also in NDM and VIM enzymes, with the exception of OXA-48-like enzymes. In the case of ESBL, clonal expansion coexists with a more significant horizontal spread among multiple lineages and interspecies. Second, as at the beginning of the emergence of ESBL producers in early 1990s, the

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most important species associated with the spread of these resistance determinants is *Klebsiella pneumoniae*.¹ Finally, unlike what occurs with the *bla*_{ESBL} genes that have been captured in different genetic platforms,² carbapenemase genes are currently vehiculated by a reduced number of plasmids and transposons. These peculiar features (the acquisition of successful multiresistant platforms by highly penetrant clones) have led to their rapid global expansion. The biological aspects of this dissemination have been fuelled by international travel and immigration from endemic areas, as reviewed below.

Chronicle of a vertiginous expansion

KPC enzymes

The speed with which carbapenem resistance has spread in *K. pneumoniae* has often exceeded the capacity of governments and health institutions to react. Thus far, the most widespread carbapenemase gene has been KPC. This type of enzyme has spread due to the rapid expansion of a few clones of *K. pneumoniae*. The first report of KPC-producing isolates was in North Carolina in 2001.³ Several studies in 2004 showed that the epicenter was located in New York, and the same clone was involved in producing both KPC-2⁴ and KPC-3.⁵ Outside the United States, these New York strains were reported in France in 2005 in a patient with links to the USA⁶ and in 3 patients not linked to the USA, in Colombia⁷ and China.⁸ Five years after they were first detected, the first large outbreaks caused by the same strain outside the New York area occurred in hospitals in Brazil,⁹ Greece¹⁰ and Israel.¹¹

In Europe, primarily sporadic infections and their corresponding secondary cases were reported in Northern¹² and Western European countries^{13,14} as a result of import cases returning from Israel, Greece and the USA. In Italy, transmissions from Israel soon reached epidemic proportions,¹⁵ thus Italy became yet another documented source of imports to other European countries.¹⁶⁻¹⁸ The detection of KPC in China occurred as early as in the West (2006), but distinct genetic environments,¹⁹ plasmids⁸ and allelic variant²⁰ of the USA strains were identified. The spread in Asiatic countries is less known, but appears to be a clonal spread of ST11.²¹

Metallo carbapenemases

The transmission is not as global for metallo carbapenemases, but is present in several regions. VIM-producing *K. pneumoniae* isolates were first detected in East Asia.²² VIM type enzymes were broadly spread in *P. aeruginosa* isolates in several locations in Mediterranean countries at the end of the 20th Century.²³ Acquisition of this resistant determinant by *K. pneumoniae* later occurred almost immediately along the entire Mediterranean basin.^{24,25} An epidemic scenario that developed in Greek intensive care units during 2005-2006 was caused by 3 major clonal complexes, one of which was an international strain of ST147.²⁶ As in the case of KPC, import transfer from Greece was documented as initiating outbreaks in other European countries.²⁷ Regarding IMP-producing *K. pneumoniae*, outbreaks caused by IMP producers were found centered in Japan²⁸ and in neighboring countries such as South Korea, Taiwan, China²⁹ and Australia.³⁰ Only single reports were found outside of Asia.

Unlike the above, which concerns metallo carbapenemases, the spread of NDM enzymes has been explosive. The ongoing epicenter is the Indian subcontinent, where a high prevalence has been detected in the close environment, including in tap water.³¹ Its global spread has been clearly attributed in most cases to patients acquiring NDM genes from the Indian subcontinent.³² A secondary source of importation has been related to the central Balkans.³³ These determinants have actively spread both on a horizontal level³⁴ and through international *K. pneumoniae* strains such as ST11, ST340 and

ST147 from South Asia to Europe,³⁵ China³⁶ and Oceania.³⁴ Until recently, outbreaks outside India had been locally controlled, but a large ongoing outbreak in Greece³⁷ and active transmission in China³⁸ could change the course of the prevalence of these determinants.

OXA enzymes

The epidemiology of OXA-48 is completely different from what we have observed with other carbapenemases. First described in Turkey in 2001,³⁹ OXA-48 producers were identified soon after in North Africa and Europe.⁴⁰ The primary focus of transmission appears to be from North Africa, and several international transfers to Europe have been documented by colonized patients from African countries⁴¹ and Turkey.⁴² Important outbreaks have been reported in European countries,⁴³⁻⁴⁵ although these episodes could not be reliably linked with endemic areas. Although some clones are predominant in certain countries, such as ST395 in France⁴³ and ST405 in Spain,⁴⁶ different lineages could be recovered simultaneously in the same area.⁴⁷ Furthermore, species other than *K. pneumoniae* frequently vehiculated OXA-48-like enzymes,⁴⁰ indicating that horizontal transmission likely plays a more important role than clonal spread.

The role of particular clones

In view of the epidemiological behavior of carbapenemase producers, several questions concerning the international clones arise. Woodford et al posed the question regarding whether those clones were previously successful or if the acquisition of resistance led to their success.⁴⁸ In the database of MLST for *K. pneumoniae*, more than 1570 sequence types are now identified, but only certain STs (ST147, ST383 and ST101) and clonal complexes (CC258/340, CC15/14 and ST405/663) appear to disseminate carbapenemase genes.

Clonal complexes (CCs) have been defined as sequence types with an allelic difference in no more than one locus from at least one other profile. There is a large CC comprising 96 STs (CC292), with ST292 as the predicted founder.⁴⁸ This CC includes many internationally prevalent and multiresistant STs, including STs of the ST258/340 cluster (ST258, ST340, ST437, ST512 and ST11) and cluster ST14/15. The worldwide dissemination of KPC has been associated with ST258 in the USA, Israel and Greece; with ST437 in South America; with ST11 in East Asia; and more recently with ST512 in Europe (Table 1). Isolates belonging to ST11 have been most frequently implicated in the international spread of NDM-1, but other enzymes also contribute, such as the VIM and OXA-48 type. ST15 has been found in the cross border transmission of the OXA-48 gene in Europe and North America and ST340 in the dissemination of NDM-1.³⁵

Several efforts have been made to study virulence traits, including whole genome (WG) approaches, with the aim of understanding the success of complex 258. In a mouse septicemia model, Tzouveleakis et al found that the strain was virtually avirulent.⁴⁹ A comparative study of the ST258 genome and a non-epidemic strain showed that genes related to cell motility, the secretion group and DNA repair were unique to ST258 isolates.⁵⁰ Notably, some of these particular genes were plasmid-encoded and were carried by all isolates despite variability in plasmid content.

Concerning CC258, *K. pneumoniae* ST147 can be found on 5 continents, capturing genes of class A, B and D enzymes (Table 1).^{15,36,51,52} ST101, however, appears to be confined to the Mediterranean basin⁴⁷ and cases imported to Northern European countries.⁵³ Finally, ST405 and its allelic variant ST663 has only been found to date in Spain, causing inter-hospital spread.⁴⁶ In the case of *Escherichia coli*, previously successful clones such as ST131,^{54,55} ST410⁵⁶ and ST101⁵⁷ have been prone to capture plasmids vehiculating NDM, VIM, KPC and OXA-48 genes in various locations. Some of these successful *E. coli* clones were previously well known as ESBL producers. In

Table 1
Distribution of carbapenemase-producing successful clones of *Klebsiella pneumoniae*

Area	ST	Enzyme	Country (year of isolation*)
North America	ST258	KPC-2	USA (2007), ⁹⁰ Canada (2008), ⁵¹ Puerto Rico (2010) ⁹¹
		KPC-3	USA (2007), ⁹⁰ Canada (2009) ⁵¹
	ST340	NDM-1 + KPC	Canada (2010) ⁹²
	ST147	NDM-1 + KPC	Canada (2010) ⁹²
	ST15	OXA-48	USA (2010) ⁵¹
Latin America	ST258	KPC-2	Brazil (2007), ⁹³ Argentina (2008) ⁹⁴
		KPC-3	Mexico (2010) ⁹⁵
	ST11	KPC-2	Brazil (2006) ⁹⁶
		OXA-48	Argentina (2010) ⁵¹
	ST437	KPC-2	Brazil (2010) ⁹⁶
Europe	ST258	KPC-2	Norway (2007), ⁷⁰ Hungary (2008) ⁹⁷
		KPC-3	UK (2007), ¹³ Sweden (2008) ¹²
	ST512	KPC-3	Italy (2009), ⁹⁸ Czech Republic (2011), ¹⁸ Spain (2012) ¹⁷
	ST11	KPC-2	Poland (2009), ⁹⁹ UK (2011) ¹⁰⁰
		NDM-1	Greece (2010), ³⁷ UK (2012), ³⁵ Sweden (2012) ³⁵
		VIM type	Hungary (2009), ¹⁰¹ Spain (2010), ¹⁰² Czech Republic (2011) ¹⁸
		OXA-48	Greece (2011), ³⁷ Spain (2011) ⁴⁶
		ST340	UK (2012), ³⁵ Sweden (2012) ³⁵
		ST147	Italy (2009), ¹⁵ Greece (2009) ¹⁰³
		NDM-1	Finland (2010), ⁵³ UK (2012) ³⁵
		VIM types	Denmark (2005), ⁹⁴ Sweden (2005), ⁵¹ Finland (2010), ⁵³ Greece (2010), ¹⁰⁴ Italy (2014) ¹⁰⁵
		ST101	Finland (2011) ⁵³
		KPC-2	Spain (2012) ⁴⁶
		ST15	UK (2008) ⁴⁵
Western Asia	ST405	OXA-48	Spain (2011) ⁴⁶
	ST258	KPC-3	Israel (2006) ¹⁰⁶
		KPC-3	Israel (2006) ¹⁰⁷
	ST340	KPC-2	Israel (2006) ¹⁰⁸
	ST11	OXA-48	Turkey (2012) ⁵¹
		NDM-1	United Arab Emirates (2009) ¹⁰⁹
	ST147	OXA-48	Turkey (2007) ⁵⁴
South Asia	ST11	NDM-1	India (2012) ³⁴
	ST147	NDM-1	India (2013) ⁵¹
		OXA-48 like	India (2013) ⁵¹
East Asia	ST258	KPC-2	Korea (2013) ¹¹⁰
	ST11	KPC-2	China (2006), ²⁰ Taiwan (2010), ¹¹¹ Singapore (2011), ²¹ Japan (2012) ¹¹²
	ST147	NDM-1	China (2011) ³⁶

*Year of publication when isolation date was not available.

particular, the ST131 *E. coli* clone had been previously found predominantly carrying *bla*_{CTX-M-15}.⁵⁸ It has subsequently been observed that the ST131 *E. coli* clone not only prevails between CTX-M-15 producers, but also predominates among all types of clinical *E. coli* isolates in national surveys in Spain⁵⁹ and the USA.⁶⁰

Reservoirs and routes of transmission

As we have seen, clonal expansion is a major cause of carbapenemase genes increasing in the case of KPC and metallo carbapenemases, but it is less significant in the cases of OXA-48-like genes. Several reservoirs should be considered depending on the frequency with which carbapenemase producers are found in a given

area: endemic regions or regions with low or very low prevalence. In the latter, we must differentiate between outbreak situations in hospitals and isolated cases.

KPC producers

In the case of KPC, the primary reservoirs are the colonized patients transferred from long-term facilities, institutions with outbreaks or readmissions. In a multicenter study in the metropolitan area of Chicago, it was observed that patients from nursing homes or long-term facilities were more likely to be colonized, whereas none of the community patients were colonized.⁶¹ We currently have very few studies of carriers outside hospital outbreak situations. The

studies that have been performed showed no evidence of KPC dissemination in the community to date in the USA⁶¹ or Switzerland.⁶² Nor is there evidence that dissemination occurs through the food chain, but some cases of patients infected with KPC-2-producing *Salmonella* strains have been documented in the USA⁶³ and Colombia.⁶⁴ Although KPC-producing *E. coli* has occasionally been detected in a river in Portugal,⁶⁵ the precise origin of this finding is unknown, and environmental contamination appears to be exceptional.

In many cases, transfer of a colonized patient has been the origin of an outbreak in countries with very low prevalence,^{13,14} although in many other countries there has been no transfer identified. In an active survey performed in the Paris area, 10 events involving colonized/infected patients led to outbreaks during 2004-2011 and 6 were initiated by patients repatriated from foreign hospitals.⁶⁶ The persistence of intestinal carriage after hospital discharge can last up to 1 year, and multiple hospitalizations could extend the duration of KPC carriage.⁶⁷ Once introduced into a hospital, the vicinity of colonized patients is often contaminated, with the bed area the most contaminated site.⁶⁸ Although the patient's environment is more likely to be colonized, other environmental sites could serve as secondary reservoirs. In a hospital in Chicago, surveillance cultures of the surfaces of a ward with positive clinical cases yielded low frequencies of colonization (0.5%).⁶⁹ However, the point of these studies is to discern whether environments reflect transient or permanent reservoirs. In a long-term low-frequency outbreak in Norway, a persistent colonization of sinks with isolates harboring a KPC-2 plasmid prolonged maintenance of the outbreak, which initially was linked with a patient who was previously hospitalized abroad.⁷⁰ Personnel and healthcare worker (HCW) attire during routine care could also be a vehicle, as has been proven with other nosocomial pathogens. In a study conducted in Baltimore, 10% of HCW-patient interactions resulted in contamination with KPC-producing *K. pneumoniae* of HCW gloves or gowns.⁷¹ The colonization of HCWs has been scarcely studied, but some colonized individuals have been found in outbreak situations.⁷²

Metallo carbapenemases

In the group of metallo carbapenemases, we should distinguish the various epidemiological behaviors for each type of enzyme. In the case of IMP, hospital outbreaks are primarily associated with exposure of critically ill patients to hidden and primarily moist environmental reservoirs. Among reservoirs associated with IMP-producing Enterobacteriaceae are showers at 2 burn units in Australia,³⁰ the drains of an ICU in Spain,⁷³ incubators in a neonatal ICU in China,⁷⁴ mechanical ventilators, ICU surfaces and toilets in Tunisia.⁷⁵ In other IMP-causing outbreaks, the potential environmental reservoir has not been further investigated. As far as we know, IMP fecal carriage in humans and animals has only been identified sporadically as is also the case with colonized food, but some isolates have been recovered in the waters of American and Tunisian rivers.⁷⁶ However, the hands of HCWs have only once been associated with an outbreak caused by IMP producers,⁷⁴ and the colonization of HCWs has not been explored.

In the case of VIM, however, both fecal carriers and cross-border spread have been detected, as well as links to the food chain. In an area of Madrid, coinciding with VIM episodes in a tertiary hospital, a prevalence of 1% of fecal carriers was found, showing the capacity of VIM plasmids to disseminate even among non-hospitalized patients, and contributing to the maintenance of outbreaks.⁷⁷ In the south of France in 2009, 2.3% of fecal samples from patients hospitalized with acute diarrhea harbored VIM-producing *Enterobacter* isolates.⁷⁸ In this survey, almost 90% of patients had a previous hospitalization or lived in a nursing home or a healthcare center in the last year. VIM producers have also been involved in episodes initiated by colonized

patients who had a link to a cross-border exchange with North Africa and Greece.⁶⁶ As with other nosocomial pathogens, hospital surfaces could be contaminated in the context of an increase in hospitalized cases.⁷⁵ VIM-producing Enterobacteriaceae have been detected in river samples in Tunisia and Switzerland.⁷⁶ Regarding the food chain, both VIM-producing *Salmonella* and *E. coli* isolates have been recovered from production animals in Germany and caused human *Salmonella* infections in Morocco.⁷⁹

NDM producers show a more ubiquitous distribution and broader dissemination than other metallo carbapenemases, including in the environment, community and goods. The prevalence of NDM carriers in endemic areas such as India and Pakistan reaches figures of 18% among hospitalized patients⁸⁰ and 10% in the community.⁸¹ In this area, a high number of NDM-1 positive isolates were recovered from the Ganges River during seasonal pilgrimages.⁸² Consequently, production animals and vegetables from India were found to be colonized with carbapenem-resistant *Salmonella* isolates,⁸³ although the resistance determinants were not characterized. Human infections caused by NDM-producing *Salmonella* have been reported in a patient transferred from India and in a child from China.⁷⁹ Single or sporadic hospital outbreaks have been reported in many countries that were caused by NDM-producing strains originated from a patient transferred from endemic areas.^{32,66} Although in some outbreaks the causative strain was recovered from the surfaces of the ICU, in-depth studies were not carried out and available data indicate secondary contamination. Other non-human sources have been identified in low-prevalence countries. Clinical samples from companion animals from various locations in the USA recently yielded NDM-1 producers, with no genetic relationship among the isolates.⁸⁴

OXA enzymes

OXA-48 producers appear to be confined to the Mediterranean basin, actively disseminated by similar plasmids. The prevalence of carriers differs between inpatient and nonhospitalized individuals, based on the studies that have been conducted in North Africa. There are currently no studies of asymptomatic carriers in European Mediterranean countries. The figures vary between 13% of hospitalized patients in Morocco⁸⁵ and 1.5% of healthy children in Lebanon.⁸⁶ Similar to NDM, OXA-48 producers have been found in the environment of endemic countries, such as puddles around Marrakech,⁸⁷ leading most likely to community acquired and zoonotic infections. In a collection of isolates recovered from community acquired urinary tract infections in Morocco, almost 4% were OXA-48-producing strains.⁸⁸ On the other hand, *Salmonella* infections have been reported in patients returning from Egypt, Morocco and Syria.⁷⁹ Eight OXA-48 *E. coli* and *K. pneumoniae* producers were isolated from dogs admitted to a veterinary clinic in Germany, however, specific epidemiologic features were not available.⁷⁹ Transfer from endemic areas has been well documented, but large outbreaks have also been described that have no link to Northern Africa.⁴⁴ In the case of OXA-48, the duration of colonization is unknown, but it must play an important role.⁸⁹ A significant inter-hospital spread of ST405 has occurred in Madrid, where recurrent hospitalizations appear to permit the perpetuation of spread, rather than from a potential environmental reservoir.^{44,46} Nevertheless, the survival of OXA-48-producing Enterobacteriaceae has been documented until one month later than detection of clinical cases.⁷⁴

Final remarks

The current scenario with carbapenemase-producing Enterobacteriaceae shows the beginning of a spread, which tend to stabilize. Clonal dissemination of carbapenemase-producing *K. pneumoniae* and *E. coli* isolates is favored by the increased flow of

people and goods among countries and continents. The contribution of other environmental bacteria is unknown. As Woodford et al have noted,⁷⁶ efforts on several fronts must be undertaken to prevent a dissemination that could be similar to that of ESBL producers.

Conflicts of interest

The authors have no conflicts of interest to declare.

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