Enterobacteriaceae and the CTX-M extended-spectrum β-lactamases (CTX-M ESBLs): What we should know?

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Introduction

Enterobacteriaceae are a common source of both community- and hospital-acquired infections. They frequently cause several diseases such as urinary tract, cystitis, pyelonephritis, pneumonia, peritonitis, septicemia, meningitis and infections associated with prosthetic devices such as catheters. *Klebsiella pneumonia*, *Klebsiella oxytoca*, *Escherichia coli*, and *Enterobacter cloacae*, are the most important pathogens of this family. Infections caused by many genera and species of *Enterobacteriaceae* family are mainly treated by beta-lactam, aminoglycoside and quinolone-antibiotics. However, resistance to these antibiotics has been increasingly reported and high rates of resistance are becoming worrisome in many countries. In addition, multidrug resistant enterobacteria have been increasingly reported in hospital setting, which reduce therapeutic choice for the treatment of infections caused by the aforementioned species.

The CTX-M ESBL

In *Enterobacteriaceae*, resistance to beta-lactam antibiotics is mainly caused by enzymatic hydrolysis of the antibiotic by the production of beta-lactamase enzymes. The most important ones are acquired AmpC β-lactamases (plasmidic AmpC β-lactamases), extended-spectrum β-lactamases (ESBL), and carbapenemases. Many works have investigated the genetic basis and the molecular characterization of these enzymes, and more than 1500 β-lactamase enzymes have been characterized until now. In addition, isolates harboring more than one type of these β-lactamases especially ESBLs and pAmpC β-lactamases, are common. The ESBL enzymes are the most predominant β-lactamases (more than 600 enzymes) owing to their high diversity and owing to their genetic localization on highly mobiles genetic elements as well as the clonal spread of pandemic clone such as *E. coli* of sequence type 131 (*E. coli* ST131). They are effective against β-lactam antibiotics like ceftazidime, ceftriaxone, cefotaxime, and oxyiminomonobactam, but not cephamycins or carbapenems and they are inhibited by clavulanic acid, sulbactam and tazobactam. The predominance of ESBL-producing *Enterobacteriaceae*, is not limited to human isolates but also in enterobacteria isolated from animals (livestock, wild animals), vegetables and aquatic environments. Until the 2000s, ESBL enzymes derived from Sulfhydryl variable (SHV) and Temoneira (TEM) β-lactamases enzymes were the major cause of hospital-acquired infections [1]. However, since 17 years ago, a new type of ESBL, called CTX-M β-lactamases (Cefotaximase-Munich), gained prominence and this presents huge challenges to healthcare, with restricted options to treat infections caused by CTX-M-producing bacteria. Besides the TEM, SHV and CTX-M-group ESBLs, some other groups of ESBLs are sporadically reported, but they remain relatively scarce (e.g. OXA, PER, GES, and VEB-group ESBLs). CTX-M enzymes can be divided into five major groups (CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9 and CTX-M-25) and each group includes a number of minor allelic variants which differ from each other by one or few amino acid substitutions (≤ 5% amino acid residues) [1,2]. Amongst these variants, the $bla_{\text{CTX-M-15}}$ gene (group 1) is dominant worldwide; except in China, South-East Asia, South Korea, Japan and Spain, where group 9 variants (especially CTX-M-14) are dominant, and in South America, where $bla_{\text{CTX-M-2}}$ is largely distributed. CTX-M enzymes (more than 170 variants) are now the most widely distributed ESBL type in *Enterobacteriaceae* isolates independently to their origins (human, animal, and environment). In clinical settings, enterobacteria infections are mainly caused by monobacteria. Therefore, the dominance of CTX-M-producing isolates can reflect the real predominance of these isolates over TEM-, SHV-producing isolates amongst the ESBL-producing enterobacteria. However, it is interesting to highlight that the reported predominance of CTX-M-producing isolates amongst the ESBL-producing populations from animal and environment might not be true. This hypothesis is based on the protocols used to detect ESBL-producing isolates from samples of animal (feces, milk, and meat) and environmental origins (water, soil…). Indeed, according to many reports, ESBL-producing isolates are mainly selected on selective medium (MacConkey, or Hektoen) containing 2 mg/mL of cefotaxime [3]. In reality, this concentration selects isolates that are highly resistant to cefotaxime which is a fundamental trait of CTX-M enzymes (Cefotaxime MICs ranging from 8 to ≥ 256 mg/L, whereas, ceftazidime MICs ranging from 0.5 to 128 mg/L). Consequently, by this selective protocol, TEM-, and SHV-producers isolates (these enzymes hydrolyze more efficiently ceftazidime than cefotaxime) are counter selected and only CTX-M-producers isolates are recovered. However, this hypothesis needs further investigations. The expansion of CTX-M enzymes is linked to two phenomenons: (i) clonal spread of particular clones (especially for *E. coli*), and (ii) spread of specific conjugative plasmids called 'epidemic plasmids'. Indeed, the international ESBL *E. coli* clone ST131, which belongs to phylogenetic group B2, serotype O25b:H4, and carrying the $bla_{\text{CTX-M-15}}$ gene is now the major global extraintestinal pathogenic *E. coli* strain. This clonal lineage is isolated not only in human clinical *E. coli* isolates, but also in animals and the environment. However, this phenomenon is less documented for CTX-M-producing *K. pneumonia*, and epidemic clonal spread is particularly reported

for carbapenemase-producing *K. pneumoniae* (producers of KPC carbapenemase) including ST11, ST258, ST265, ST270, ST277, ST340, ST379, ST407, ST418, and ST437. Concerning the dissemination of plasmids, plasmids of the IncF family are the predominant group that carry $bla_{\text{CTX-M-15}}$ (e.g. pC151a plasmid), whereas $bla_{\text{CTX-M-14}}$ is carried on a variety of plasmid types, including on IncF and on IncK (e.g. pCT and pHK01 plasmids).

Multidrug Resistant ESBL-Producing *Enterobacteriaceae*

ESBL-producing *Enterobacteriaceae* are mainly multi-drug resistant (MDR) (resistance to three or more families of antibiotic). Multi-drug resistance, in addition to β-lactams, is particularly observed for quinolones/fluoroquinolones, aminoglycosides, tetracycline, and trimethtoprim/sulfamethoxazole. Multi-drug resistance is the result of the collection of various genes encoding resistance determinants on mobile genetic elements such as plasmids and transposons as well as integrons that might be located on plasmids or on the chromosome. Genes encoding ESBL are not integron-related; however, they have been mainly reported in integron-positive isolates. The 'genetic capitalism' (the rich become richer) described for the first time by Rice LB at 2002 [4], is a process by which a susceptible isolate become multidrug resistant by acquiring a 'packaged' various genes encoding antibiotic resistance during a unique horizontal transfer, by conjugation, from resistant bacteria or by sequential processes of horizontal transfer. One interesting trait of such ESBL-producing MDR isolates is the accumulation of genes encoding resistance to the same antibiotic such as bla_{SHV}, bla_{TEM}, and $bla_{\text{CTX-M}}$ for beta-lactams resistance; or *sul1*, *sul2*, and *sul3* for sulfonamides-resistance; or *tetA*, and *tetB* for tetracycline-resistance. Herein, scientific researchers have only the choice to describe what they observe and to explain genetic traits of these bacteria, a mysterious genome that never ceased to give us lessons every day!

Biotechnological progress in medicine will be meaningless if the antibiotic resistance trend will not be stopped or at least limited in the nearest years. Humanity fights against an old enemy (bacteria appeared 3 billion years ago) that escaped from enormous life threatening conditions by developing a highly adaptive genome, therefore, we have to realize how hard is this challenge.

References

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