



# Enfermedades Infecciosas y Microbiología Clínica

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## Carbapenemase-producing Enterobacteriaceae: The end of the antibiotic era?

Álvaro Pascual<sup>a,b,\*</sup>, Vicente Pintado<sup>c</sup>, Jesús Rodríguez-Baño<sup>a,d</sup> and José María Miró<sup>e</sup>

<sup>a</sup>Unidad de Enfermedades Infecciosas y Microbiología Clínica, Hospitales Universitarios Virgen Macarena y Virgen del Rocío, Sevilla, Spain

<sup>b</sup>Departamento de Microbiología, Universidad de Sevilla, Sevilla, Spain

<sup>c</sup>Servicio de Enfermedades Infecciosas, Hospital Universitario Ramón y Cajal, Madrid, Spain

<sup>d</sup>Departamento de Medicina, Universidad de Sevilla, Sevilla, Spain

<sup>e</sup>Servicio de Enfermedades Infecciosas, Hospital Clínic-IDIBAPS, Universidad de Barcelona, Barcelona, Spain

### ABSTRACT

#### Keywords:

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Antimicrobial resistance

Infections produced by carbapenemase-producing Enterobacteriaceae (CPE) are increasing worldwide. Therapeutic options are scarce because many of these bacteria are resistant to other antimicrobial groups. Furthermore, the dissemination of some carbapenemases and CPE is occurring rapidly. Health care authorities should be aware of the relevance of this problem, and coordinated surveillance and control strategies at all levels of the health system should be undertaken. The Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC) and The Spanish Network for Research on Infectious Diseases (REIPI, Institute of Health Carlos III, Ministry of Health, Spain) has selected a panel of Spanish experts on infections caused by CPE from the areas of clinical microbiology, infectious diseases and public health to review and discuss the most controversial issues regarding this increasing threat.

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### Enterobacterias productoras de carbapenemasas: ¿el fin de la era antibiótica?

#### RESUMEN

#### Palabras clave:

Carbapenemasas  
Enterobacterias  
Resistencia antimicrobiana

Las infecciones causadas por enterobacterias productoras de carbapenemasas (EPC) están aumentando en el mundo entero. Las posibilidades terapéuticas son escasas, puesto que estas bacterias suelen ser resistentes a diferentes grupos de antibacterianos. Además, la diseminación de algunos tipos de carbapenemasas y de EPC está ocurriendo con mucha rapidez. Las autoridades sanitarias deberían ser conscientes de la relevancia de este problema y coordinar medidas de vigilancia y control en todos los ámbitos sanitarios. La Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC) y la Red Española de Investigación en Patología Infecciosa (REIPI; Instituto de Salud Carlos III, Ministerio de Sanidad, España) han seleccionado un panel de expertos en infecciones producidas por EPC que provienen del campo de la microbiología clínica, enfermedades infecciosas y salud pública para revisar y discutir los aspectos más controvertidos de esta amenaza.

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Antimicrobial resistance constitutes one of the most relevant public health problems worldwide.<sup>1</sup> In the USA, the estimated minimum number of illnesses and deaths caused by antimicrobial resistance in 2013 were 2,049,442 and 23,000, respectively.<sup>2</sup> In Europe, the number of deaths in 2007 caused by antimicrobial resistant bacteria was 25,100, and the estimated yearly economic burden of infections due to selected antimicrobial resistant bacteria was €1.5 billion.<sup>3</sup> Antimicrobial resistance has been increasing for decades in both Gram-positive and Gram-negative bacteria. Although

antimicrobial resistance in Gram positives is worrisome, there remain some therapeutic alternatives for the treatment of infections caused by these microorganisms, and some drugs active against these microorganisms are being developed. Nevertheless, antimicrobial resistance in Gram negatives is a real threat complicated by the fact that almost no therapeutic treatments are expected for the next decade.

Carbapenems are the most potent group of antimicrobial agents available. Carbapenems are commonly used for the treatment of severe nosocomial infections caused by multidrug-resistant (MDR) *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Carbapenems are also the treatment choice for invasive infections caused by extended-spectrum beta-lactamase-producing (ESBL)-

\*Corresponding author.

E-mail address: apascual@us.es (A. Pascual).

Enterobacteriaceae.<sup>4</sup> As a consequence of their use and other factors, carbapenem-resistant Gram negative bacteria developed rapidly.<sup>5</sup> Infections caused by carbapenem-resistant *P. aeruginosa* and *A. baumannii* are a significant problem in many hospital centers.<sup>6,7</sup> Resistance to carbapenems in these species is usually multifactorial, and extensively resistant (XDR) isolates have been reported elsewhere.

The first report of carbapenemase-producing Enterobacteriaceae (CPE) occurred in 1993.<sup>8</sup> CPE have since been described worldwide as a consequence of the acquisition of carbapenemase genes.<sup>9</sup> In a recent report on antimicrobial resistance published by the Centers for Disease Control and Prevention (CDC), it was established that the urgent threats of antimicrobial resistance in USA were carbapenem-resistant Enterobacteriaceae (CRE), *Clostridium difficile* and drug-resistant *Neisseria gonorrhoeae*.<sup>2</sup>

The carbapenemases described in Enterobacteriaceae belong to 3 beta-lactamase classes: the Amber classes A, B and D.<sup>9</sup> Some class C beta-lactamases showing an extended spectrum against carbapenems have also been reported.<sup>10</sup> The most relevant carbapenemases are the class A carbapenemase KPC and the metallo-beta-lactamases (MBLs) VIM, IMP and NDM.<sup>5,9</sup> In recent years, a high prevalence and dissemination of class D carbapenemases (primarily OXA-48) are being reported in Enterobacteriaceae.<sup>11</sup> All these carbapenemases have been reported in various species, particularly in *Klebsiella pneumoniae* and *Escherichia coli*.<sup>11</sup> As has been reported for ESBL-producing Enterobacteriaceae, the epidemiology of the infections caused by CPE differs according to the species and carbapenemase type.<sup>5</sup> The inclusion of carbapenemase genes in different transferable genetic elements (e.g., transposons, plasmids) favors horizontal transmission.<sup>5,9,11</sup> The acquisition of these mobile genetic elements by some successful clones has rapidly increased its transmission. One of the most striking examples is the international transmission of KPC-producing *K. pneumoniae* belonging to ST-258.<sup>11</sup>

Phenotypic detection of CPE is not easy because many yield minimum inhibitory concentration (MIC) values of carbapenems in the susceptibility range.<sup>11</sup> Thus, the prevalence of CPE is likely underestimated, and we are only detecting the tip of the iceberg. Other CPE, however, are multidrug-resistant because of expressing resistance to other antimicrobial families such as fluoroquinolones and aminoglycosides. Furthermore, combinations of beta-lactamase genes, including two carbapenemases or the combination of an ESBL and a carbapenemase have been reported in the same isolate.<sup>9,11</sup>

In a technical report published by the European CDC (eCDC) in 2013, CPE were detected in 36 of 39 participating European countries.<sup>12</sup> The situation is particularly worrisome in Greece and Italy due to the high prevalence of KPC-producing *K. pneumoniae*, but the problem can arise in other countries if adequate measures are not undertaken.<sup>12</sup> In some countries, such as Israel, the magnitude of the problem was so great that measures at the national level were required to slow it down.<sup>13</sup> Outbreaks caused by MBL and OXA-48 producers have been reported in many other European countries, including Spain.<sup>12</sup>

The first isolation of a CPE in Spain was in 2005,<sup>14</sup> since which the prevalence and characteristics of CPE in our country have rapidly changed. In the first multicentric study developed in Spain in 2009, the prevalence of CPE was as low as 0.04%, and only VIM and IMP-producing isolates were found.<sup>15</sup> In a subsequent report published in 2012, the prevalence had increased several times.<sup>16</sup> The most prevalent carbapenemase was OXA-48, and both KPC and NDM-producing isolates were detected.<sup>16</sup> Since then, several outbreaks caused by various CPE have been reported, including an important outbreak caused by KPC-3-producing *K. pneumoniae* belonging to the ST-512 imported from Italy.<sup>17</sup>

Although there is great variability in susceptibility patterns among the species of CPE, most isolates are resistant to the vast majority of beta-lactams, quinolones and cotrimoxazole, and

treatment options are usually limited to colistin, aztreonam, aminoglycosides, fosfomycin and/or tygecycline.<sup>18-21</sup> Most reports have revealed a high proportion of treatment failures associated with these infections, and the reported mortality rates have ranged from 19% to 72%, which can be even higher in patients with bloodstream infections.<sup>22-25</sup> Clinical studies have found that monotherapy is associated with a high rate of clinical failure and/or increased mortality. Recent reports have suggested that combined antibiotic therapy might be superior to monotherapy for the treatment of severe infections caused by CPE.<sup>22-25</sup> Unfortunately, many of these outbreaks are caused by MDR or XDR isolates (resistant to all antimicrobials active against Gram-negative bacteria) for which the therapeutic alternatives are limited.<sup>26</sup> With the lack of new antimicrobial agents being developed in the near future added to this scenario, it appears that we are finally reaching the end of the antibiotic era. To emphasize this worrisome situation, and by comparison with the classical epidemics of bubonic plague (the "Black Death") and tuberculosis (the "White Plague"), the widespread epidemic of Gram-negative resistance has been named the "Red Plague".<sup>27</sup>

Apart from aggressive campaigns to encourage governments and pharmaceutical industries to join efforts to discover new antimicrobial families, such as the 10 × 20 initiative of the Infectious Diseases Society of America or the activities around the European Antibiotic Awareness Day (eAACD) and other institutions, the possibilities of new antimicrobial agents being developed in the next few years are scarce.<sup>28,29</sup> The antibiotic period could be ending, while a new era based more on the surveillance and control of infections caused by MDR bacteria and antimicrobial stewardship is beginning.

As previously noted, the epidemiology of infections caused by CPE varies according to the bacterial species, clone and carbapenemase class. CPE produce primarily nosocomial outbreaks in which person-to-person transmission plays an important role.<sup>18</sup> Nevertheless, there is an increasing interest on the role of environmental reservoirs in the dynamics of outbreaks caused by CPE when standard control measures are not effective.<sup>30</sup> An active search of potential environmental reservoirs, including sinks and water drainage systems, should be performed in these circumstances.

The threat posed by CPE has caused some regions in Spain to develop guidelines to prevent this phenomenon,<sup>31</sup> but the lack of initiatives at a national level to coordinate these activities is unexplained. The Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), through their Study Groups on Nosocomial Infections (GEIH) and Mechanisms of Action and Resistance to Antimicrobials (GEMARA), has recently published a positioning report exposing the need for a definitive and coordinated reaction by all health professionals and authorities involved, and has encouraged an adaptation of health systems to facilitate the early control of CRE and to minimize their impact.<sup>32</sup>

In this scenario, the SEIMC and the Spanish Network for Research in Infectious Diseases (REIPI, Institute of Health Carlos III, Ministry of Health, Madrid, Spain), have decided to join efforts to develop a high scientific-level supplement to the Spanish journal *ENFERMEDADES INFECCIOSAS Y MICROBIOLOGÍA CLÍNICA*, called the Clinical Impact of Carbapenemases. For this purpose, a representative panel of Spanish experts on infections caused by CPE has been selected from the areas of clinical microbiology, infectious diseases and public health to discuss the most controversial issues regarding this increasing threat.

In this supplement, the primary classes of carbapenemases and the molecular and clinical epidemiology of CPE will be assessed. The evolution of CPE in Spain will be compared with that in other countries. The technical difficulties in detection at different health levels will be evaluated and the most reasonable diagnostic algorithms will be established. The impact of the various breakpoint guidelines in the detection of CPE and in the management of patients

infected by CPE will also be evaluated. From a clinical point of view, the most relevant risk factors for colonization or infection by the most important CPE and the current therapeutic alternatives will be discussed. The potential role of new drugs being developed in the next few years will be critically evaluated. Finally, the most adequate measures to control and prevent the dissemination of CPE at different health levels will be assessed.

The current situation of infections caused by CPE is disturbing, particularly because our health authorities are possibly not aware of the magnitude of the problem. It is therefore imperative to develop greater coordination between the various levels of the health system to address this complex situation. Let us learn from what has occurred in other countries and avoid the same mistakes. There is still time, but each hour that passes without taking the right measures could have severe consequences.

### Conflicts of interest

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J.R.B. has been speaker for and served as scientific consultant for MSD, Pfizer, Novartis, and Astellas, and has received funding for research from Novartis.

V.P. and J.M.M. have no conflicts of interest.

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