THE INVASION BY CARBAPENEMASE-PRODUCING *ENTEROBACTERIACEAE*

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Since 2000's, a spread of community-acquired enterobacterial isolates (*Escherichia coli*) that produce extended-spectrum ß-lactamases (ESBLs) capable of hydrolyzing almost all ß-lactams except carbapenems have been reported worldwide[24]. Carbapenems (imipenem, ertapenem, meropenem, doripenem) have become antibiotics of last resort in may part of the world. Unfortunately carbapenem-resistant *Enterobacteriaceae* have been reported worldwide as a consequence mostly of acquisition of carbapenemase genes[32]. Carbapenemase are enzymes that hydrolyze at least carbapenems. Whereas, there is no consensus definition of a carbapenemase, they have been categorized as enzymes capable of hydrolyzing imipenem with $K_{cat}/V_{max} > 1$ $\mu M^{-1}S^{-1}$[10]. They belong to three classes of ß-lactamases; the Ambler class A, B and D ß-lactamases[21].

The Ambler class A carbapenemases

Although variety of class A carbapenemases have been described (NmcA, Sme, IMI-1, SFC-1, IMI-2, GES, derivatives), the most important are KPC enzymes[19,32,36]. They hydrolyze carbapenems effectively and are least partially inhibited by clavulanic acid and boronic acid[32]. The first KPC producer (KPC-2 in *Klebsiella pneumoniae*) was identified in 1996 in the eastern part of the USA[36]. Within a few years, KPC producers went global and have been described on the entire territory of the US (still mostly in the East coast states) and in particularly, in Puerto Rico, in Columbia, in Greece, in Israel and in China[18,19]. Outbreaks of KPC producers have been also in many European countries and in South America. KPC producers have been reported mostly from nosocomial *K.pneumoniae* isolates and to a much lesser extent from *E.coli* (especially in Israel) and from other enterobacterial species[19]. A single *K.pneumoniae* clone (ST-258) was identified extensively worldwide indicating that it may have contributed significantly to the spread of the bla KPC genes[6].Within a given geographical location, several KPC clones are disseminating differing by MLST type, by additional ß-lactamase content, by size, number and structure of plasmids but the blaKPC genes are associated to a single genetic element (transposon Tn4401)[6]. Although community-acquired KPC producers have been reported, they remain rare, at the exception of isolates in Israel, a few years ago[19]. KPC producers are usually multidrug resistant (especially to all ß-lactams) and therapeutic options for treating KPC-related infections remain limited[19]. Attributed mortality to infections due to KPC producers is high (50 % or more)[3,23,33].

The class B metallo ß-lactamases (MBL)

The class B metallo ß-lactamases (MBL) are mostly of the VIM- and IMP- types and more recently of the NDM type[32,34]. The first acquired MBL, IMP-1 was reported from *Serratia marcescens* in Japan in 1991[13]. Then, MBLs have been described worldwide[32,34]. Endemic spread of VIM/IMP-type enzymes is known in Greece, Taiwan and Japan[32,34], although outbreaks and single reports of VIM and IMP producers have been reported in many other countries. These enzymes hydrolyze all ß-lactams except aztreonam[34]. Their activity is inhibited by EDTA but not by clavulanic acid[34]. Most of the MBL producers are hospital-acquired and multidrug-resistant *K.pneumoniae*[32,34]. Resistance levels to carbapenems of MBL producers may vary. Attributed mortality associated to MBL producers ranges from 18 to 67 %[8].

Discovered in 2008 in Sweden from an Indian patient hospitalized previously in New Delhi[37], NDM-1-positive *Enterobacteriaceae* are now the focus of worldwide attention[16,22,37].

Since mid-August 2010, NDM-1 producers have been identified on all continents (except Central and South America) with, in most of the cases, a direct link with the Indian subcontinent[22]. A very few cases have been reported from the US and from Canada[22]. Recent findings suggest that the Balkan states and the Middle East may act as secondary reservoirs of NDM-1 producers[22].

The blaNDM-1 gene is not associated to a single clone to non-clonally related isolates and species[16,22]. It has been identified mostly in *E. coli* and *K. pneumoniae* and to a lesser extent in other enterobacterial species[16,22]. The level of resistance to carbapenems of NDM-1 producers may vary. Plasmids carrying the blaNDM-1 gene are diverse and can harbor a high number of resistance genes associated sometimes to other carbapenemase genes (OXA-48-, VIM-types), plasmid-mediated cephalosporinase genes, ESBL genes, aminoglycoside resistance genes (16S RNA methylases), macrolide resistance genes (esterase), rifampicin (rifampicin modifying enzymes) and sulfamethoxazole resistance genes as a source of multidrug resistance and pandrug resistance[16,22]. The association of such an high number of resistance genes in single isolates has been rarely observed even among the other carbapenemase producers. Many NDM-1 producers remain susceptible only to tigecycline, colistin (Figure 2, panel B), and to a lesser extend to fosfomycin[16,22]. NDM-1 brings several factors that are deeply disconcerting for public health worldwide. They are factors, (i) the occurrence of the blaNDM-1 gene not in a single species but in many unrelated species and its spread in the environment at least in the Indian subcontinent[35]; (ii) frequent acquisition in *K.pneumoniae*, a typical nosocomial pathogen but also in *E.coli* that is by far the main (community-acquired) human pathogen. (iii) the size of the reservoir; the Indian subcontinent has more than 1.4 billion people. Unpublished data indicate that up to 20 % of the population may carry NDM-1 producers in certain areas in Pakistan. Of particular concern, NDM-1 has been identified in *E.coli* ST-type 131 as a source of community-acquired infection[28], a ST-type which is known to mobilize efficiently the ESBL CTX-M-15 worldwide. *E.coli* is the number one cause of diarrhoea in children in India. Therefore, this may increase the risk of resistant strains to be release in the environment and further spread among humans. Accordingly, NDM-1 producers have been recently identified in tap and environmental water in New Delhi among many unrelated Gram-negative species[35].

The class D enzymes of the OXA-48 type

OXA-48-type carbapenem-hydrolysing class D β-lactamases are increasingly reported in enterobacterial species[21]. The very first OXA-48 producers were identified from Turkey where they are widespread[1,12,15,27,29]. To date, six OXA-48-like variants have been identified, with OXA-48 being the most widespread[29]. They differ by few amino acid substitutions or deletions (one to five amino acids[26,29,31]. Those enzymes hydrolyse penicillins at high level, and carbapenems at low level, sparing broad-spectrum cephalosporins, and are not susceptible to β-lactamase inhibitors[12,27,29]. When combining permeability defects, OXA-48-like producers may exhibit high level of resistance to carbapenems[21]. OXA-163 is an exception, hydrolysing broad-spectrum cephalosporins but carbapenems at a very low level, and being susceptible to β-lactamase inhibitors[26]. The blaOXA-48-type genes are always plasmid-borne and have been identified in association with insertion sequences involved in their acquisition and expression. The current spread of the blaOXA-48 gene is mostly linked to the dissemination of a single IncL/M-type self-transferable plasmid of ca. 62 kb that does not carry any additional resistance gene[25]. OXA-48-type carbapenemases have been identified mainly from North African countries, the Middle East, Turkey, and India, those areas constituting the most important reservoirs, however occurrence of OXA-48 producers in European countries is now well documented with some reported hospital outbreaks[2,4,5,7,11,14,17,30]. Since many OXA-48-like producers do not exhibit resistance to broad-spectrum cephalosporins, or only decreased susceptibility to carbapenems, their recognition and detection can be challenging[21].

Conclusion

Carbapenemase producers in *Enterobacteriaceae* are not the source of specific types of clinical infections. The importance of those multidrug-resisant bacteria is related to the difficult-to-treat infections rather than to expression of specific virulence traits. Adequate screening and detection methods are therefore required to prevent and control their dissemination[20].

The real prevalence of carbapenemase producers is still unknown since many countries which are likely to be their main reservoirs, have not established any search protocol for their detection.

The dearth of novel antibiotics in the pipeline means that we must conserve the efficacy of existing antibiotics as much as possible. Carbapenemase producers in *Enterobacteriaceae* are different from other multidrug bacteria in that they rely on a very few (if any) antibiotics left for their treatment[9].

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Eş Zamanlı Oturum: Panel 1 sunularından

NOZOKOMİYAL MRSA

Yöneten: **Serhat ÜNAL**

- MRSA direnç mekanizmaları:
  Dünyada ve Türkiye'de epidemiyolojisi
  Banu SANCAK