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The Mediterranean Region: A Reservoir for CTX-M-ESBL-Producing *Enterobacteriacae*

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Abstract

The incidence of ESBL-producing bacteria is increasing worldwide, which represents a challenge for the healthcare systems. More recently, the emergence of the CTX-M group has been frequently reported as being associated with both nosocomial and community acquired infections. CTX-M-15 was identified as being the most prevalent in a large geographic area including Europe and the Middle East, suggesting the presence of a community reservoir of CTX-M enzymes disseminating in the Mediterranean area. Thus, this review will focus on the Mediterranean region to highlight the increasing prevalence of CTX-M-ESBL producing *Enterobacteriacae.*

Keywords: ESBL, CTX-M, Mediterranean, *Enterobacteriacae*, Multi-drug Resistance, *E. coli*, *Klebsiella pneumonia*, UTI.

1. Introduction

Since the initial report in Germany in 1983, extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* emerged as a major pathogenic threat worldwide (Paterson and Bonomo, 2005; Livermore *et al.*, 2007; Pitout and Laupland, 2008; Qian-Hong *et al.*, 2011). The increasing prevalence of ESBLs producing pathogens and their alarming evolution can be attributed to the frequent prescription of β-lactam agents such as penicillins, cephalosporins, monobactams and carbapenems. ESBLs were identified shortly after the introduction of oxyimino-β-lactam antibiotics (Medeiros, 1997; Pitout *et al.*, 2005). Initially, the classic ESBLs occurred due to mutations in the genes encoding the common plasmid-mediated SHV-1, TEM-1, or TEM-2 beta-lactamases (Jacoby and Munoz-Price, 2005). More recently, a novel group of ESBLs, the CTX-M family, have emerged and rapidly disseminated worldwide (Canton and Coque, 2006). This CTX-M emergence led to further dissemination of ESBLs in both community and hospital settings (Woerther *et al.*, 2011).

2. Overview of ESBLs

These enzymes are termed ESBLs since they confer bacterial resistance to penicillins, all cephalosporins and aztreonam and frequently resistant to fluoroquinolones and aminoglycosides but not to cephamycin, carbapenems or β-lactamase inhibitors (Tham *et al.*, 2012; Patterson and Bonomo, 2005; Drawz and Bonomo, 2010). ESBLs are mostly encoded by genes found on large plasmids which include as well genes encoding resistance for a variety of antimicrobial agents including aminoglycosides, sulphonamides, trimetho-prim, chloramphenicol and tetracyclines (Paterson, 2000). Consequently, ESBLs are characterized by a broad antibiotic resistance extending to multiple classes (Bradford, 2001). This resistance is even extending to carbapenems which represent the treatment of choice for ESBL associated serious infections (Rahal, 2008; Doumith *et al.*, 2009). Historically, mutations in the genes encoding the common plasmid-mediated TEM-1 and SHV-1 enzymes were the initial cause of the occurrence of ESBLs (Jacoby and Munoz-Price, 2005). Currently, 175 different TEM enzymes and 127 SHV different enzymes are described (www.lahey.org/ studies/). Nevertheless, a new group of ESBLs, the CTX-M family, have emerged and spread rapidly worldwide (Canton & Coque, 2006). These enzymes are prominent among *Enterobacteriaceae* from Europe, Africa, Asia, South America and North America (Bonnet, 2004). The number of CTX-M-type ESBLs is rapidly escalating and they were identified in every inhabited continent (Patterson and Bonomo, 2005). At present, the number of CTX-M β-lactamases identified exceeds 140 allelic variants (http://www.lahey.org/ Studies/other.asp#table1) which can be classified, based

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on their amino acid structure, into six distinct phylogenetic groups, namely groups 1, 2, 8, 9, 25 and 45 (Rossolini *et al.,* 2008). For a period of time, CTX-M ESBLs were mainly detected in three geographic regions: South America, the Far East, and Eastern Europe, while they appeared to be sporadic in Western Europe and North America; however, more recently, the arrival of CTX-M-type ESBLs in these regions have been reported extensively (Dechamps *et al.,* 2000). Furthermore, CTX-M-type ESBLs were largely reported in China and India, and hence CTX-M-type ESBLs can be considered as the most prevailing ESBL type (Pitout *et al.,* 2005). In addition, some of the CTX-M enzymes were identified in particular countries, like CTX-M-1 in Italy, CTX-M-9 and CTX-M-14 in Spain, and CTX-M-2 in the majority of South American countries and Japan, while CTX-M-15 was detected worldwide (Bonnet, 2004; Ben-Ami *et al.,* 2006; Canton and Coque, 2006). However, CTX-M-15 was identified as being the most prevalent in a broad geographic area which includes North America, Europe, The Middle East, and India, while a number of CTX-M-32-producing strains were recently detected in both humans and farm animals in Spain, Italy, Greece and Portugal (Eckert *et al.,* 2006). This suggested the presence of a community reservoir of CTX-M enzymes disseminating in the Mediterranean area (Cartelle *et al.,* 2004; Oteo *et al.,* 2006).

3. Predominant ESBLs Circulating in European Countries on the Mediterranean

All published studies have confirmed that the prevalence of ESBL producing isolates is higher in southern Europe than in the rest of European countries and the wide dissemination of CTX-M-15 enzyme is increasingly reported from both hospital and community settings. A nationwide Spanish study including 40 medical centers reported CTX-M-9 (27.3%), SHV-12 (23.9%), and CTX-M-14 (20.5%) as the most prevalent ESBL-producing *E. coli*, and clonal dissemination was not detected among the 170 isolates included (Hernandez *et al.,* 2005). In another Spanish study, Oteo *et al.* (2006) reported the dissemination of *bla*CTX-M-15 alleles linked to an ISEcp1-like element between the community, long-term care centers, and hospitals, and the majority of the tested isolates harbored the same three virulence genes: *iut*A and *fyu*A (siderophores), and *tra*T (serum survival factor). Moreover, Valverde *et al.* (2008) identified high rates of colonization with ESBL-producing *Enterobacteriacae* in patients with community infections and their household members with 66% of the ESBL-producing isolates being indistinguishable between patients and their healthy household contacts. These results highlight the high risk of the spread of these multi-drug resistant isolates to healthy individuals and their dissemination in both hospital and community settings (Valverde *et al.,* 2008). In 2009, Valverde *et al.* demonstrated that the dissemination of IncK plasmids is responsible for the high incidence CTX-M-14-producing *E. coli* isolates which represents a frequent cause of community-acquired urinary tract infections in Spain (Valverde *et al.,* 2009). In 2010, ESBL-producing *E. coli* was collected from 27 Spanish centers as part of European Antimicrobial Resistance Surveillance Network for susceptibility testing and typing and an increase in fosfomycin resistance was shown. The higher rate of fosfomycin resistance was 15.3% belonging to CTX-M-15-ESBL-producing isolates (Oteo *et al.,* 2010). In a recent study, Dahbi *et al.* (2013) highlighted the emergence of new variants of ST131 clonal group among extra-intestinal pathogenic CTX-M-15 ESBL producing *E. coli* with a significantly elevated virulence score and novel virulence profile. In France, before 2008 the prevalence of ESBL producing *Enterobacteriaceae* was under 1% (Galas *et al.,* 2008). However, since then, this prevalence has increasingly been reported in both community and nosocomial settings. In a study that aimed to report the evolution of ESBL production between 1999 and 2007 at a general hospital from south France, ESBL prevalence in *E. coli* augmented during this episode from 0.3 to reach 2.5% (Anastay *et al.,* 2013). Concurrently, the predominant ESBL in 1999, TEM-24 was substituted by CTX-M in 2007, with CTX-M-15 being the most prevalent (88% of CTX-M) (Anastay *et al.,* 2013). CTX-M variants were also identified predominantly in the southern coastal region of France, and the zoonotic spread was detected through gulls carrying bacteria that harbored mostly the CTX-M-1 group (Bonnedahl *et al.,* 2009). In 2006, a nationwide survey was conducted in Italy and the widespread of CTX-M-producing ESBLs was described. Although the rate of CTX-M production varied between hospitals (1.2 to 49.5% of ESBL producers), all these isolates belonged to CTX-M group 1 with CTX-M-15 and CTX-M-1 being the most prevalent variants (60% and 35%, respectively) and CTX-M-32 carried only by a minority (5%). In 2011, the dominance of CTX-M group 1 ESBL-producing *E. coli* causing urinary tract infections among outpatients was reported (Huemer *et al.,* 2011). More recently, an outbreak of colonization by ESBL producing *E. coli* sequence type 11 was identified in a neonatal intensive care unit. This epidemiological investigation highlighted the importance of detecting the silent spread of ESBLs (Giuffre *et al.,* 2013). In addition, the emergence of *K. pneumoniae* clone carrying both VIM-1-MBL and CTX-M-15-ESBL was reported from different hospitals in Italy (Nucleo *et al.,* 2013). In Greece, a multiclonal epidemic of *K. pneumonia* producing both VIM-1 and SHV-5 was reported to be under way in the major hospitals (Psichogiou *et al.,* 2008). Sequencing analysis of ESBL-producing *Enterobacteriacae*, collected between 2007 and 2011, showed that *bla*CTX-M-3 gene is predominant, followed by the *bla*CTX-M-15 gene and *bla*SHV-5 gene (Kristo *et al.,* 2013). In 2008, Turkey was added to the list of countries concerned by community-acquired CTX-M-15-ESBL *E. coli* clone O25-ST131 among outpatients with *E. coli* urinary tract infection (Yumuk *et al.,* 2008). More recently, in a nationwide study including ESBL-producing *E. coli* isolates collected from 10 different Turkish hospitals, CTX-M-1 was the most prevalent (366/440) followed

by TEM (194/440) and CTX-M-2 (140/440) (Cicek *et al.*, 2013).

4. Prevalence and Distribution of ESBL Production in African Countries on the Mediterranean

In 2006, CTX-M production was initially detected and the high rate of ESBLs was confirmed in Egypt reaching 60% among urinary tract infections patients; three different enzymes were found CTX-M-14, CTX-M-15 and CTX-M-27 (Alagamy *et al.,* 2006). Later on, Hassan *et al.* (2013) reported the high prevalence of quinolone resistance determinants qnr, aac(6')-Ib-cr , qep A4, and their association with CTX-M positive *E. coli* isolates from Egypt (Hassan *et al.,* 2013). The extensive community acquired CTX-M-15 carriage reaching 57% was also described in a recent study (Newire *et al.,* 2013). In Tunisia, the initial identification of a CTX-M-producing strain (CTX-M-3) was recovered in 2001. Later on, CTX-M-27 originated a nosocomial outbreak in a Tunisian neonatal center. The first report of CTX-M-15 and CTX-M-16-producing *Enterobacteriaceae* in Tunisia was submitted in 2006 (Mamlouk *et al.,* 2006). Later, Dahmen *et al.* (2010) corroborated the high prevalence of CTX-M-15 with 91% of the isolates producing this enzyme. The majority of CTX-M-15-ESBL-producing *E. coli* belonged to B2 phylogenetic group and to the sequence type 131 and was associated with Qnr-like determinants (Dahmen *et al.,* 2010). It was also found that this CTX-M-15-B2-ST131 *E. coli* clone is also highly disseminating in community-acquired urinary tract infections in Tunisia (Hammami *et al.,* 2013). The molecular analysis of a collection of ESBL producers isolated between 1989 and 2009 confirmed the prominence of *bla*CTX-M-15 gene followed by *bla*CTX-M-14 gene, *bla*SHV-12 gene, *bla*SHV-2a gene and *bla*TEM-26, with the frequent dissemination of CTX-M-15 producing *E. coli* being attributed to the spread of various IncF-type plasmids (Mnif *et al.,* 2013). In Algeria, the results obtained were similar to the other Mediterranean countries, and in 2008 the prevalence of ESBLs belonging to CTX-M-1 group was noticed (Messai *et al.,* 2008). It was determined that the size of the self-transferable plasmid reached 85 kb and included in addition to the *bla*TEM and *bla*CTX-M genes, determinants for aminoglycosides and sulfonamides resistance (Messai *et al.,* 2008). Similarly, in a study that tried to determine the overall incidence of ESBL production among *Enterobacteriacae*, predominance of CTX-M-1 group was revealed, TEM and SHV were also detected. But the conjugative plasmids carrying these genes were of higher molecular weight (≥125kb) (Nedjai *et al.,* 2012). Ahmed *et al.* (2012) detected the CTX-M-15 ESBLs in the intensive care unit of an Algerian hospital and determined that this gene was genetically linked to insertion sequence lSEcp1B (Ahmed *et al.,* 2012). More recently, in a study that aimed at characterizing environmental ESBLs and quinolone resistance, it has been found that the antibiotic resistance mechanisms are similar in both the environment and the clinical setting, and wastewater treatment plant might represent a cause of dissemination of resistance genes (Alouache *et al.,* 2013)**.** Morocco is another country where the production of CTX-M-type beta-lactamase *bla*CTX-M-15 is the most recurrently found mechanism of resistance to beta-lactams. In a nationwide study conducted over a 2-year period in the Moroccan community, *bla*CTX-M-15 was the most frequent gene detected among ESBLs causing urinary tract infections, followed by *bla*CTX-M-1, SHV-12 and PER-2**.** The *bla*OXA-48 and *bla*IMP-1 carbapenemases genes were also detected and qnr genes were harbored by only a small percentage of the isolates (Barquiqua *et al.,* 2013).

5. ESBL-Producing E. coli in the Middle-East

In Lebanon, an increase in the prevalence of ESBL-producing bacteria was observed from 2.3% in 2000 to reach 8% in 2005 and 16.8% in 2009 (Kanafani *et al.,* 2005; Daoud and Afif, 2011). The escalating numbers of ESBL-producing bacteria were not only noted for *E. coli*, but also for *K. pneumoniae*, *Salmonella spp*. and *Shigella spp* (Araj *et al.,* 2012). The predominance and fast emergence of the CTX-Ms has been reported in Lebanon (Moubareck *et al.,* 2005; Kanj *et al.,* 2008) and sequence analysis indicated that the *bla*-CTX-M-15 is the most prominent (Matar *et al.,* 2007; Baroud *et al.,* 2013). In a recent study, resistance to carbapenemase production was detected in ESBL *E. coli* and *K. pneumoniae* isolates (Baroud *et al.,* 2013). There is a lack of sufficient information about the prevalence of ESBLs and their molecular characterization in Syria; however, in a recently published article, the high prevalence of ESBL producing *E. coli* was revealed reaching 52% among urinary tract infections patients (Al-Assil *et al.,* 2013). In Jordan, the prevalence of ESBLs has been reported to be relatively high compared to other reported data worldwide (Youssef *et al.,* 1999; Shehabia *et al.,* 2000). More recently, clinical specimens have been collected from three major hospitals in Northern Jordan, and ESBL-producing gram negative bacteria comprised 22.9% of all isolates which included *E. coli*, *K. pneumoniae*, *K. oxytoca* and *Enterobacter cloacae* as the most prominent (Batchoun *et al.,* 2009). A study by Aqel *et al.* (2013) suggested the endemicity of ESBL producing bacteria in Jordanian hospitals, where CTX-M-1 and CTX-M-9 ESBLs were detected in two geographically distant hospitals. Moreover, the results of another recent study revealed that ESBL urinary *E. coli* isolates with high levels of *sul*2, *bla*CTX-M and *bla*TEM are circulating in the Jordanian community with associated multidrug resistance profile (Nimri and Azaizeh, 2012). Similarly, in a recently published study, ESBL producers were isolated from patients with urinary tract infections from three hospitals in the West Bank and the results showed that all isolates harbored CTX-M, TEM was also detected but none harbored the SHV gene (Adwan *et al.,* 2013). The dissemination of CTX-M sequence type 131 ESBLs was also detected in Israel among patients with community-onset bacteremia (Karfunkel *et al.,* 2013). Moreover, in an investigation conducted over 7 years, the association

between the increase of such infections and CTX-M ESBLs was suspected, and specifically it appeared to be related to the clonal extension of *bla* CTX-M-15 or *bla* CTX-M-14 carrying ST131(Karfunkel *et al.,* 2013).

6. Conclusion

The data provided in a large number of studies conducted in the Mediterranean area show that the dissemination of CTX-M genes, in both community and hospital settings, have been increasing extensively. This expansion is enhanced by environmental and zoonotic spread. Moreover, it is associated with a significantly elevated virulence score and multidrug resistance profiles, which highlights the importance of identifying the silent spread of ESBLs, and of implementing additional measures to prevent ESBL associated infections.

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