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General review

Carbapenemase-producing Enterobacteriaceae: Overview of a major public health challenge

Entérobactéries et carbapénémases : bilan et enjeux d'un problème de santé publique majeur

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Abstract

Bacterial resistance to antibiotics has become a major source of concern for public health. Enterobacteriaceae are among the most common human pathogens, causing community-acquired as well as hospital-acquired infections. Carbapenem-resistant Enterobacteriaceae have been increasingly reported worldwide since their first identification more than 20 years ago. Three main classes of carbapenemases have been identified: Ambler class A beta-lactamase (KPC), class B (metallo-enzymes), and class D (OXA-48 type). *Klebsiella pneumoniae* carbapenemases (KPC) was first reported in the United States in the late 1990s and since then worldwide, with a marked endemicity in the United States, Greece, and now Italy. Carbapenemase NDM-1 (New Delhi metallo-beta-lactamase-1) is one of the most recently reported metallo-enzymes. It has spread widely in the Indian sub-continent and now worldwide. Carbapenemases of the oxacillinase-48 type (OXA-48) have been identified mostly in Mediterranean and southern European countries with a rapid spread. An early and quick identification of carbapenemase-producing infected patients, but also of carriers, is mandatory to prevent the spread of these highly resistant pathogens. The early identification of carriers and implementing of cohorting strategies is the only means to prevent nosocomial outbreaks caused by carbapenemase, with very few, if any, therapeutic options.

Keywords: Enterobacteriaceae; Carbapenemase; Metallo-beta-lactamase; Oxacillinase OXA-48; New Delhi metallo-beta-lactamase-1; *Klebsiella pneumoniae* carbapenemase

Résumé

La résistance bactérienne aux antibiotiques est d'incidence croissante notamment parmi les entérobactéries qui sont les bactéries pathogènes les plus fréquentes pour l'Homme et sont la source de nombreuses infections communautaires et nosocomiales. Des entérobactéries résistantes aux carbapénèmes ont été rapportées avec une fréquence croissante dans le monde depuis leur première description il y a plus de 20 ans. Trois principales classes de carbapénémases ont été décrites : classe A (KPC), classe B (métallo-enzymes) et classe D (OXA-48). Depuis leur première description aux États-Unis à la fin des années 1990, les carbapénémases *Klebsiella pneumoniae* (KPC) ont été observées sur les cinq continents. La plus forte endémicité se situe aux États-Unis, en Grèce, et plus dernièrement en Italie. Parmi les carbapénémases du groupe des métallo-enzymes, New Delhi metallo-beta-lactamase-1 (NDM-1) est de description plus récente. Elle a une prévalence très élevée dans l'ensemble du sous-continent indien. Les carbapénémases de type oxacillinase-48 (OXA-48) ont été rapportées essentiellement dans le pourtour de la Méditerranée et en Europe du Sud où leur diffusion est particulièrement rapide. Pour prévenir l'extension de la diffusion de ces bactéries pathogènes multirésistantes, l'identification précoce et rapide des sujets infectés, mais aussi des patients porteurs, devient une nécessité. Elle permet la mise en œuvre d'une stratégie d'isolement par *cohorting* qui représentent l'unique moyen d'éviter la propagation d'épidémies nosocomiales causées par des souches productrices de carbapénémases, pour lesquelles les possibilités thérapeutiques sont limitées.

Mots clés : Entérobactéries ; Carbapénémases ; Métallo-β-lactamase ; Oxacillinase-48 ; New Delhi metallo-beta-lactamase-1 ; *Klebsiella pneumoniae* carbapénémase

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Bacterial resistance to antibiotics has become a major source of concern for public health. The reality of this menace was fully acknowledged by world decision makers in 2013 at the Davos Economic Forum (Switzerland). With as subtitle "Health and hubris", the global press release at the end of this forum presents the size of the risk in the following terms "Huge strides forward in health have left the world dangerously complacent. Rising resistance to antibiotics could push overburdened health systems to the brink, while a hyper-connected world allows pandemics to spread. This risk case draws on the connections between antibiotic resistance, chronic disease and the failure of the international intellectual property regime, recommending more international collaboration and different funding models". The risk for Europe was assessed financially at 1.5 billion euros. The severity of this menace is amplified by the fact that research for new antibiotic agents is currently stalled. It may be possible that no totally new agent active against multiresistant bacteria will be put on the market in a close future. The 20th century was "the century of antibiotics", marked by the discovery and the continuous development of new more and more active antibiotics, but no new family has been available for clinicians since lipopeptides in 1987.

Virologists have discovered numerous viruses in the previous 3 decades: HIV, hepatitis virus, SARS, or the new flu viruses; at the same time many agents active on some of these viruses were developed and the antiviral therapeutic arsenal has never stopped growing. Conversely, in bacteriology, we have selected strains resistant to all antibiotics among the most frequent bacterial species — Enterobacteriaceae — without being able to develop agents capable of destroying them or effective strategies to prevent their extension. These carbapenemase-producing Enterobacteriaceae are progressively spreading throughout the world [1].

1. General features and classification

The enterobacterial carbapenemases differ from the extended spectrum beta-lactamases (ESBL) which include (CTX-M), which hydrolyze or inactivate the beta-lactams and 2nd and 3rd generation cephalosporins, but not carbapenems. Most carbapenemases hydrolyze beta-lactams and cephalosporins, but also monobactams and carbapenems, so that no beta-lactam can remain effective (Fig. 1).

The Ambler classification proposed in 1980 is based on analogies of the peptide sequence; beta-lactamases are classified in 4 groups, A to D. Groups A, C, and D enzymes are serine-enzymes, while those of group B are metallo-enzymes. Carbapenemases mainly belong to 3 great groups of beta-lactamases, A, B, and D, the differences of which have not only a genetic and biochemical interest, but also a clinical one, because the profile of resistance and the epidemiology of these strains differ.

The first group, called Ambler class A, is that of penicillinases. The most common is KPC (*Klebsiella pneumoniae* carbapenemase), but there are others, such as *Serratia Marcescens* (SME), non-metallo carbapanemase (NMC), imipenemase (IMI), Guyana extended-spectrum-lactamase (GES), etc. First identified in the 1980s, they are enzymes the activity spectrum

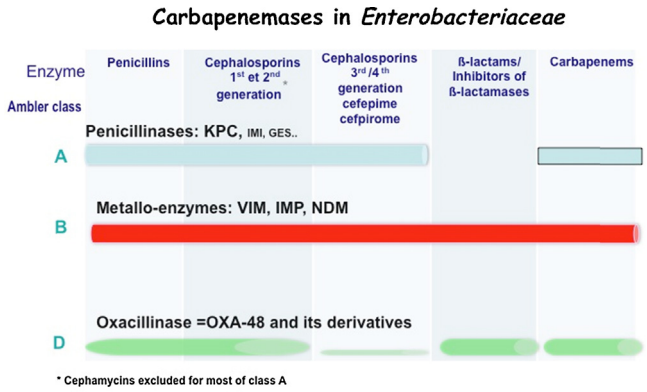

Fig. 1. Activity spectrum of carbapenemases in Enterobacteriaceae.
Spectre d'activité des carbapénémases des entérobactéries.

of which extends to carbapenems. They remain inhibited, at least in vitro, by beta-lactamase inhibitors, especially clavulanic acid.

The second group, class B, is that of metallo-proteins, one of the latest of with a large spread is NDM-1. These metallo-proteins hydrolyze all antibiotics, except aztreonam. The third group, class D, is that of oxacillinases, OXA-48 derivatives. They hydrolyze penicillins, 1st generation cephalosporins, and carbapenems; they are resistant to beta-lactamase inhibitors, and weakly active against 2nd and 3rd generation cephalosporins such as cefotaxime or ceftazidime, and hydrolyze only partly carbapenems.

None of the beta-lactamase inhibitors currently available, nor even the new inhibitors under development, allow inhibiting the 3 groups of carbapenemases.

2. Group of penicillinases: KPC

The term KPC, for *K. pneumoniae* carbapenemase, is relatively inadequate because these are enzymes the genes of which transfer very easily from an enterobacterium to another, whatever the type, and thus are not limited to *K. pneumoniae*. The strains expressing KPC are resistant to all beta-lactams, but also resistant to most of the other antibiotics families.

Class A carbapenemases have been identified sporadically in clinical isolates clinical since the 1980s; they were most often chromosomal enzymes. A strain carrying a plasmid carbapenemase, KPC-1, was first observed in North Carolina in 1996 [2]. KPC strains remained rare in the USA until 2005, when KPC-producing Enterobacteriaceae were identified in outbreaks, in several New York and New Jersey hospitals. A spread was then observed throughout North America [3,4]. In 2012, more than 1,200 strains of *K. pneumoniae* producing KPC type enzymes were isolated from blood cultures in a New York teaching hospital, proving their large spread (P. Nordmann, personal communication). This menace has now been taken into account at the highest level in the USA where major research grants have been attributed by the federal authorities to fight against this major public healthcare challenge.

KPC strains have spread largely, as all enteric bacteria, via colonized patients and air transportation [5]. After the East coast of the USA, KPC plasmid strains were isolated almost