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The emerging threat of acquired carbapenemases in Gram-negative bacteria

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Since their introduction into clinical practice, carbapenems have been among the most powerful antibiotics for treating serious infections caused by Gram-negative nosocomial pathogens, including *Enterobactericeae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [1]. Remarkable stability towards most β-lactamases, including the extended-spectrum β-lactamases (ESBLs), is one of the features accounting for the unprecedented broad spectrum of activity exhibited by carbapenems. Therefore, the emergence of β-lactamases with carbapenem-hydrolyzing activity (carbapenemases)—which can confer resistance to carbapenems in major Gram-negative pathogens—is of major clinical concern. This concern is further reinforced by the awareness that carbapenems are the most effective agents for treatment of serious infections caused by ESBL-producing *Enterobacteriaceae* [2,3], which are undergoing a massive increase both in hospitals and in community settings [4].

Carbapenem resistance caused in strains of Gram-negative pathogens by acquired carbapenemases has been reported since the early 1990s [5,6]. However, its prevalence was originally quite limited, with only sporadic cases or small outbreaks being reported in Japan, caused by *P. aeruginosa* and *Enterobacteriaceae* producing IMP-type metallo-β-lactamases (MBLs) [7,8]. A progressive emergence of strains producing different types of MBL has since been observed in several countries from various continents, with an overall increasing trend and some major nosocomial outbreaks [9,10]. However, the clinical impact of Gram-negative pathogens producing carbapenemases remained, overall, limited until the mid-2000s; this is by no means comparable with the pandemic dissemination of ESBL-producing *Enterobacteriaceae* observed during the same period (especially after the emergence of the CTX-M-type enzymes).

More recently, however, the field of carbapenemase research has experienced quite dramatic changes in terms of enzyme diversity and epidemiological patterns. In fact, the repertoire of acquired carbapenemases has become increasingly complex, including not only several different types of MBL (e. g. IMP, VIM, SPM, GIM, SIM, KHM, AIM, NDM and DIM) and allelic variants thereof, but also various types of class A (e.g. KPC, NMC/IMI and SME) and class D (e.g. OXA-23, OXA-24, OXA-48 and OXA-58) serine carbapenemases [11–13]. Also, strains producing some of these enzymes have spread at an alarming rate in some areas, where they have attained a high level of endemicity.

The most paradigmatic examples of rapidly evolving dissemination of carbapenemase-producing strains are represented by *Klebsiella pneumoniae* strains producing KPC-type serine carbapenemases or VIM-type metalloenzymes. The KPC-producing klebsiellae have become a serious clinical problem in several areas of North America, Israel and Greece, and are now emerging in several additional countries in Europe, Latin America and Asia [14]. In the New York area, for instance, the dissemination of *K. pneumoniae* producing KPC enzymes caused an impressive increase in carbapenem resistance rates in this species (from 0.1% to 22%) during the period 1999–2006 [15]. Similar rapid dissemination was observed in Israel, where KPC-producing *K. pneumoniae* strains were first reported in 2004 [16] and subsequently underwent substantial countrywide dissemination, with high rates in some institutions [17] (EARSS results at http://www.rivm.nl/earss/result/). Some clones, such as the one belonging to sequence type 258, have recently been shown to play important roles in the spread of KPC-type enzymes, even at the international and intercontinental levels [18], thus emphasizing the importance of recognizing these 'high-risk multidrug-resistant clones' when tracing the molecular epidemiology of antibiotic-resistant strains. On the other hand, *K. pneumoniae* strains producing the VIM-1 MBL have undergone massive dissemination in Greece since the mid-2000s, and this is the main cause of the impressive increase in carbapenem resistance rates among *K. pneumoniae* strains isolated from that area, with values of non-susceptibility now exceeding 40% [19] (EARSS results at http://www.rivm.nl/earss/result/). Clonal expansion and plasmid-mediated horizontal spread were found to underlie the rapid dissemination

of VIM-1-producing klebsiellae [20], with implications for infection control. Strains of *K. pneumoniae* and other enterobacterial species producing acquired carbapenemases (either KPCs or MBLs) pose remarkable clinical challenges, not only because they often exhibit an extended drug-resistant phenotype for all antibiotics except colistin and tigecycline, but also because, for some of them, the conventional susceptibility tests interpreted according to the current breakpoints may show carbapenem MICs falling in the susceptible range, although at higher than modal levels for strains of the respective species [11]. The latter phenomenon has major implications for the detection and surveillance of similar strains, and raises the obvious question of whether carbapenems can be effectively used for the treatment of serious infections caused by carbapenemase-producing strains with low MIC values.

Similar problems, although with an overall lower impact, are caused by carbapenem-resistant *A. baumannii* strains producing OXA-type carbapenemases, which often remain susceptible only to colistin and have undergone considerable dissemination in some countries [21].

The increasing diversity of acquired carbapenemases, the complex resistance phenotypes typical of these strains, and the growing evidence that carbapenemase-producing strains can rapidly disseminate and attain high prevalence rates has definitively sanctioned the role of carbapenemases as antibiotic resistance determinants of the utmost clinical importance in Gram-negative bacterial pathogens. This has resulted in a growing interest in carbapenemase-producing strains on the part of the scientific community, which is evident from the increase in the number of publications on this subject appearing in the Medline database during recent years (38 in 2000–2002, 58 in 2003–2005, and 134 in 2006–2008, as retrieved from the Medline database at http://www.ncbi.nlm.nih.gov/pubmed/, using the term 'carbapenemase' as query).

An increasing awareness of this problem prompted the ESCMID Study Group for Antibiotic Resistance Suveillance to convene, in late 2005, a meeting of experts to discuss the current European perspective. The meeting, which was held in Siena (Italy), was focused on MBLs, which, at that time, appeared to be the major emerging problem in Europe. As a follow-up to that meeting, the expert panel produced a discussion paper on the emerging problem of MBL producers, in which several open issues were addressed in relation to the detection, surveillance and control of these resistance determinants and to the treatment of infections caused by MBL producers [22]. Since then, the epidemiology of carbapenemase producers has rapidly changed, resulting in major clinical challenges such as the global emergence of KPC-producing strains, the massive dissemination of VIM-producing klebsiellae in some settings, and the diffusion of extended drug-resistant clones of *A. baumannii* producing OXA-type carbapenemases (see above). Thus, in late 2008, the ESCMID Study Group for Antibiotic Resistance Suveillance reconvened a meeting of experts to discuss the most recent developments in the field, with a broader perspective on Gram-negatives producing acquired carbapenemases in general. At that meeting, which was held in Athens (Greece), several issues were discussed concerning the detection, surveillance and control of these emerging resistance determinants, as well as the treatment and outcome of infections caused by carbapenemase-producing strains. As a follow-up to that meeting, the expert panel has prepared two papers, which are grouped as a theme section in this issue of *Clinical Microbiology and Infection*. The papers examine the major challenges posed by carbapenemase producers, and report some consensus recommendations for dealing with specific aspects concerning either the detection and surveillance of carbapenemase-producing Gram-negatives or infection control and treatment strategies.

Transparency Declaration

The authors have no conflicts of interest to declare.

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