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Drug Resistance due to Elaboration of Beta Lactamases and the Role of CTX-M in Enterobacteriaceae

Rida Sohail, Yasmeen Taj, Luqman Satti, Shaista Bakhat

ABSTRACT:

The *Enterobacteriaceae* family are the most common pathogens associated with hospital and community acquired infections worldwide. These bacteria are treated with broad spectrum antibiotics especially 3rd generation cephalosporins. Over the period of time due widespread and rigorous use of these medications, *Enterobacteriaceae* has developed antibiotic resistance (AMR). Among all, the most compelling antibiotic resistance mechanism is production of β-lactamases enzymes by this microorganism. Over the course of time β-lactamase has evolved more than 1300 distinct enzymes. Amongst these most deleterious is extended spectrum beta lactamases (ESBL). ESBL producing *Enterbacteriacaeae* are responsible for a high number of deaths worldwide. These enzymes are considered challenging as they are difficult to be identified in the laboratory wShich cause delay in diagnosis and administration of appropriate antimicrobial therapy. The coexistence of ESBL with other antibiotic resistance gene is another therapeutic challenge rendering empirical antibiotic treatment ineffective.

Key words: *Enterbacteriacaeae*, AMR, ESBL, CTX-M

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INTRODUCTION:

Antibiotic resistance is a subject under constant evaluation, and multiple researches and new data addresses this problem every day. Resistance to β-lactam antibiotics like penicillin and cephalosporin is due to the elaboration of β-lactamase enzymes, which are responsible for degrading β-lactam drugs and have been assessed from different perspectives including dissemination and classification. These β-lactam drugs are bactericidal as they block the formation of Ala-Ala dimer required for the formation of bacterial cell wall peptidoglycan layer. β-lactams are similar to penicillin binding proteins (PBP) that mediate the cross-linking processes of peptidoglycan synthesis of bacteria. In the presence of β-lactam drugs this processes of cross-linking doesn't initiate. The constant chemical stress against these β-lactam drugs results in genetic alternation within the bacterial cell which concludes with the elaboration of â -lactamase enzymes. These enzymes thus break the beta-lactam ring of the incoming drug, ensuring bacterial cell propagation and survival. β-lactamases have been used as a model to study the enhanced evolution following Darwinian principle where the huge burden of antibiotics use allows the existence of the fittest.[1] The constant pressure due unwarranted use of antibiotics has resulted in mutations which altered the genome of bacteria so much, that targeting them has become impossible. Since the 1980s there has been a substantial rise in the number of these enzymes especially class A and D.[2] β-lactamases which include the extended-spectrum-β-lactamases (ESBL's) can degrade broad-spectrum Cephalosporins (such as Monobactams, Cefepime, Ceftriaxone and Cefotaxime) but are inhibited by Ceftazidime; this is an alarming situation.[3-4] Ambler's classification is on the basis of amino acid homology and divides the enzymes in four groups (A-D). Group A, C and D proteins shows similar folds and include an amino acid serine which is essential for the founding of an acyl–enzyme complex with the β-lactam resulting in its hydrolysis. Group B is metalloproteinase which has one or two zinc ions. These groups have specific enzyme families. Class A have TEM (Temoniera), SHV (sulf-hydryl variable) these enzymes are mostly responsible of ampicillin and penicillin resistance [5], CTX-M (cefotaximases-munich)[6] and KPC (*Klebsiella pneumoniae* carbapenemase)[7] ; NDM(New Delhi metallo-beta-lactamase) and VIM (Verona integron-borne metallo-β-lactamase (class B); and CMY (cephamycin-hydrolyzing β-lactamase) and ADC (Acinetobacter-derived cephalosporinase) class C. [8] Class D enzymes are all termed

Rida Sohail *(Corresponding Author)*
M.Phil. Student, Department of Pathology
Bahria University Health Sciences, Karachi
Email: Sohailrida14@gmail.com

Yasmeen Taj
Professor, Department of Pathology
Bahria University Health Sciences, Karachi

Luqman Satti
Professor, Department of Pathology
Bahria University Health Sciences and PNS Shifa Hospital, Karachi

Shaista Bakhat
Assistant Professor, Department of Pathology
Bahria University Health Sciences, Karachi

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oxacillinase (OXA) responsible for high hydrolytic activity against Cloxacillin and Oxacillin. [9-10] CTX-M β-lactamases are thought to be the prototype in development of resistance in microorganism against antibiotics.[11] Integration of various blaCTX-M genes originating from various kind of Kluyvera has resulted different CTX-M clusters.[12] In Silico analysis and TREE VIEW program (http://taxonomy.zoology.gla.ac.uk/rod/treeview.html), based on a multiple sequence alignment of the publicly available CTX-M sequences(http://www.lahey. org/Studies/) shows that these events have happened at least nine stretches resulting in CTX-M-1 cluster, CTX-M-2 and CTX-M-9 clusters and CTX-M-8 and CTX-M-25 clusters. [13] Each cluster has been further divided in to groups and subgroups based amino acid similarity. The most prominent amongst these clusters are Group 1 and Group 9. Within these groups the CTX-M15, CTX-M-3 and CTX-M-14 are the most widespread and rapidly emerging in humans and well as in the animals. CTXM-15, the most prominent and commonest CTX-M enzyme is a derivative of CTX-M-3, which belongs to Amblers group A and cluster 1. The structural analysis of the enzymes suggest that single amino acid mutation can change the entire hydrolytic activity of the enzyme against a drug. For example the CTX-M-15 varies from its cluster 1 enzyme by single point mutation. This alternation marks increased CTX-M-15 enzymatic activity against Ceftazidime. This hydrolytic enhancement is not demonstrated by any other CTX-M enzyme.

These new genetic variants harbor mobile genetic elements such as insertion sequences like transposons and class 1 integrons.[14] The acquisition of bla CTX-M genes from the environment on these genetic elements could have been a random incident. However β-lactam selective force applied by excessive use of Cefotaxime and Ceftazidime has triggered mutations leading to modification of different clusters. Infiltration and worldwide dissemination of CTX-M producing organisms are the result of the designated "epidemic resistance plasmids" harboring resistance and high-risk virulent clones.[15] Amalgamation of these factors including co-selection of resistance element within CTX-M harboring bacteria which also produces Carbapenemases is alarming. The processes of co-selection is when a single resistant gene mediates resistance against all other drugs. This may be true as all the antibiotic resistance gene resides on the same plasmid.

The TEM and SHV ESBLs dominant in 1980s and 1990s scenario were mainly linked with nosocomial infections associated with *Klebsiella pneumoniae* and *Escherichia coli* whereas CTX-M were less dominant.[10] . However recently this epidemiology has drastically changed and now CTX-M has become the most prevalent beta-lactamases. Although first revealed in 1989, the ESBL CTX-M enzymes did not achieve dominance over other enzymes till 21th century when increased dissemination of these enzymes were detected.[16-17] They were not only restricted to nosocomial infections but disseminated is community with *E. coli* being the most prominent pathogens elaborating these enzymes.[18]

This review article is searched through PubMed, Google, and Google Scholar engine with several key words like β-lactamases, Enterobacteriaceae *salmonella typhi*, XDR, and CTM genes. A total of 70 articles were critically analyzed from 2001-2021. The data was collected and processed within six months.

1. Epidemiology of CTX-M β-lactamase-producing bacteria:

The CTX-M was present in enterobacters before cephalosporin's being dominant treating options in healthcare. Although CTX-M advent was appreciated in 1980s, its prominence become recognizable in the year 2000. Studies over the last decade have shown that CTX-M enzymes are the most dominant ESBL enzymes in *Enterobacteriaceae* .[19-20] This is a consequence of the surprising spread of the blaCTX-M gene within mobile genetic elements inside susceptible clones.[22-24] In addition there is a co-existence with other antibiotics including Aminoglycosides and Fluoroquinolones.[25-26] These isolates exhibit decrease Ciprofloxacin susceptibility (DCS, MIC value 0.38mg/L) and Luminex based assay to detect mutations in quinolone resistant determining regions (QRDR) and plasmid mediated quinolone resistant gene (PMQR) reveal that DCSs was linked with the single mutation in residue ser83 of gyrA gene. This is one of the prominent genetic elements among *salmonella typhi* (*S.* Typhi) exhibiting DCS.[27]

Among the CTX-M family, the CTX-M-14 and CTX-M-15 are the most prevalent in the human, animals and environment.[28-29] In this scenario CTX-M can be distinguished into various phases. The first phase comprises of different CTX-M β-lactamases in diverse geographic areas and these events may have happened until the mid of the 1990 decade. The second phase was marked by the appearance of CTX-M-3, CTX-M-9, CTX-M-14, and CTX-M-15 enzymes and these events might have occurred over decade ending to 2000. The third phase after 2000 is noted by the worldwide dissemination of these lactamases. The first report identified Cefotaxime resistance but Ceftazidime susceptible, was strain of *E.coli* isolated from otitis media specimen of four month old child in Munich Germany.[30]

Up till now the most disseminated CTX-M enzymes globally have been CTX-M 15 followed by CTX-M 14. These two enzymes have enhanced degrading potential and increased MIC's against Ceftazidime, an antibiotic which is not inhibited by other CTX-M family enzyme.

Recently, a new variant of CTX-M-15 has emerged, which has received incredible attention. This enzyme is CTX-M-33 which has decreased degrading activity against Ceftazidime but on the contrary increased hydrolytic activity against Carbapenams e.g. Meropenams. The increased use of Carbepenams against resistant 3rd generation

Cephalosporin's has resulted in the emergence of these strains. et al, 2019 has identified that this increase hydrolytic activity is due to point mutation which has altered amino acid sequence from serine-to-asparagine. [59]

2. Penetration and globalization of CTX-M enzymes all over the world: The worldwide expansion of CTX-M-1 cluster was represented with growing new variant over the 1990s. For example, CTX-M-10 was primarily found in the region of Mediterranean (Spain and France[10-31] and where the CTX-M-15 first found in 1999 in *Enterobacteriacea* in New Delhi, India [32] but nowadays reported from all around the world. These modifications are due to amino acid substations which are reported to have been developed from common ancestors. [33-34]

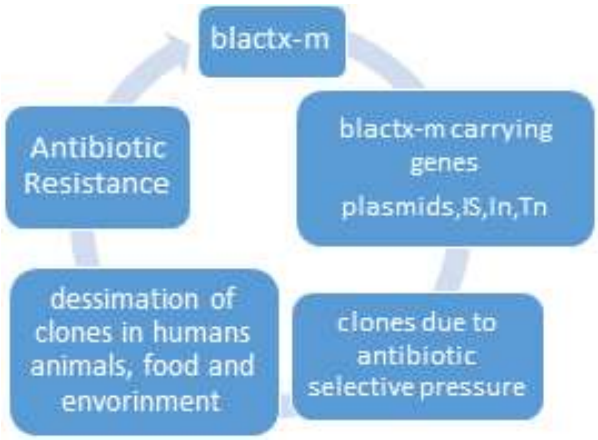
The CTX-M-15 spread in United Kingdom after it was first reported and the isolates were linked to *E.coli*.[35-36] International travel and immigration added to the speedy appearances and spread of CTX-M enzymes all over the world.[37-38] This has been recently proved with Carbapenemases in particular with NDM-1 metallo-β-lactamase producing pathogens.[39-40] However the existence of CTX-M enzymes in animals and food merchandises that are moved among different countries have proposed the likely paths for spread and dispersion. [41] Moreover this rapid dissemination has also been attributed to presence of blaCTX-M of plasmid and transposons, which confer rapid transfer of resistant elements not only within the specie but also to any bacteria it comes in contact to.

Although the global prevalence of CTX-M family is not well documented especially from developing areas making estimation of prevalence challenging and complex, published articles from Africans and Asian countries indicate rapid increase in the prevalence of this enzyme. African countries data demonstrate increase in prevalence to 13.6% within two years' time where as 95.5% isolates were positive of CTX-M in 2018 from Ethiopia. Compared to these similar findings among clinical Enterobacteriaceae isolates with prevalence rates of 91% in Brazil[60], 80.3% in Germany [61] and 79% in Switzerland [62] have been documented. A nationwide survey in china indicated 91% ESBL producing bacteria harbored CTX-M. European data from nine different countries also suggest that the most common ESBL is CTX-M which was found to be 66.4%.

3. CTX-M enzymes in bacteria other than *Enterobacteriaceae*:

CTX-M enzymes were first reported in *E. coli, K. pneumonia* and other nosocomial infection associated bacteria like *Acinetobacter, Serratia etc,* but later begin to be reported in other Enterobacteriaceae as well. This was the result of chromosomal changes which induced AmpC in Enterobacteriaceae spp, *Citrobacter* species, *Serratia marcescens*, *Enterobacter* species and *Morganella morganii* species enabling these organisms to degrade oxy-imino-cephalosporins. [16, 42-43]

Figure 1: Cycle of global dissemination of CTX-M ESBL



The first CTX-M enzymes reported in *Pseudomonas aeruginosa* from a patient of cystic fibrosis sputum sample but still presences of CTX-M enzyme in non-fermenting rods is not common.[44] This point may be the result instability of plasmids carrying these enzymes. *Vibrio* spp. or *Aeromonas* spp. isolates with CTX-M enzymes have also been reported.[45,46]

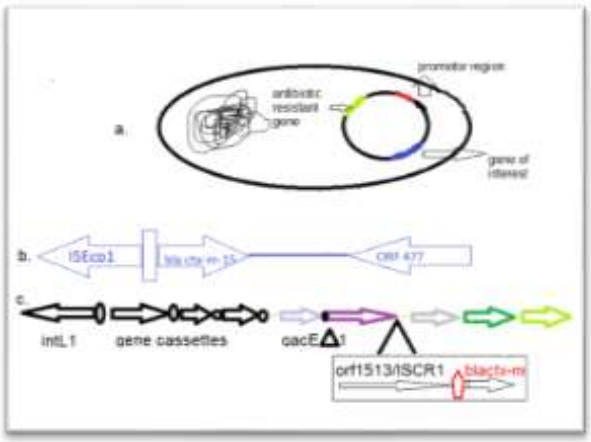
4. Foundation of the blaCTX-M genes: According to phylogenetic trees analysis the CTX-M β-lactamases can be categorized into five major clusters. Usually each cluster can be allied to chromosomal bla genes in various *kluyvera spp*, which are present in normal human intestinal floral but at very low numbers, and is a saprophytic and an opportunistic pathogen. The enterobacter captured the blaCTX-M gene on the plasmids probably from the chromosomal blaCTX-M of *kluyvera*. Also *kluyvera* has been sporadically linked with human urinary tract skin and soft tissue infections.[47] They are habitually present in the environment in water, sewage, soil, food products and animals [48-49]

5. Evolution and diversification of CTX-M β-lactamases: Presently higher than 60% of the isolates harboring CTX-M exhibit resistance towards Cefotaxime and Ceftazidime at the same time. Although the first report of CTX-M harboring resistance towards Cefotaxime but were not able to hydrolyze Ceftazidime. It can be therefore presumed that its Ceftazidime that was the potential factor in backing the divergence of CTX-M. [50-51]

6. Plasmids and spread of bacterial genes: According to research studies the widespread dissemination of blaCTX-M gene is closely linked with IncF plasmid especially FII. IncF plasimds are epitome of autonomous replication and contributor to bacterial fitness and survival. These FII are narrow range plasmids whose significance is limited to horizontal gene transfer in closely related bacterial species like E.Coli, Salmonella and Shigella. These incF plasmids are usually in low number in the bacteria but harbor all

sorts of virulent gene.[52-53] These incompatibility plasmids are associated with gram negative bacteria and labelled 'epidemic resistant plasmid' because of their affinity to attain and transfer resistant elements among the bacteria. These plasmids have evolved through the recombination of various plasmids and thus are not homogenous. A notable fact about these plasmids is that these were prevalent among the *Enterobacteriaceae f*amily even before the use of antibiotic and were well adapted to these organisms.[54-55] These events without a doubt suggests the persistence and globalization of these resistant elements including blaCTX-M genes.[56-57]

Figure 2: Structure of *Enterbacteriacae* genetics elements (plasmids and transposons)



7. Dispersion of multi-drug resistant and virulent high-risk clones:

One of the reason allowing dissemination of enzyme elaborating CTX-M is the contribution of defined copies predominately from *K. pneumoniae* and *E. coli*. current research founded on MLST(Multi-Locus Sequence Typing) have confirmed although there is a varity amongst CTX-M producer, however few conjugated (clonal complexes) are commonly linked to CTX-M enzymes and designate high-risk clones st131 is example of international disseminated clone. At individual basis risk factors which allow adherence to the host and host adherence and binding also facilitate its perseverance and have been found in food products, wild-life, and animals.

8. *Salmonella typhi* **and CTM: the everlasting endemic**

Salomella typhi is held responsible for typhoid or enteric fever. Enteric fever is characterized by step-wise fever which if not treated immediately and properly, ends up in complication and mortality. This disease predominantly affects children below 10 years of age but recent reports suggest that it affects male in their 20's as well. This bacteria is transmitted to human by the consumptions of dirty water or contaminated food. Typhoid is common in developing countries mostly due improper sewerage system, larger families sharing single washroom, improper hygiene and mostly importantly unjust use of antibiotics. In the areas where *S.Typhi* is endemic different types of strains are circulating but only restricted strains cause outbreaks. In the year 1948 Chloramphenicol was introduced as the most efficient drug to treat typhoid fever. But in merely two years due to pervasive use of drugs, the first resistant isolate was reported. This battle became worrisome in the 1980s when resistant strains started emerging to the first line of antibiotics Co-trimoxazole, Chloramphenicol and Ampicillin, and these strain were defined as multidrug resistance (MDR).[58] Since then 3rd Cephalosporins have been used as empirical treatment of typhoid. In 1999, Bangladesh reported 1st XDR (extensively drug resistant) isolate. This isolate was resistant to ceftriaxone (3rd generation cephalosporin) as well as 1st like of drugs. In the following years various reports of 2-5 cases of XDR *S.Typhi* were being reported, raising concerns. In 2016 Pakistan reported a major "XDR endemic" in the city of Sindh effecting more than 500 in a week. According to Pakistan National Institute of Health, till the month of Aug 2021, in Karachi alone 1,739 XDR S.Typhi have been reported. Alongside "The Centers for Disease Control and Prevention" (CDC) declares that the world has once again entered the "post-antibiotic era," wherein we would face lack of effective treatment options due to marked antibiotic resistance (AMR).

The gene sequencing of these XDR *Salmonella* strains indicated that these belonged to haplotype 58 (H58) which elaborates CTX-M enzymes. S.Typhi has a remarkable capability to express CTX-M family that encompasses more than 200 enzymes. These enzymes degrade Ceftriaxone, Cefotaxime but CTX-M 15 enzymes also degrades Ceftazidime, leaving behind Carbapenems for the treatment, to which resistance has also started to emerge. The last decade shows substantial increase in CTX-M producing variants and most of the research has been conducted in the developed world. Studies in various countries show that once a β-lactamases enters a defined geographic area, it superimposes and replaces other ESBL variants. In this review our objective was to research the antibiotic resistant pattern in salmonella in our part of the world and look for the presence of CTX-M 15 gene of beta lactamases. Although other non-typhoidal Salmonella enterica serovar Typhimurium consist CTX-M-2, CTX-M55 and CTX-M27, Salmonella enterica serovar typhi affecting humans elaborates CTX-M14 and CTX-M15. It has been proposed that these typhiodal serovar caught CTX-M15 on their mobile genetic material e.g plasmid from *E.Coli* in sewerage water.

XDR *S.Typhi* were only reported from Pakistan, Bangladesh, India, Nepal and African countries.But recent reports from developed countries like England, Canada, USA etc has raised concerns of the authorities. The WGS of these strains indicated that they identical to the one's that caused endemic in Pakistan and India. The global reports of *S.Typhi*

elaborating CTX-M15 is alarming and tragic. Even before the advent of these strains, typhoid had killed and has affected millions of people. Typhoid has become a symbol of fear amongst many civilizations and if prompt measures are not taken to combat this strain, treating *S.Typhi* infection would become impossible.

CONCLUSION:

Although the magnitude of infections caused by antibiotic resistant *Enterobacteriaceae* strains vary globally but South East Asia remains a major reservoir of these resistant strains. The widespread and prominent amongst these are *E.coli*, *K.pneumoniae* and *S.Typhi*. Since last few years these strains have acquired further resistant elements, challenging the health care system to provide with the better treatment options. At this point of time it is of utmost importance to address these increasing XDR strains outbreaks especially from Pakistan, India and Bangladesh. The pooled prevalence of ESBL and MBL-producing E. coli in South Asia is 33% and 17% respectively. The prevalence of blaCTX-M type was 58% with blaCTX-M-15 being the most prevalent (51 %) variants.

Today CTX-M-type enzymes are the most commonly found ESBL type with the CTX-M-15 variant dominating worldwide, followed in prevalence by CTX-M-14, and CTX-M-27 is emerging in certain parts of the world. This ESBL *Enterobacteriaceae* (ESBL.E) can disseminate by direct contact with an infected person's bodily fluids (blood, urine, drainage from a wound, fecal matter). They may also spread by contact with surfaces or equipment harboring these bacteria's. Immigrations and travel from endemics areas is another prominent reason for increased dissemination. Thus this overhauled emergence of CTX-M gene is responsible for increasing reports of nosocomial infections, ICU outbreaks and related mortality. The CTX-M family warrants research and is a pattern reflecting increasing antibiotic resistance. Genetic sequences and data bases suggests that blaCTX-M have originated from *Kluyvera* spp and merging of these various genetic elements in various *Enterbacteriacaea* by mode of plasmids and clone. The co-existence of blaCTX-M genes with other resistant elements contributes towards the significant increase of CTX-m enzymes justifies the in-depth study so as to foresee a pandemic scenario of antibiotic resistance. Considering this we propose that rapid preventive measure should be implemented to control the widespread dissemination of these virulent strains. This constant evolution of ESBL.E should be controlled by monitoring the ESBL fecal carriage especially in ICU patients, assurance of hygiene protocols, screening of meat and dairy products, regular antibiograms indicating antibiotic susceptibility patterns in a given region, antimicrobial stewardship programs insuring synchronized and appropriate use of antibiotics, and restricted and monitored travel from endemic areas, and finally prohibiting injudicious use of antibiotics. The present and future from today is very critical because if we failed to control and restrict these antibiotic resistant strainss in Enterobacteriacaea we would unquestionably end up being in post antibiotic era, where only death and fever prevailed.

Authors Contribution:
Rida Sohail: Conception, designing, literature search and writing the article
Yasmeen Taj: Conception, critical analysis and proof reading
Luqman Satti: Conception, critical analysis and proof reading
Shaista Bakhat: Literature search, layout and review

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