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Review

Spread of CTX-M-15 Extended Spectrum β-lactamases Encoding Genes Among Enterobacteriaceae in the Middle Eastern Region

Maysa Baroud[1], George F. Araj[2] and Ghassan M. Matar[1*3]

1 Experimental Pathology, Immunology and Microbiology.
2 Pathology and Laboratory Medicine, Faculty of Medicine, American University of Beirut, Beirut, Lebanon.
3 Faculty of Medicine, American University of Beirut Beirut, Lebanon

* **Correspondence:**
Ghassan M. Matar, Ph.D.

E-mail: gmatar@aub.edu.lb

Tel: +961-1-350000/6128

Abstract

The CTX-M type enzymes have become the most prevalent extended spectrum β-lactamases (ESBLs) worldwide. Among the CTX-M type enzymes, CTX-M-15 is the most widespread and has been reported from all continents. It has been recovered from different *Enterobacteriaceae* and has been isolated from both community and hospital acquired infections. This review primarily highlights the prevalence of CTX-M-15 in addition to other ESBLs in the Middle East. Detection of any type of ESBL is of importance in therapeutic treatment.

Keywords: CTX-M-15, ESBL, Middle East, antimicrobial resistance, Enterobacteriaceae.

Introduction

As is the case for many antimicrobial agents, over-use of the extended spectrum oxyimino-cephalosporins, which are agents developed to treat organisms producing β-lactamases, resulted in the production of enzymes capable of hydrolyzing these agents. In 1983, the first extended spectrum β lactamase, an SHV β-lactamase derivate, was isolated in Germany from a *Klebsiella* isolate (1,2). Since then, the family of ESBLs has grown to include enzymes belonging to Ambler Classes A, including many derivates of plasmid mediated TEM and SHV penicillinaces, and a small number of Class D OXA-type β-lactamases (2,3). A third type of Class A ESBLs, the cefotaximase, or CTX-M enzyme, was first identified from an *Escherichia coli* isolate in Germany in 1990 (4). Unlike other ESBLs, this enzyme hydrolyzed cefotaxime more efficiently than ceftazidime, and in general, CTX-M enzymes tend to confer resistance to cefotaxime but not to ceftazidime (4,5).

Outbreaks of organisms producing CTX-M type ESBLs were reported from around the world as early as the 1990s, however, with a few exceptions, organisms expressing these enzymes were not identified in the Middle East till earlier this decade (2,5,6,7). Over the past ten years, the CTX-M enzymes have become the most prevalent ESBLs among multidrug resistant organisms worldwide, especially in certain countries in Europe and South America (6,8,9,10). As for the Middle East, there is little data on the prevalence and distribution of these enzymes. These enzymes are of special importance because they have been isolated from both hospital and community-acquired isolates, particularly *Escherichia coli* isolates causing urinary tract infections; and, also because of their clonal, plasmid-mediated nature (6,7,8). The majority of CTX-M type enzymes are associated with the insertion sequence *IS*Ecp1 (9,11).

A major enzyme among the CTX-M ESBLs is CTX-M-15, an enzyme that has been associated with epidemic and mosaic plasmids, and that may play a role in conferring carbapenem resistance when found in isolates showing outer membrane impermeabilities (3,9,12,13). Unlike other CTX-M enzymes, CTX-M-15 efficiently hydrolyzes both cefotaxime and ceftazidime (14). In addition CTX-M-15, encoded by the $bla_{\text{CTX-M-15}}$ gene, is sometimes associated with other ESBLs encoding genes, such as bla_{TEM} and bla_{SHV} derivatives and $bla_{\text{OXA-1}}$ as well as genes encoding for resistance to other antimicrobial agents, such as the *qnrA* and *qnrB* genes conferring resistance to fluoroquinolones, and *aac(6')-Ib-cr*, conferring resistance to aminoglycosides and fluoroquinolones (15,16,17,18,19). It was first detected in an *E. coli* isolate in India in 2001, but since then, it has become the most disseminated ESBL worldwide, mainly as a single clone ST131 O25:H4 (14,20). It is the predominant CTX-M enzyme in Europe, and in India, which may be considered a major reservoir for *E. coli* isolates harboring the $bla_{\text{CTX-M-15}}$ gene (6,20,21,22). It has also been identified in *E. coli* isolates from North and South America, Asia, Australia, Africa and the Middle East (10,23-28).

Distribution of $bla_{CTX-M-15}$ in the Middle East

Among the Middle Eastern countries, CTX-M-15 is most widespread and is the predominant ESBL in Egypt, Kuwait, Lebanon, and the United Arab Emirates; as for other countries in the region, distribution and prevalence varies or has not been reported yet (28-31).

Egypt

High rates of ESBL production have been reported for Egypt since 2003, however, the presence of $bla_{CTX-M-15}$ was not reported until 2006, in a study conducted by Al-Agamy et al (29,32,33). Al-Agamy et al found that 25 of 28 ESBL producing *E. coli* isolates were carriers of CTX-M type enzymes, and that of these isolates, 13 harbored $bla_{CTX-M-15}$ (29). At the time, there was no information available on the spread of CTX-M enzymes in Egypt (29). Since then, a more thorough study conducted by Fam et al identified 74 isolates producing $bla_{CTX-M-15}$, constituting all ESBL producers that were available for molecular study (34).

Iran

Feizabadi et al reported in 2006 a high prevalence of ESBL production among *K. pneumoniae* isolates collected at two teaching hospitals in Tehran, Iran (35). A similar study conducted in 2008 by Mehrgan et al reported that among the high number of ESBL producing *E. coli* isolates identified, some showed an antimicrobial resistance profile suggestive of the presence of a CTX-M type enzyme, but molecular data was lacking (36).

In 2009, Ramazanzadeh et al studied the spread of ESBLs in Intensive Care Units in two major hospitals in Sanandaj and found that the most prevalent ESBL belonged to the CTX-M family, but the types of CTX-M enzymes present were not determined (37). Following in 2010, Feizabadi et al reported the presence of the $bla_{CTX-M-15}$ gene in a high number of ESBL producing *K. pneumoniae* isolates among those tested (38). Later studies conducted by Feizabadi et al showed an increase in the CTX-M phenotype among ESBL producing *K. pneumoniae* isolates collected from hospitalized patients (39). In Iran, CTX-M-15 has also been identified among different *Salmonella enterica* serovars and among non-typhoidal *Salmonella* strains (40,41).

Iraq

ESBL production has been reported in Iraq, however, molecular data is scarce in the country (42). Reports of Iraqi isolates producing the CTX-M-15 enzyme come from studies conducted in France and Germany (43,44). In both cases, the isolates were transferred to these respective countries by patients from Iraq (43,44). In France, the CTX-M-15 enzyme was associated with bla_{NDM-1} production in a *K. pneumoniae* isolate (43). In Germany, the CTX-M-15 enzyme was isolated from a *Salmonella enterica* serovar Typhi (44). This data suggests that CTX-M-15 may be prevalent in Iraq.

Kuwait

Two studies from 2008 identifying the *E. coli* ST131 clone producing CTX-M-15 in a number of countries worldwide also identified this clone in Kuwait (45,46). Also in 2008, Rotimi et al reported for the first time in Kuwait, and in the gulf region, an outbreak of Salmonella spp producing CTX-M-15 (47). In 2009, Ensor et al tried to identify the prevalence of CTX-M enzymes in Kuwait by randomly selecting 43 ESBL producing *E. coli* and *K. pneumoniae* isolates collected at the Mubarak hospital and found that among these isolates, CTX-M-15 was the predominant enzyme (30). In 2010 and 2011, CTX-M-15 was identified from *Klebsiella pneumoniae* isolates in a number of studies, and a CTX-M-15-like enzyme clone was identified from an outbreak occurring in a neonatal intensive care unit at Al Jahra hospital (48,49). The *K. pneumoniae* isolate identified at the Al Jahra hospital also carried bla_{TEM-1} and $bla_{SHV-112}$ genes (49).

In 2010, Al Hashem et al attempted to investigate the extent and distribution of bla_{CTX-M} genes among *E. coli* isolates from all government hospitals in Kuwait. Isolates were collected from eight major hospitals in Kuwait and 136 ESBL producers were identified. The most prevalent enzyme among the ESBL producers, with a prevalence of 84.1%, was CTX-M-15, suggesting that Kuwait may be an important source for CTX-M-15 producing *E. coli* isolates (50).

Lebanon

In Lebanon, there is a countrywide dissemination of the $bla_{CTX-M-15}$ gene (28). CTX-M-15 has been identified in many members of the *Enterobacteriaceae* from both community and hospital acquired infections (28,51,52,53). In a nationwide study conducted in 2005 that included six tertiary care centers in Lebanon, Moubareck et al identified CTX-M-15 from *E. coli*, *Klebsiella pneumoniae,* and *Enterobacter cloaceae* isolates (28). That same year, Moubareck et al identified the first *Salmonella enterica* serovar Typhimurium isolate producing CTX-M-15 in the country, reporting for the first time in Lebanon an ESBL producing *Salmonella* isolate (53). Subsequently, Kanj et al reported a high prevalence of CTX-M-15 production in *E. coli* and *K. pneumoniae* isolates from a tertiary care center in Lebanon and Matar et al reported CTX-M-15 from two *Salmonella enterica* serovar Typhimurium isolates and three *Shigella sonnei* isolates, making CTX-M-15 the predominant ESBL identified in the country (51,52, 54,55).

Oman

Studies conducted in Oman on isolates collected from pediatric patients, intensive care unit and other hospitalized patients and from outpatient clinics suggest an increasing prevalence of ESBL producers, however, these studies did not attempt to identify the types of ESBL genes present (56,57,58). In a review on susceptibilities of common bacterial isolates collected from the Royal Hospital in Oman, resistance to third generation cephalosporins varied among the *Enterobacteriaceae*, and, as

mentioned by the authors, was possibly due to CTX-M type enzymes, which had been detected at the center previously (59). The only report of an isolate producing CTX-M-15 coming from Oman is from a *K. pneumoniae* isolate also harboring bla_{NDM-1} (60).

Saudi Arabia

Al Agamy et al identified the first CTX-M enzymes from Saudi Arabia in 2009 in a study they conducted to determine the prevalence of ESBLs among *K. pneumoniae* isolates in Riyadh (61). Prevalent among these enzymes were $bla_{CTX-M-15}$ like genes belonging to the CTX-M-1 group (61). Furthermore, Bindayna et al reported in 2010 that the most prevalent ESBL among 100 isolates collected in Dhahran was CTX-M, however, in this study the specific type of CTX-M enzyme present was not determined (62). In 2011, Tawfik et al reported a high prevalence of CTX-M-15 among 110 ESBL producing clinical *K. pneumoniae* isolates collected in Al-Qassim (63).

Turkey

In 2003, Lartigue et al reported the first clinical isolate, a *Klebsiella pneumoniae,* producing CTX-M-15 in Turkey (64). In 2007, Yildirim et al reported a *Klebsiella pneumoniae* isolate that produced blaCTX-M-15 as well as a carbapenemase (65). Following in 2008, a study conducted at a university hospital in Istanbul by Gonullu et al revealed a high prevalence of CTX-M-15 among *E. coli* isolates recovered from inpatients and outpatients treated at the center (66). Similarly, between 2008 and 2010, studies to determine the prevalence of CTX-M-15 production in *E. coli* isolates from community acquired infections reported that the prevalence of CTX-M-15 was quite high among those isolates producing ESBLs (67,68,69).

United Arab Emirates

In a first report of the production of CTX-M-type enzymes in the Arabian Peninsula**,** five entero-aggregative *E. coli* isolates from the United Arab Emirates were found to harbor $bla_{CTX-M-15}$ and bla_{TEM-1} (31). CTX-M-15 was then identified in a single *Salmonella* group C isolate in the 2008 study conducted by Rotimi et al mentioned previously (47). In 2011, in a study collecting ESBL producing isolates from hospitalized patients in three hospitals across the UAE, the majority of the isolates among those identified as ESBL producers harbored $bla_{CTX-M-15}$ (70).

Others

In the Gaza Strip, Jordan, and Bahrain, resistance data suggests the production of extended spectrum β-lactamases but to date no studies have attempted to identify and characterize the genetic determinants causing this ESBL phenotype (33,71,72). In one study from Jordan, Shehabi et al observed a high rate of *Klebsiella pneumoniae* isolates resistant to extended spectrum cephalosporins among ICU patients, suggesting that these isolates were potentially ESBL producers; extended spectrum cephalosporin resistance was also observed among *E. coli* and *Enterobacter* spp isolates, but at a lower rate (74). Though there have been no reports of CTX-M-15 throughout the rest of Palestine, other CTX-M enzymes, especially CTX-M-2, have been identified from *E. coli* isolates (75). No data has been published on ESBLs for Yemen, Qatar and Syria.

Conclusion

Data from the Middle East shows that CTX-M-15 is prevalent in more than one country, and that the encoding gene is many times associated with other resistance encoding genes, including other ESBLs (31,38,51). This is not surprising as in many countries in the Middle East antimicrobials can be purchased without a prescription and are commonly misused, possibly resulting in the selection of antimicrobial resistant strains (29,36,50). In Kuwait, a number of studies attributed part of the high prevalence of CTX-M-15 to a large population of non-nationals; this could also be the case for other countries in the gulf region, where many non-nationals also live (30,50).

Since the ST131 clone carrying CTX-M-15 was identified in Kuwait, Multi-Locus Sequence Typing may shed light on whether the same clone is prevalent in other countries in the Middle East (45,46). Similar to reports from other countries, CTX-M-15 was identified from both hospital and community acquired infections and in a number of members of the Enterobacteriaceae, including *E. coli*, *K. pneumoniae*, and *Salmonella* spp (6,9). In many instances, the $bla_{CTX-M-15}$ gene was found to be encoded by an *IS*Ecp1 insertion sequence, as reported elsewhere (31,47, 51-53,64).

Finally, though some countries in the Middle East have reported molecular data on the types of ESBLs present, many countries fail to routinely identify ESBls and lack data on the prevalence of isolates producing these enzymes at the national level. The high prevalence of ESBL production among all types of *Enterobacteriaceae* reported from a number of countries implies that there is an urgent need for regular screening for extended spectrum β-lactamases production, in order to identify such genes as CTX-M-15, but also others. Determining the presence of an ESBL and then identifying its type is important for prescribing proper antimicrobial treatment and for avoiding therapeutic failure or an unwanted clinical outcome (37,75,76,77).

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